Promoting the Quality of Medicines Plus (PQM+)

Scientific and technical information package for COVID-19 antivirals prescribed to prevent serious disease and death in high-risk populations infected with COVID-19

Nirmatrelvir tablets co-packaged with Ritonavir tablet; Molnupiravir capsule

August 2023

Package 2A

USAID FROM THE AMERICAN PEOPLE

usp

Contact Information

Promoting the Quality of Medicines Plus Program
United States Pharmacopeia
12601 Twinbrook Parkway
Rockville, MD 20852 USA
Tel: +1-301-816-8166
Fax: +1-301-816-8374
Email: PQMplus@USP.org

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About PQM+

The Promoting the Quality of Medicines Plus (PQM+) Program is a six-year cooperative agreement between USAID and USP to sustainably strengthen medical product quality assurance systems in low- and middle-income countries. The program works to improve medical product quality through cross-sectoral and systems strengthening approaches and the application of international quality assurance standards across the pharmaceutical system. By sharing scientific expertise and providing technical support and leadership, PQM+ helps create resilient and robust local health systems that address diseases such as HIV/AIDS, tuberculosis, malaria, and neglected tropical diseases, as well as improve maternal, newborn, and child health.

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Contents

Acknowledgements

European Medicines Agency (EMA) authored documents are cited in their original form as published by EMA (either as a PDF or online publication).

U.S. Food and Drug Administration (FDA) authored documents are cited in their original form as published by U.S. FDA. Advisory committee briefing documents provided to the U.S. FDA by Pfizer and Merck Sharp & Dohme LLC are for public release and were published on the U.S. FDA website.

U.S. National Institutes of Health (NIH) documents were authored by the COVID-19 Treatment Guidelines Panel. Specifically, the Coronavirus Disease 2019 (COVID-19) Treatment Guidelines, National Institutes of Health available at https://www.covid19treatmentguidelines.nih.gov/. Accessed June 1, 2023. The COVID-19 Treatment Guidelines Panel regularly updates the recommendations in these guidelines as new information on the management of COVID-19 becomes available. The most recent version of the guidelines can be found on the COVID-19 Treatment Guidelines website (https://www.covid19treatmentguidelines.nih.gov/).

World Health Organization (WHO)-authored documents are cited in their original form as published by WHO (either as a PDF or online publication). Individual titles, place of publication, and year are contained in each original document except the one listed below. All documents were issued under License: CC BY-NC-SA 3.0 IGO

PQM+ would like to thank our implementing partner programs, Meeting Targets and Maintaining Epidemic Control (EpiC) and Reaching Impact, Saturation, and Epidemic Control (RISE), for their collaboration and support throughout the test-to-treat (T2T) program. We would also like to thank our collaborators from the national medicines regulatory authorities (NMRA) in each of the Test to Treat countries:

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Acronyms

API	active pharmaceutical ingredients
EMA	European Medicines Agency
EUA	emergency use authorization
EUAL	emergency use assessment and listing
EUL	emergency use listing
FDA	U.S. Food and Drug Administration
NIH	U.S. National Institutes for Health
PHEIC	public health emergency of international concern
PQM+	Promoting the Quality of Medicines Plus
T2T	test-to-treat
USAID	U.S. Agency for International Development
USP	U.S. Pharmacopeial Convention
WHO	World Health Organization

Package 2A. Tier A Document information (click each entry to link to document)

#	DOCUMENT TITLE	SOURCE
2A.1	Therapeutics and COVID-19: Living Guideline (January 13, 2023) – 6.2 Nirmatrelvir, pages 13-27	WHO
2A.2	NIH Guidance for Ritonavir-Boosted Nirmatrelvir (Paxlovid)	NIH
2A.3	NIH Guidance for Drug-Drug Interactions Between Ritonavir Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications	NIH
2A.4	Liverpool Drug Interactions Group Drug-Drug Interactions with Outpatient Medicines & Nirmatrelvir/ ritonavir (NMV/r)	Liverpool Drug Interactions Group
2A.5	Liverpool Drug Interactions Group Drug-Drug Interactions with Essential Medicines & Nirmatrelvir/ ritonavir (NMV/r)	Liverpool Drug Interactions Group
2A.6	EMA European Public Assessment Report of Paxlovid (updated February 24, 2022)	EMA
2A.7	EMA European Public Assessment Report – Product Information (Annex I-III; updated June 27 2023)	EMA
2A.8	EMA Article 5 (3) Assessment Report of Paxlovid (December 16, 2021)	EMA
2A.9	EMA Conditions of Use, Conditions for Distribution and Patients Targeted and Conditions for Safety Monitoring Addressed to Member States for Unauthorized Product Paxlovid (PF-07321332 150 mg and ritonavir 100 mg) Available for Use	EMA
2A.10	U.S. FDA Center for Drug Evaluation and Research Application number: 217188Orig1s000 Product Quality Review	U.S. FDA
2A.11	U.S. FDA Center for Drug Evaluation and Research Application number: 217188Orig1s000 Integrated Review	U.S. FDA
2A.12	U.S. FDA Center for Drug Evaluation and Research Application number: 217188Orig1s000 Risk Assessment and Risk Mitigation Review(s)	U.S. FDA

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2A.13	U.S. FDA Center for Drug Evaluation and Research Application number: 217188Orig1s000 Other Reviews	U.S. FDA
2A.14	U.S. FDA Paxlovid Approved Label	U.S. FDA
2A.15	U.S. FDA Emergency Use Authorization (EUA) for Paxlovid (nirmatrelvir tablets co-packaged with ritonavir tablets) Center for Drug Evaluation and Research (CDER) Review (December 22, 2021)	U.S. FDA
2A.16	U.S. FDA Fact Sheet for Patients, Parents, and Caregivers Emergency Use Authorization (EUA) of Paxlovid for Coronavirus Disease 2019 (COVID-19)	U.S. FDA
2A.17	U.S. FDA Fact Sheet for Healthcare Providers: Emergency Use Authorization for Paxlovid	U.S. FDA

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Document 2A.1

Therapeutics and COVID-19: Living Guideline (January 13, 2023) – 6.2 Nirmatrelvir, pages 13-27

Document URL

https://app.magicapp.org/#/guideline/nBkO1E

Reference website URL

https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2023.1

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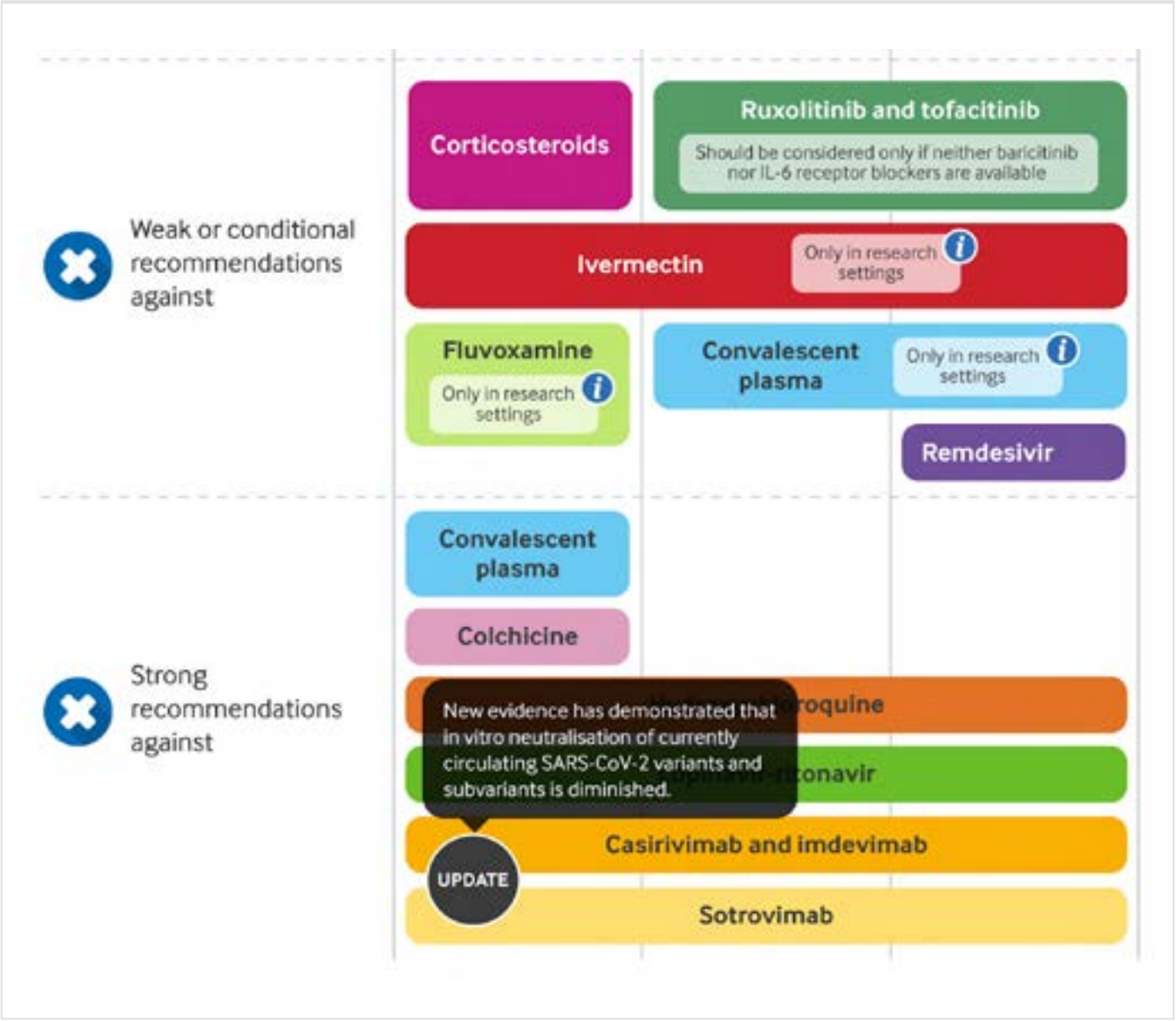

6.2 Nirmatrelvir-ritonavir (updated 13 January 2023)

Info Box

An initial strong recommendation concerning nirmatrelvir-ritonavir for patients with non-severe COVID-19 at highest risk of hospitalization and a conditional recommendation against use for patients at low risk of hospitalization were published on 22 April 2022 as the 10th version of the WHO living guideline and in the BMJ as Rapid Recommendations. This was based on data from two RCTs which were available at the time *(1)*. Applicability of the recommendations to children, breastfeeding and pregnant women was uncertain, as the included RCTs enrolled only non-pregnant women.

In this 13th iteration, an updated recommendation was made concerning the use of nirmatrelvir-ritonavir in breastfeeding and pregnant women with non-severe illness, based on data mainly available through the WHO VigiBase | UMC. While there were no reported serious adverse events linked to nirmatrelvir-ritonavir in pregnant or breastfeeding women - either in mother or child - there was residual uncertainty pertaining to the denominator to which this estimate of no undesirable effects applied. Therefore, given the likely benefits and residual uncertainty regarding undesirable effects, the recommendation was updated to reflect the GDG's belief that shared, fully informed decision-making between mother and health care provider should determine the use or non-use of nirmatrelvir-ritonavir in pregnant or breastfeeding women with non-severe COVID-19.

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For patients with non-severe COVID-19 at highest risk of hospitalization

Strong recommendation for

Updated

We recommend treatment with nirmatrelvir-ritonavir *(strong recommendation for).*

- *See Section 6.1 for help to identify patients at highest risk.*
- *Several therapeutic options are available: see decision support tool that displays benefits and harms of nirmatrelvir-ritonavir, molnupiravir and remdesivir.*
- *The GDG concluded that nirmatrelvir-ritonavir represents a superior choice because it may have greater efficacy in preventing hospitalization than the alternatives; has fewer concerns with respect to harms than does molnupiravir; and is easier to administer than intravenous remdesivir and the antibodies.*
- *Clinicians should review all medications and not consider nirmatrelvir-ritonavir in patients with possible dangerous drug interactions (note: many drugs interact with nirmatrelvir-ritonavir).*
- *Fully informed shared decision-making should determine whether nirmatrelvir-ritonavir should be used in pregnant or breast-feeding women, given possible benefit and residual uncertainty regarding potential undesirable effects.*
- *Nirmatrelvir-ritonavir should be administered as soon as possible after onset of symptoms, ideally within 5 days.*

Practical Info

Route, dosage and duration: Additional considerations are available in three summaries of practical issues (nirmatrelvir-ritonavir for COVID-19, administration of nirmatrelvir-ritonavir for COVID-19, safety and monitoring for patients receiving nirmatrelvir-ritonavir for COVID-19). Here follows a brief summary of key points:

- The recommended dose for nirmatrelvir-ritonavir is 300 mg (two 150 mg tablets) of nirmatrelvir and 100 mg of ritonavir every 12 hours daily for 5 days, as per the regimen evaluated in large trials informing the recommendation.
- In renal insufficiency (GFR 30–59 mL/min) the dose reduction is 150 mg of nirmatrelvir and 100 mg of ritonavir every 12 hours daily for 5 days.
- Administration should be as early as possible in the time course of the disease. In the included studies, nirmatrelvir-ritonavir was administered within 5 days of disease onset.

In any patient being considered for nirmatrelvir-ritonavir use, clinicians need to give serious consideration to drug interactions. The Liverpool COVID-19 drug interaction checker may be useful in this regard *(19).*

Evidence To Decision

Benefits and harms

In highest risk patients in whom an appreciable decrease in hospitalization with nirmatrelvir-ritonavir is likely, the benefits clearly outweigh the harms, thus warranting the strong recommendation in favour of the drug.

In patients with non-severe COVID-19, nirmatrelvir-ritonavir likely reduces admission to hospital (moderate certainty evidence). It may have little or no impact on mortality (low certainty evidence). There are no data reported for time to symptom resolution or mechanical ventilation. Treatment does not increase the likelihood of adverse effects leading to drug discontinuation (high certainty evidence), though diarrhoea and dysgeusia (loss of taste) have occurred more frequently with nirmatrelvir-ritonavir as compared with placebo.

The GDG acknowledged that there was a paucity of information relating to emergence of resistance and much more data were needed to inform the recommendation.

Certainty of the Evidence

The evidence summary on nirmatrelvir-ritonavir was informed by two trials (EPIC-SR and EPIC-HR) with 3100 participants included in the LNMA study *(1)(20)(21).*

Certainty of evidence was rated as: moderate for decreased hospitalization (rated down due to concerns regarding imprecision and risk of bias), low for mortality (rated down due to serious imprecision and indirectness), and high for adverse effects leading to drug discontinuation. We did not rate the certainty of the evidence for diarrhoea and dysgeusia.

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Limitations in available empirically developed risk prediction tools for establishing patients' risk of hospitalization represent the major source of indirectness for which the GDG rated down the certainty of the evidence *(22)*.

Values and preferences

Applying the agreed upon values and preferences (see Section 7), the GDG inferred that almost all well-informed patients with a higher risk of hospitalization would choose to use nirmatrelvir-ritonavir.

Resources and other considerations

Acceptability and feasibility

Nirmatrelvir-ritonavir is unlikely to be available for all individuals who, given the option, would choose to receive the treatment. This reinforces that nirmatrelvir-ritonavir should be reserved for those at higher risk.

Obstacles to access in low- and middle-income countries (LMICs) may prove formidable due to cost and availability. Those with socioeconomic disadvantages tend to have less access to services, including diagnostic testing and treatments, in the first 5 days of symptoms, and thus less access to the interventions. Therefore, if patients at higher risk receive the intervention, this may exacerbate health inequity. It is important that countries integrate the COVID-19 clinical care pathway in the parts of the health system that may provide care for patients with non-severe COVID-19 (i.e. primary care, community care settings).

The recommendations should provide a stimulus to engage all possible mechanisms to improve global access to the intervention. In promoting access, WHO has prequalified generic versions of molnupiravir and one generic version of nirmatrelvir-ritonavir. In addition, there are additional applications under review for both products. United Nations (UN) partners procure these products and are making them available to LMICs. WHO and UN partners support allocation and procurement mechanisms for countries to ensure that these medicines are available and integrated into national supply chains. Individual countries may formulate their guidelines considering available resources and prioritize treatment options accordingly.

Access to SARS-CoV-2 diagnostics: Since this recommendation involves ideally administering treatment with nirmatrelvir-ritonavir within 5 days of symptom onset, increasing access and ensuring appropriate use of diagnostic tests is essential for implementation. Thus, availability and use of appropriate SARS-CoV-2 diagnostic tests is needed to improve access to drugs, especially those targeting the early phase of disease. The appropriate use of rapid diagnostic tests such as antigen-detection assays can improve early diagnosis in the community and in primary health care settings. Health care systems must, however, gain expertise in choosing and implementing rapid tests, choosing those most applicable to their settings.

Justification

Moderate certainty evidence of a substantial relative risk reduction in hospitalization, and high certainty evidence of no adverse effects requiring drug discontinuation, motivated the strong recommendation in individuals at higher risk of hospitalization. Such individuals are likely to achieve an important reduction in the absolute risk of hospitalization in comparison with those not receiving nirmatrelvir-ritonavir.

Alternative or combination therapy

The GDG has previously made a conditional recommendation for molnupiravir (see Section 6.9) and remdesivir (see Section 6.3) in the highest risk non-severe population. Indirect comparisons in higher and highest risk patients found nirmatrelvir-ritonavir may reduce hospitalization when compared with molnupiravir (low certainty); however, found little or no difference when compared with remdesivir (low certainty). Without direct data comparisons and low certainty confidence in indirect comparisons, the GDG chose not to make comparative recommendations between drugs, but rather remarked that nirmatrelvir-ritonavir may be superior based on its efficacy compared with standard of care (moderate certainty), and that ultimately the choice of therapeutic may be made based on practical issues, such as ease of administration and risk profiles.

There is no evidence for combining antiviral therapies; the GDG therefore advised against this.

Applicability

Because pregnancy represents a risk factor for severe or critical illness in those with non-severe COVID-19, pregnant women

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might consider using medication that reduces the risk of disease progression *(6)*. Nirmatrelvir-ritonavir, the drug combination the WHO recommends most highly in the context of non-severe illness for patients at highest risk of hospitalization, represents a possible option.

Nevertheless, as with any medication not formally tested in pregnancy, in considering nirmatrelvir-ritonavir, concerns regarding undesirable effects in both mother and fetus immediately arise. Data from the WHO VigiBase, a comprehensive collection of worldwide unpublished reports of possible adverse reactions to drugs – in this case, nirmatrelvir-ritonavir in pregnant women – can inform the issue of undesirable effects.

Up to now, there have been no reports linking nirmatrelvir-ritonavir to serious adverse reactions in pregnant or breastfeeding women, either in mother or child. This is reassuring, but only to an extent: we are uncertain of the denominator to which this estimate of no undesirable effects applies. If a large number of women have been exposed, the absence of reported undesirable effects provides considerable reassurance; if only a small number, not so. We are uncertain which is the case.

In providing guidance on nirmatrelvir-ritonavir use in pregnancy, the GDG considered the likely benefits (there is no reason to think the drug will be less effective in pregnant women than in other people) and the uncertainty regarding undesirable effects. The GDG believes that shared, fully informed decision-making between mother and health care provider should determine the use or non-use of nirmatrelvir-ritonavir in pregnant or breastfeeding women with non-severe COVID-19.

Clinical Question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Nirmatrelvir-ritonavir
Comparator: No nirmatrelvir-ritonavir

Summary

The LNMA for nirmatrelvir-ritonavir was informed by two RCTs (EPIC-SR and HR) which enrolled 3100 patients with non-severe illness in outpatient settings. The two RCTs were registered; and one was published in a peer-reviewed journal *(21)*. None of the included studies enrolled children or pregnant women. The Table shows the characteristics of the RCTs.

For patients with non-severe COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of nirmatrelvir-ritonavir compared with standard care for the outcomes of interest, with certainty ratings, informed by the LNMA *(3)*.

The planned subgroup analyses were limited by available data but did not detect credible subgroup effects for serological status and age (children were not enrolled). As all patients were unvaccinated and were randomized within 5 days of symptom onset, and no patients received therapeutic co-interventions, these subgroup analyses could not be performed.

New evidence for pregnant and breastfeeding women

In September 2022, the WHO Pharmacovigilance team searched the WHO database called VigiBase | UMC to retrieve ICSRs on nirmatrelvir-ritonavir. The purpose of this database is to ensure that early signs of previously unknown medicines-related safety problems are identified as rapidly as possible. VigiBase holds over 32 million anonymized reports of suspected adverse events of medicines and vaccines. ICSR retrieved came solely from the United States and one case of spontaneous abortion was identified. However, there was not an established causal link to prove that nirmatrelvir-ritonavir caused the outcome and important information was missing. Four ICSRs showed lactation impairment, suggesting a need for follow up to determine whether this is a signal or not.

Alternative sources of information searched consisted of PubMed and Early Warning System. The latter is a platform used by the WHO Pharmacovigilance team to leverage machine learning and artificial intelligence to support safety preparedness and signal detection functions. Although this system captures a lot of noise, it allows to identify adverse events, provided confirmation. The posts identified concerning experiences of pregnant or lactating women using nirmatrelvir-ritonavir were balanced, and do not allow to conclude on any adverse event or signal.

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Outcome Timeframe	**Study results and measurements**	**Comparator** No nirmatrelvir-ritonavir	**Intervention** Nirmatrelvir-ritonavir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 28 days	Odds ratio 0.04 (CI 95% 0 — 0.67) Based on data from 3,100 participants in 2 studies. (Randomized controlled)	6 per 1000 Difference:	0 per 1000 **6 fewer per 1000** (CI 95% 6 fewer — 2 fewer)	**Low** Due to serious imprecision and indirectness [1]	Nirmatrelvir-ritonavir may have a small effect on mortality
Mechanical ventilation				No data	The effect of nirmatrelvir-ritonavir is unknown
Admission to hospital Risk in trials	Odds ratio 0.15 (CI 95% 0.06 — 0.38) Based on data from 3,078 participants in 2 studies. (Randomized controlled)	35 per 1000 Difference:	5 per 1000 **30 fewer per 1000** (CI 95% 33 fewer — 21 fewer)	**Moderate** Due to concerns with risk of bias and imprecision [2]	Nirmatrelvir-ritonavir probably reduces hospitalization
Admission to hospital Higher risk	Odds ratio 0.15 (CI 95% 0.06 — 0.38) Based on data from 3,078 participants in 2 studies. (Randomized controlled)	60 per 1000 Difference:	9 per 1000 **51 fewer per 1000** (CI 95% 56 fewer — 36 fewer)	**Moderate** Due to concerns with risk of bias and imprecision [3]	Nirmatrelvir-ritonavir probably reduces hospitalization
Admission to hospital Highest risk	Odds ratio 0.15 (CI 95% 0.06 — 0.38) Based on data from 3,078 participants in 2 studies. (Randomized controlled)	100 per 1000 Difference:	16 per 1000 **84 fewer per 1000** (CI 95% 93 fewer — 59 fewer)	**Moderate** Due to concerns with risk of bias and imprecision [4]	Nirmatrelvir-ritonavir probably reduces hospitalization
Adverse effects leading to drug discontinuation	Odds ratio 0.48 (CI 95% 0.29 — 0.8) Based on data from 2,246 participants in 1 study. (Randomized controlled)	0 per 1000 Difference:	0 per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 0 fewer)	**High**	Nirmatrelvir-ritonavir has little or no risk of adverse effects leading to drug discontinuation
Time to symptom resolution				No data	The effect of nirmatrelvir-ritonavir is unknown

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1. **Indirectness: serious.** Some patients may be at substantially higher risk of death. Nirmatrelvir-ritonavir probably reduces mortality in these patients. **Imprecision: serious.** There were only 12 events (all in the placebo group); and only one study.
2. **Risk of Bias: serious.** The study was stopped early for benefit. **Imprecision: serious.** The total sample size does not meet the optimal information size.
3. **Risk of Bias: serious.** The study was stopped early for benefit. **Imprecision: serious.** The total sample size does not meet the optimal information size.
4. **Risk of Bias: serious.** The study was stopped early for benefit. **Imprecision: serious.** The total sample size does not meet the optimal information size.

Clinical Question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Nirmatrelvir-ritonavir
Comparator: Molnupiravir

Outcome Timeframe	**Study results and measurements**	**Comparator** Molnupiravir	**Intervention** Nirmatrelvir-ritonavir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 28 days	Odds ratio 0 (CI 95% 0 — 0.29)	0 per 1000 Difference:	0 per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 0 fewer)	**Moderate** Due to serious indirectness [1]	There is probably little or no difference in mortality
Mechanical ventilation				No data	The effect of nirmatrelvir-ritonavir is unknown
Admission to hospital Risk in trials	Odds ratio 0.29 (CI 95% 0.1 — 0.88)	19 per 1000 Difference:	6 per 1000 **13 fewer per 1000** (CI 95% 17 fewer — 2 fewer)	**Low** Due to risk of bias and imprecision [2]	Nirmatrelvir-ritonavir may reduce hospitalization more than molnupiravir
Admission to hospital Highest risk	Odds ratio 0.29 (CI 95% 0.1 — 0.88)	57 per 1000 Difference:	17 per 1000 **40 fewer per 1000** (CI 95% 51 fewer — 6 fewer)	**Low** Due to risk of bias and imprecision [3]	Nirmatrelvir-ritonavir may reduce hospitalization more than molnupiravir
Admission to hospital Higher risk	Odds ratio 0.29 (CI 95% 0.1 — 0.88)	33 per 1000	17 per 1000		

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Outcome Timeframe	**Study results and measurements**	**Comparator** Molnupiravir	**Intervention** Nirmatrelvir-ritonavir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		Difference:	**40 fewer per 1000** (CI 95% 51 fewer — 6 fewer)	**Low** Due to risk of bias and imprecision [4]	Nirmatrelvir-ritonavir may reduce hospitalization more than molnupiravir
Adverse effects leading to drug discontinuation		0 per 1000 Difference:	0 per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 0 fewer)	**High**	There is little or no difference in the risk of adverse effects leading to drug discontinuation.
Time to symptom resolution				No data	The effect of nirmatrelvir/ritonavir is unknown

1. **Indirectness: serious.** Some patients may be at substantially higher risk of death. There may be an important difference in mortality in these patients.
2. **Risk of Bias: serious.** The nirmatrelvir-ritonavir study was stopped early for benefit. **Imprecision: serious.** The total sample size does not meet the optimal information size.
3. **Risk of Bias: serious.** The nirmatrelvir-ritonavir study was stopped early for benefit. **Imprecision: serious.** The total sample size does not meet the optimal information size.
4. **Risk of Bias: serious.** The nirmatrelvir-ritonavir study was stopped early for benefit. **Imprecision: serious.** The total sample size does not meet the optimal information size.

Clinical Question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Remdesivir
Comparator: Nirmatrelvir-ritonavir

Outcome Timeframe	**Study results and measurements**	**Comparator** Nirmatrelvir-ritonavir	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 28 days		0 per 1000 Difference:	3 per 1000 **3 more per 1000** 2 more — 5 more	**Very low** Due to serious risk of bias, indirectness, and imprecision [1]	The impact on mortality is uncertain

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Outcome Timeframe	**Study results and measurements**	**Comparator** Nirmatrelvir-ritonavir	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mechanical ventilation				No data	The impact on mechanical ventilation is unknown
Hospital admission Risk in trials	Odds ratio 1.64 (CI 95% 0.33 — 7.57) (Randomized controlled)	6 per 1000 Difference:	9 per 1000 **3 more per 1000** (CI 95% 4 fewer — 38 more)	**Low** Due to serious risk of bias and imprecision [2]	There may be little or no difference in hospital admission
Hospital admission Higher risk	Odds ratio 1.64 (CI 95% 0.33 — 7.57) (Randomized controlled)	9 per 1000 Difference:	15 per 1000 **6 more per 1000** (CI 95% 6 fewer — 55 more)	**Low** Due to serious risk of bias and imprecision [3]	There may be little or no difference in hospital admission
Hospital admission Highest risk	Odds ratio 1.64 (CI 95% 0.33 — 7.57) (Randomized controlled)	16 per 1000 Difference:	26 per 1000 **10 more per 1000** (CI 95% 11 fewer — 94 more)	**Low** Due to serious risk of bias and imprecision [4]	There may be little or no difference in hospital admission
Adverse events leading to drug discontinuation		0 per 1000	9 per 1000	**Very low** Due to very serious risk of bias, serious indirectness, and very serious imprecision [5]	The impact on adverse effects leading to drug discontinuation is uncertain
Time to symptom resolution				No data	The effect of nirmatrelvir-ritonavir is unknown

1. **Risk of Bias: serious. Indirectness: serious.** Some patients may be at substantially higher risk of death. There may be an important difference in mortality in these patients. **Imprecision: serious.** Few events: 50 total events for remdesivir vs. control and 11 events for molnupiravir vs. control.
2. **Risk of Bias: serious.** The EPIC-HR study of nirmatrelvir-ritonavir was stopped early for benefit. **Imprecision: serious.** Credible interval includes no difference and important harm.
3. **Risk of Bias: serious.** The EPIC-HR study of nirmatrelvir-ritonavir was stopped early for benefit. **Imprecision: serious.** Credible interval includes no difference and important harm.
4. **Risk of Bias: serious.** The EPIC-HR study of nirmatrelvir-ritonavir was stopped early for benefit. **Imprecision: serious.** Credible interval includes no difference and important harm.
5. **Risk of Bias: very serious. Indirectness: serious. Imprecision: very serious.**

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For patients with non-severe COVID-19 at low risk of hospitalization

Conditional recommendation against

Updated

We suggest not to use treatment with nirmatrelvir-ritonavir *(conditional recommendation against).*

- *In the GDG's assessment, only a minority of low-risk patients will choose to consider using nirmatrelvir-ritonavir.*
- *Trials on antivirals included patients with some risk factors for hospital admission, resulting in a baseline risk of 3% that the GDG applied to generate the recommendation. The risk of hospitalization is likely to be lower in the general population.*
- *Clinicians should not consider nirmatrelvir-ritonavir in patients with possible dangerous drug interactions (note: many drugs interact with nirmatrelvir-ritonavir).*
- *Fully informed shared decision-making should determine whether nirmatrelvir-ritonavir should be used in pregnant or breast-feeding women, considering possible benefits and uncertainty regarding potential undesirable effects.*

Practical Info

Route, dosage and duration: Additional considerations are available in three summaries of practical issues (nirmatrelvir-ritonavir for COVID-19, administration of nirmatrelvir-ritonavir for COVID-19, safety and monitoring for patients receiving nirmatrelvir-ritonavir for COVID-19).

In any patient being considered for nirmatrelvir-ritonavir use, clinicians need to give serious consideration to drug interactions. The Liverpool COVID-19 drug interaction checker may be useful in this regard *(19).*

Evidence To Decision

Benefits and harms

In patients with non-severe COVID-19, nirmatrelvir-ritonavir probably reduces admission to hospital. However, in low-risk patients, the absolute benefit is very small and unlikely to be important to most patients. Nirmatrelvir-ritonavir probably has little or no impact on mortality. Highly relevant to patients at low risk of hospitalization, studies have reported no data for time to symptom resolution. EPIC-SR did, however, report a very closely related outcome: time to 4 consecutive days of mild or no symptoms. For this analysis, the median time was 13 (95% CI 12 to 15) days for nirmatrelvir-ritonavir, and 13 (95% CI 11 to 14) days for placebo (p=0.47). Treatment does not increase the likelihood of adverse effects leading to drug discontinuation, though diarrhoea and dysgeusia have occurred more frequently with nirmatrelvir-ritonavir, as compared with placebo.

Certainty of the Evidence

The evidence summary on nirmatrelvir-ritonavir was informed by two trials (EPIC-SR and EPIC HR) with 3100 participants included in the LNMA study *(1)(20)(21).*

Certainty of evidence was rated as: moderate for decreased hospitalization (rated down due to concerns regarding serious imprecision and risk of bias), low for mortality (rated down due to serious imprecision and indirectness), and high for adverse effects leading to drug discontinuation. We did not rate certainty of evidence for diarrhoea and dysgeusia.

Values and preferences

The GDG believes that most low-risk patients would be reluctant to use a medication for which the evidence left high uncertainty regarding effects on outcomes they consider important. This consideration is particularly relevant for shortening of the duration of symptoms, for which we have no direct evidence supporting a positive impact of nirmatrelvir-ritonavir.

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Resources and other considerations

Nirmatrelvir-ritonavir is unlikely to be available for all individuals who, given the option, would choose to receive the treatment. This reinforces that nirmatrelvir-ritonavir be reserved for those at highest risk.

Justification

Most patients who contract COVID-19 are at very low risk of hospitalization (under 1%) and at a vanishingly small risk of mortality. Such patients will experience trivial benefits from the use of nirmatrelvir-ritonavir. The panel inferred that most such patients would be uninterested in using the drug for these trivial benefits. Thus, for most patients, sufficient risk – and thus sufficient benefit of nirmatrelvir-ritonavir – to make nirmatrelvir-ritonavir use an attractive option will require the presence of at least one if not a combination of risk factors. This is particularly true in low-income settings in which resource constraints and feasibility issues will make nirmatrelvir-ritonavir use less attractive.

The GDG, nevertheless, was cognizant that there are likely to be an appreciable number of individuals who place a high value on very small reductions in the risk of hospitalization and who would thus choose use of nirmatrelvir-ritonavir; therefore, a conditional rather than strong recommendation was made.

Clinical Question/ PICO

Population:	Patients with non-severe COVID-19
Intervention:	Nirmatrelvir-ritonavir
Comparator:	No nirmatrelvir-ritonavir

Summary

The LNMA for nirmatrelvir-ritonavir was informed by two RCTs (EPIC-SR and HR) which enrolled 3100 patients with non-severe illness in outpatient settings. The two RCTs were registered; and one was published in a peer-reviewed journal *(21)*. None of the included studies enrolled children or pregnant women. The Table shows the characteristics of the RCTs.

For patients with non-severe COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of nirmatrelvir-ritonavir compared with standard care for the outcomes of interest, with certainty ratings, informed by the LNMA *(3)*.

The planned subgroup analyses were limited by available data but did not detect credible subgroup effects for serological status and age (children were not enrolled). As all patients were unvaccinated and were randomized within 5 days of symptom onset, and no patients received therapeutic co-interventions, these subgroup analyses could not be performed.

New evidence for pregnant and breastfeeding women

In September 2022, the WHO Pharmacovigilance team searched the WHO database called VigiBase | UMC to retrieve ICSRs on nirmatrelvir-ritonavir. The purpose of this database is to ensure that early signs of previously unknown medicines-related safety problems are identified as rapidly as possible. VigiBase holds over 32 million anonymized reports of suspected adverse events of medicines and vaccines. ICSR retrieved came solely from the United States and one case of spontaneous abortion was identified. However, there was not an established causal link to prove that nirmatrelvir-ritonavir caused the outcome and important information was missing. Four ICSRs showed lactation impairment, suggesting a need for follow up to determine whether this is a signal or not.

Alternative sources of information searched consisted of PubMed and Early Warning System. The latter is a platform used by the WHO Pharmacovigilance team to leverage machine learning and artificial intelligence to support safety preparedness and signal detection functions. Although this system captures a lot of noise, it allows to identify adverse events, provided confirmation. The posts identified concerning experiences of pregnant or lactating women using nirmatrelvir-ritonavir were balanced, and do not allow to conclude on any adverse event or signal.

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Outcome Timeframe	**Study results and measurements**	**Comparator** No nirmatrelvir-ritonavir	**Intervention** Nirmatrelvir-ritonavir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 28 days	Odds ratio 0.04 (CI 95% 0 — 0.67) Based on data from 3,100 participants in 2 studies. (Randomized controlled)	6 per 1000 Difference:	0 per 1000 **6 fewer per 1000** (CI 95% 6 fewer — 2 fewer)	**Low** Due to serious imprecision and indirectness [1]	Nirmatrelvir-ritonav may have a small effe on mortality
Mechanical ventilation				No data	The effect of nirmatrelvir-ritonavi unknown
Admission to hospital Risk in trials	Odds ratio 0.15 (CI 95% 0.06 — 0.38) Based on data from 3,078 participants in 2 studies. (Randomized controlled)	35 per 1000 Difference:	5 per 1000 **30 fewer per 1000** (CI 95% 33 fewer — 21 fewer)	**Moderate** Due to concerns with risk of bias and imprecision [2]	Nirmatrelvir-ritonav probably reduces hospitalization
Admission to hospital Higher risk	Odds ratio 0.15 (CI 95% 0.06 — 0.38) Based on data from 3,078 participants in 2 studies. (Randomized controlled)	60 per 1000 Difference:	9 per 1000 **51 fewer per 1000** (CI 95% 56 fewer — 36 fewer)	**Moderate** Due to concerns with risk of bias and imprecision [3]	Nirmatrelvir-ritonav probably reduces hospitalization
Admission to hospital Highest risk	Odds ratio 0.15 (CI 95% 0.06 — 0.38) Based on data from 3,078 participants in 2 studies. (Randomized controlled)	100 per 1000 Difference:	16 per 1000 **84 fewer per 1000** (CI 95% 93 fewer — 59 fewer)	**Moderate** Due to concerns with risk of bias and imprecision [4]	Nirmatrelvir-ritonav probably reduces hospitalization
Adverse effects leading to drug discontinuation	Odds ratio 0.48 (CI 95% 0.29 — 0.8) Based on data from 2,246 participants in 1 study. (Randomized controlled)	0 per 1000 Difference:	0 per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 0 fewer)	**High**	Nirmatrelvir-ritonavir little or no risk of adverse effects leadi to drug discontinuati
Time to symptom resolution				No data	The effect of nirmatrelvir-ritonavi unknown

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1. **Indirectness: serious.** Some patients may be at substantially higher risk of death. Nirmatrelvir-ritonavir probably reduces mortality in these patients. **Imprecision: serious.** There were only 12 events (all in the placebo group); and only one study.
2. **Risk of Bias: serious.** The study was stopped early for benefit. **Imprecision: serious.** The total sample size does not meet the optimal information size.
3. **Risk of Bias: serious.** The study was stopped early for benefit. **Imprecision: serious.** The total sample size does not meet the optimal information size.
4. **Risk of Bias: serious.** The study was stopped early for benefit. **Imprecision: serious.** The total sample size does not meet the optimal information size.

Clinical Question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Nirmatrelvir-ritonavir
Comparator: Molnupiravir

Outcome Timeframe	**Study results and measurements**	**Comparator** Molnupiravir	**Intervention** Nirmatrelvir-ritonavir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 28 days	Odds ratio 0 (CI 95% 0 — 0.29) (Randomized controlled)	**0** per 1000 Difference:	**0** per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 0 fewer)	**Moderate** Due to serious indirectness [1]	There is probably little or no difference in mortality
Mechanical ventilation				No data	The effect of nirmatrelvir-ritonavir is unknown
Admission to hospital Risk in trials	Odds ratio 0.29 (CI 95% 0.1 — 0.88) (Randomized controlled)	**19** per 1000 Difference:	**6** per 1000 **13 fewer per 1000** (CI 95% 17 fewer — 2 fewer)	**Low** Due to risk of bias and imprecision [2]	Nirmatrelvir-ritonavir may reduce hospitalization more than molnupiravir
Admission to hospital Highest risk	Odds ratio 0.29 (CI 95% 0.1 — 0.88) (Randomized controlled)	**57** per 1000 Difference:	**17** per 1000 **40 fewer per 1000** (CI 95% 51 fewer — 6 fewer)	**Low** Due to risk of bias and imprecision [3]	Nirmatrelvir-ritonavir may reduce hospitalization more than molnupiravir

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Outcome Timeframe	Study results and measurements	Comparator Molnupiravir	Intervention Nirmatrelvir-ritonavir	Certainty of the Evidence (Quality of evidence)	Plain language summary
Admission to hospital Higher risk	Odds ratio 0.29 (CI 95% 0.1 — 0.88) (Randomized controlled)	33 per 1000 Difference:	17 per 1000 **40 fewer per 1000** (CI 95% 51 fewer — 6 fewer)	Low Due to risk of bias and imprecision [4]	Nirmatrelvir-ritonavir may reduce hospitalization more than molnupiravir
Adverse effects leading to drug discontinuation		0 per 1000 Difference:	0 per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 0 fewer)	High	There is little or no difference in the risk of adverse effects leading to drug discontinuation.
Time to symptom resolution				No data	The effect of nirmatrelvir/ritonavir is unknown

1. **Indirectness: serious.** Some patients may be at substantially higher risk of death. There may be an important difference in mortality in these patients.
2. **Risk of Bias: serious.** The nirmatrelvir-ritonavir study was stopped early for benefit. **Imprecision: serious.** The total sample size does not meet the optimal information size.
3. **Risk of Bias: serious.** The nirmatrelvir-ritonavir study was stopped early for benefit. **Imprecision: serious.** The total sample size does not meet the optimal information size.
4. **Risk of Bias: serious.** The nirmatrelvir-ritonavir study was stopped early for benefit. **Imprecision: serious.** The total sample size does not meet the optimal information size.

Clinical Question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Remdesivir
Comparator: Nirmatrelvir-ritonavir

Outcome Timeframe	Study results and measurements	Comparator Nirmatrelvir-ritonavir	Intervention Remdesivir	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality 28 days		0 per 1000 Difference:	3 per 1000 **3 more per 1000** 2 more — 5 more	Very low Due to serious risk of bias, indirectness, and imprecision [1]	The impact on mortality is uncertain

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Outcome Timeframe	**Study results and measurements**	**Comparator** Nirmatrelvir-ritonavir	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mechanical ventilation				No data	The impact on mechanical ventilation is unknown
Hospital admission Risk in trials	Odds ratio 1.64 (CI 95% 0.33 — 7.57)	6 per 1000 Difference:	9 per 1000 **3 more per 1000** (CI 95% 4 fewer — 38 more)	**Low** Due to serious risk of bias and imprecision [2]	There may be little or no difference in hospital admission
Hospital admission Higher risk	Odds ratio 1.64 (CI 95% 0.33 — 7.57)	9 per 1000 Difference:	15 per 1000 **6 more per 1000** (CI 95% 6 fewer — 55 more)	**Low** Due to serious risk of bias and imprecision [3]	There may be little or no difference in hospital admission
Hospital admission Highest risk	Odds ratio 1.64 (CI 95% 0.33 — 7.57)	16 per 1000 Difference:	26 per 1000 **10 more per 1000** (CI 95% 11 fewer — 94 more)	**Low** Due to serious risk of bias and imprecision [4]	There may be little or no difference in hospital admission
Adverse events leading to drug discontinuation		0 per 1000	9 per 1000	**Very low** Due to very serious risk of bias, serious indirectness, and very serious imprecision [5]	The impact on adverse effects leading to drug discontinuation is uncertain
Time to symptom resolution				No data	The effect of nirmatrelvir-ritonavir is unknown

1. **Risk of Bias: serious. Indirectness: serious.** Some patients may be at substantially higher risk of death. There may be an important difference in mortality in these patients. **Imprecision: serious.** Few events: 50 total events for remdesivir vs. control and 11 events for molnupiravir vs. control.
2. **Risk of Bias: serious.** The EPIC-HR study of nirmatrelvir-ritonavir was stopped early for benefit. **Imprecision: serious.** Credible interval includes no difference and important harm.
3. **Risk of Bias: serious.** The EPIC-HR study of nirmatrelvir-ritonavir was stopped early for benefit. **Imprecision: serious.** Credible interval includes no difference and important harm.
4. **Risk of Bias: serious.** The EPIC-HR study of nirmatrelvir-ritonavir was stopped early for benefit. **Imprecision: serious.** Credible interval includes no difference and important harm.
5. **Risk of Bias: very serious. Indirectness: serious. Imprecision: very serious.**

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6.2.1 Mechanism of action

Nirmatrelvir inhibits the SARS-CoV-2 protease (3CLpro), thereby preventing cleavage of the viral polyprotein which is needed for viral proteins to become functional *(23)*. Inhibition of the protease renders the virus unable to replicate. Nirmatrelvir is co-administered with ritonavir, an HIV protease inhibitor, used in this context to boost the pharmacokinetics of nirmatrelvir but without exerting any direct antiviral activity itself *(24)*. Therefore, the combination should be considered as antiviral monotherapy. Nirmatrelvir was developed as an orally deliverable analogue of an intravenous prodrug (lufotrelvir; PF-07304814). The drug was originally developed for SARS-CoV, and has been subsequently repurposed for SARS-CoV-2.

Nirmatrelvir exhibited antiviral activity against SARS-CoV-2 in differentiated normal human bronchial epithelial cells with an EC_{50} of 0.06 micromolar and an EC_{90} of 0.18 micromolar *(24)*. In healthy volunteers, plasma maximum concentrations of nirmatrelvir were 2210 ng/mL with a half-life of 6 hours following a 300/100 mg dose of nimatrelvir-ritonavir, and steady-state pharmacokinetics were achieved on day 2 *(25)* (an EC_{90} of 0.18 micromolar equates to approximately 90 ng/mL). High doses (300 mg/kg) of unboosted nimatrelvir was active against murine-adapted SARS-CoV-2 in mice but with maximum concentrations higher than those achieved at 300/100 mg doses in healthy human volunteers *(24)*. High doses (250 mg/kg) of unboosted nimatrelvir also had efficacy in SARS-CoV-2-infected Syrian golden hamsters but no pharmacokinetic data are available in this species *(26)*. Based upon the genome sequence of Omicron, there appears to be no molecular basis for a loss of activity. Nimatrelvir retains activity against all SARS-CoV-2 lineages studied in vitro to date *(27)(28)* but in vivo data are currently unavailable.

Much more data are required to ascertain the rate at which resistance will emerge for nirmatrelvir. Single amino acid changes introduced into the protease sequence can reduce activity of nirmatrelvir by between 23.6- and 39-fold *(25)*. Mouse hepatitis virus (used as a betacoronavirus surrogate) acquired several mutations under a selective pressure in vitro, and these reduced nirmatrelvir activity by between 4- and 91-fold *(25)*. Two amino substitutions were described in clinical trials, one of which did not impact nirmatrelvir activity.

Through its impact on metabolism and clearance, ritonavir is a perpetrator of many drug-drug interactions that will require careful consideration. Short durations of therapy needed in COVID-19 may make drug interactions easier to manage than they are for HIV, but twice daily administration means that the ritonavir dose is double that used in most modern antiretroviral regimens. The impact of ritonavir on metabolism may also outlast dosing by several days. The Liverpool COVID-19 drug interaction checker may constitute a valuable tool for management of drug interactions with nirmatrelvir-ritonavir *(19)*.

6.3 Remdesivir (updated 16 September 2022)

Info Box

An initial conditional recommendation was made on 20 November 2020, suggesting not to use remdesivir for patients with COVID-19, regardless of illness severity. This was based on data from four RCTs which were available at the time, with 7333 participants hospitalized for COVID-19. In the 10th iteration of the guideline, a new recommendation was made for the use of remdesivir for patients with non-severe illness. In the 12th iteration of the guideline, updated recommendations for patients with severe or critical COVID-19 were provided, given new trial data providing sufficiently trustworthy evidence for a subgroup effect demonstrating modest benefit in patients with severe, but not critical COVID-19.

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Document 2A.2

NIH Guidance for Ritonavir-Boosted Nirmatrelvir

Document URL

https://files.covid19treatmentguidelines.nih.gov/guidelines/section/section_171.pdf

Reference website URL

https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/ritonavir-boosted-nirmatrelvir--paxlovid-/

License

Not applicable

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Ritonavir-Boosted Nirmatrelvir (Paxlovid)

Last Updated: July 21, 2023

Nirmatrelvir is an oral protease inhibitor that is active against M^{PRO}, a viral protease that plays an essential role in viral replication by cleaving the 2 viral polyproteins.[1] It has demonstrated antiviral activity against all coronaviruses that are known to infect humans.[2] Nirmatrelvir is packaged with ritonavir (as Paxlovid), a strong cytochrome P450 (CYP) 3A4 inhibitor and pharmacokinetic boosting agent that has been used to boost HIV protease inhibitors. Coadministration of ritonavir is required to increase nirmatrelvir concentrations to the target therapeutic range.

On May 25, 2023, the Food and Drug Administration (FDA) approved the use of ritonavir-boosted nirmatrelvir for the treatment of mild to moderate COVID-19 in adults who are at high risk of progressing to severe COVID-19.[3,4] However, ritonavir-boosted nirmatrelvir is currently only available from Emergency Use Authorization (EUA) supplies; thus, its use must be consistent with the terms and conditions of the EUA.

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using **nirmatrelvir 300 mg with ritonavir 100 mg (Paxlovid)** orally (PO) twice daily for 5 days in nonhospitalized adults with mild to moderate COVID-19 who are at high risk of disease progression **(AIIa)**. Treatment should be initiated as soon as possible and within 5 days of symptom onset. For information on medical conditions that confer high risk, see the Centers for Disease Control and Prevention webpage People With Certain Medical Conditions.
- Ritonavir-boosted nirmatrelvir is available through an FDA EUA for the treatment of mild to moderate COVID-19 in nonhospitalized adolescents aged ≥12 years and weighing ≥40 kg. For recommendations on using ritonavir-boosted nirmatrelvir in nonhospitalized children with COVID-19, see Therapeutic Management of Nonhospitalized Children With COVID-19.
- Ritonavir-boosted nirmatrelvir has not been studied in hospitalized patients. For patients who are hospitalized for a diagnosis other than COVID-19, the FDA EUA allows for the use of ritonavir-boosted nirmatrelvir if the patient has mild to moderate COVID-19 (i.e., the patient does not require supplemental oxygen), is at high risk of progressing to severe disease, and is within 5 days of symptom onset.
- For more information on ritonavir-boosted nirmatrelvir, see Table 4e.
- For a discussion of the treatment of prolonged, symptomatic COVID-19 in patients with evidence of ongoing SARS-CoV-2 replication, see the section titled Patients Who Are Immunocompromised and Have Prolonged COVID-19 Symptoms and Evidence of Ongoing Viral Replication below.

Drug-Drug Interactions

The FDA prescribing information and the revised EUA fact sheet for ritonavir-boosted nirmatrelvir include a boxed warning about significant drug-drug interactions between ritonavir-boosted nirmatrelvir and other medications, primarily caused by the ritonavir component of the combination. Ritonavir, a strong CYP3A4 inhibitor and a P-glycoprotein inhibitor, may increase the blood concentration of certain concomitant medications and increase the potential for serious drug toxicities. Before prescribing ritonavir-boosted nirmatrelvir, clinicians **should carefully review the patient's concomitant medications,** including over-the-counter medications, herbal supplements, and recreational drugs, to evaluate potential drug-drug

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interactions. Clinicians should consider both the potential benefits of treatment with ritonavir-boosted nirmatrelvir and the potential risks related to drug-drug interactions. Many drug-drug interactions between ritonavir-boosted nirmatrelvir and concomitant medications **can be safely managed** (e.g., with certain statins, calcium channel blockers, or direct oral anticoagulants). For the Panel's recommendations on preferred and alternative antiviral therapies for outpatients with COVID-19, see Therapeutic Management of Nonhospitalized Adults With COVID-19. Clinicians should be aware that the drug-drug interaction potential of ritonavir-boosted nirmatrelvir may change if it is used for extended durations.

The following resources provide information on identifying and managing drug-drug interactions.

- Quick reference lists:
  - Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications. Box 1 lists select outpatient medications that are not expected to have clinically relevant interactions with ritonavir-boosted nirmatrelvir. Box 2 lists select outpatient medications that have clinically relevant drug-drug interactions with ritonavir-boosted nirmatrelvir.
- Web-based drug-drug interaction checker:
  - The Liverpool COVID-19 Drug Interactions website
- Tables with guidance on managing specific drug-drug interactions:
  - The University of Waterloo/University of Toronto drug interaction guide
  - The FDA prescribing information and the EUA fact sheet and checklist for ritonavir-boosted nirmatrelvir

Rationale

The EPIC-HR trial enrolled nonhospitalized adults with mild to moderate COVID-19 who were not vaccinated and who were at high risk of progressing to severe disease. The trial demonstrated that starting ritonavir-boosted nirmatrelvir within 5 days of symptom onset in these patients reduced the risk of hospitalization or death through Day 28 by 89% compared to placebo.[5] This efficacy is comparable to remdesivir (87% relative reduction)[6] and greater than the efficacy reported for molnupiravir (31% relative reduction).[7] However, these agents have not been directly compared in clinical trials.

Although ritonavir-boosted nirmatrelvir demonstrated a clinical benefit during the EPIC-HR trial, the benefits in unvaccinated people who are at low risk of progression to severe disease or in vaccinated people who are at high risk of progression to severe disease are unclear. The EPIC-SR trial, which included both of these populations, found that ritonavir-boosted nirmatrelvir did not reduce the duration of symptoms and did not have a statistically significant effect on the risk of hospitalization or death compared to placebo, although the event rates were low.[8] Some observational studies have shown a benefit of ritonavir-boosted nirmatrelvir in vaccinated individuals who were at high risk of progressing to severe COVID-19.[9-12] However, observational studies have inherent limitations. In particular, the results of these studies may be affected by residual confounding. For information on treatment considerations for vaccinated individuals, see Therapeutic Management of Nonhospitalized Adults With COVID-19.

Because of the potential for significant drug-drug interactions with concomitant medications, this regimen may not be the optimal choice for all patients. See Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications for more information.

Patients Who Are Immunocompromised and Have Prolonged COVID-19 Symptoms and Evidence of Ongoing Viral Replication

For patients who are immunocompromised and have prolonged COVID-19 symptoms and evidence

of ongoing viral replication (e.g., those with a low cycle threshold value, as measured by a reverse transcription polymerase chain reaction result or with a positive rapid antigen test result) despite receiving a course of antiviral therapy, the optimal management is unknown. Case reports and case series have documented the treatment of these patients with additional antiviral treatments, prolonged courses of antiviral treatments, high-titer COVID-19 convalescent plasma, or combination therapy.[13-17] For information on potential treatment options, see Special Considerations in People Who Are Immunocompromised and Therapeutic Management of Nonhospitalized Adults With COVID-19.

Viral Rebound and Symptom Recurrence

Observational studies and the EPIC-HR trial have described SARS-CoV-2 viral rebound and the recurrence of COVID-19 symptoms in some patients who have completed treatment with ritonavir-boosted nirmatrelvir.[18-21] The frequency, mechanism, and clinical implications of these events are unclear. Viral rebound and the recurrence of COVID-19 symptoms can also occur in the absence of treatment with ritonavir-boosted nirmatrelvir.[22,23]

The EPIC-HR trial demonstrated a clinical benefit of ritonavir-boosted nirmatrelvir in patients who were not vaccinated and who were at high risk of progressing to severe COVID-19. To date, the recurrence of COVID-19 symptoms following the use of ritonavir-boosted nirmatrelvir has not been associated with progression to severe COVID-19. Therefore, concerns about the recurrence of symptoms should not be a reason to avoid using ritonavir-boosted nirmatrelvir.[22,24,25]

Longer treatment courses of ritonavir-boosted nirmatrelvir are not authorized by the current EUA, and there are insufficient data on the efficacy of administering a second course.

SARS-CoV-2 Resistance

Viral mutations that lead to substantial resistance to nirmatrelvir have been selected for in in vitro studies; the fitness of these mutations is unclear. Surveillance for the emergence of significant resistance to nirmatrelvir is critical, particularly in patients who are severely immunocompromised and who experience prolonged replication of SARS-CoV-2.

Additional Considerations

- Nirmatrelvir must be administered with ritonavir to achieve sufficient therapeutic plasma concentrations.
- Patients should complete the 5-day treatment course of ritonavir-boosted nirmatrelvir because there are concerns that a shorter treatment course may be less effective or lead to resistance.
- If a patient requires hospitalization after starting treatment, the full 5-day treatment course of ritonavir-boosted nirmatrelvir should be completed unless there are drug-drug interactions that preclude its use.
- There are no data on combining ritonavir-boosted nirmatrelvir with other antiviral therapies to treat nonhospitalized patients with COVID-19. Clinical trials are needed to determine whether combination therapy has a role in the treatment of COVID-19.
- The FDA prescribing information and the EUA fact sheet for ritonavir-boosted nirmatrelvir advise against crushing nirmatrelvir and ritonavir tablets. However, some data indicate that the tablets can be split or crushed if necessary.[26]

Monitoring and Adverse Effects

The most common adverse effects of ritonavir-boosted nirmatrelvir are dysgeusia, diarrhea,

hypertension, and myalgia. Anaphylaxis, serious skin reactions, and other hypersensitivity reactions have also been reported.

Renal impairment reduces the clearance of nirmatrelvir. In patients with suspected renal impairment, clinicians may consider checking the patient's renal function to inform the dosing of ritonavir-boosted nirmatrelvir. The dose should be reduced to nirmatrelvir 150 mg with ritonavir 100 mg twice daily in patients with moderate renal impairment (i.e., those with an estimated glomerular filtration rate [eGFR] of ≥30 to <60 mL/min).

The FDA prescribing information and the EUA state that ritonavir-boosted nirmatrelvir is not recommended for patients with an eGFR of <30 mL/min until more data are available to establish appropriate dosing.[4] Additional information is available in the initial FDA Center for Drug Evaluation and Research review for the EUA of ritonavir-boosted nirmatrelvir.[18] Clinical experience on the use of ritonavir-boosted nirmatrelvir in patients who require hemodialysis is limited.[27] Based on limited data, some groups have proposed dosing adjustments for ritonavir-boosted nirmatrelvir in patients with an eGFR of <30 mL/min and in those who require hemodialysis.[28-30] A clinical trial (ClinicalTrials.gov Identifier NCT05487040) that will evaluate the use of ritonavir-boosted nirmatrelvir in patients with COVID-19 and severe renal impairment is currently underway.

Ritonavir-boosted nirmatrelvir **is not recommended** for patients with known or suspected severe hepatic impairment (i.e., Child-Pugh Class C), and it should be used with caution in patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis. No pharmacokinetic or safety data are available for this patient population.

Considerations in Pregnant and Lactating People

See Pregnancy, Lactation, and COVID-19 Therapeutics for the Panel's guidance on the use of ritonavir-boosted nirmatrelvir during pregnancy and lactation.

Considerations in Children

Ritonavir-boosted nirmatrelvir is available through an FDA EUA for the treatment of mild to moderate COVID-19 in nonhospitalized adolescents aged ≥12 years and weighing ≥40 kg. For information on using ritonavir-boosted nirmatrelvir in pediatric patients, see Special Considerations in Children, Therapeutic Management of Nonhospitalized Children With COVID-19, and Therapeutic Management of Hospitalized Children With COVID-19.

Clinical Data

The EPIC-HR study was a multinational randomized trial that compared the use of ritonavir-boosted nirmatrelvir PO twice daily for 5 days to placebo in nonhospitalized patients aged ≥18 years with mild to moderate COVID-19 who were at high risk of clinical progression. Eligible patients were randomized within 5 days of symptom onset, were not vaccinated against COVID-19, and had at least 1 risk factor for progression to severe disease.[5] Patients were excluded if they used medications that were either highly dependent upon CYP3A4 for clearance or strong inducers of CYP3A4.

A total of 2,246 patients enrolled in the trial. The mean age was 46 years, 51% of the patients were men, and 72% were White. Forty-seven percent of the patients tested negative for SARS-CoV-2 antibodies, and 66% started study treatment within 3 days of symptom onset.

Patients who were randomized within 3 days of symptom onset (n = 1,379) were included in the modified intention-to-treat (mITT) analysis. COVID-19-related hospitalizations or all-cause deaths occurred by Day 28 in 5 of 697 patients (0.72%) in the ritonavir-boosted nirmatrelvir arm and in 44 of 682 patients

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(6.5%) in the placebo arm. Among the 2,085 patients who were randomized within 5 days of symptom onset (mITT1 analysis), COVID-19-related hospitalizations and all-cause deaths occurred in 8 of 1,039 patients (0.77%) in the ritonavir-boosted nirmatrelvir arm and in 66 of 1,046 patients (6.3%) in the placebo arm (89% relative risk reduction; 5.6% estimated absolute reduction; 95% CI, 7.2% to 4.0%; $P < 0.001$). There were no deaths in the ritonavir-boosted nirmatrelvir arm and 13 deaths in the placebo arm.

A total of 2,224 patients who received at least 1 dose of either ritonavir-boosted nirmatrelvir or placebo were included in the EPIC-HR safety analysis set. Among these patients, dysgeusia and diarrhea occurred more frequently in ritonavir-boosted nirmatrelvir recipients than in placebo recipients (6% vs. 0.3% and 3% vs. 2%, respectively). Fewer ritonavir-boosted nirmatrelvir recipients discontinued the study drug due to an adverse event than placebo recipients (2% vs. 4%).

References

1. Pillaiyar T, Manickam M, Namasivayam V, Hayashi Y, Jung SH. An overview of severe acute respiratory syndrome-coronavirus (SARS-CoV) 3CL protease inhibitors: peptidomimetics and small molecule chemotherapy. *J Med Chem*. 2016;59(14):6595-6628. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26878082.
2. Owen DR, Allerton CMN, Anderson AS, et al. An oral SARS-CoV-2 MPRO inhibitor clinical candidate for the treatment of COVID-19. *Science*. 2021;374(6575):1586-1593. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34726479.
3. Ritonavir-boosed nirmatrelvir (Paxlovid) [package insert]. Food and Drug Administration. 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/217188s000lbl.pdf.
4. Food and Drug Administration. Fact sheet for healthcare providers: Emergency Use Authorization for Paxlovid. 2023. Available at: https://www.fda.gov/media/155050/download.
5. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with COVID-19. *N Engl J Med*. 2022;386(15):1397-1408. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35172054.
6. Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe COVID-19 in outpatients. *N Engl J Med*. 2022;386(4):305-315. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34937145.
7. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of COVID-19 in nonhospitalized patients. *N Engl J Med*. 2022;386(6):509-520. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34914868.
8. Pfizer. Pfizer reports additional data on PAXLOVID supporting upcoming new drug application submission to U.S. FDA. 2022. Available at: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-reports-additional-data-paxlovidtm-supporting. Accessed July 20, 2023.
9. Dryden-Peterson S, Kim A, Kim AY, et al. Nirmatrelvir plus ritonavir for early COVID-19 in a large U.S. health system: a population-based cohort study. *Ann Intern Med*. 2023;176(1):77-84. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36508742.
10. Arbel R, Wolff Sagy Y, Hoshen M, et al. Nirmatrelvir use and severe COVID-19 outcomes during the Omicron surge. *N Engl J Med*. 2022;387(9):790-798. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36001529.
11. Ganatra S, Dani SS, Ahmad J, et al. Oral nirmatrelvir and ritonavir in nonhospitalized vaccinated patients with coronavirus disease 2019. *Clin Infect Dis*. 2023;76(4):563-572. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35986628.
12. Shah MM, Joyce B, Plumb ID, et al. Paxlovid associated with decreased hospitalization rate among adults with COVID-19—United States, April–September 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(48):1531-1537. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36454693.
13. Huygens S, Gharbharan A, Serroukh Y, et al. High-titer convalescent plasma plus nirmatrelvir/ritonavir treatment for non-resolving COVID-19 in six immunocompromised patients. *J Antimicrob Chemother*. 2023;78(7):1644-1648. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37248664.

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14. Brosh-Nissimov T, Ma'aravi N, Leshin-Carmel D, et al. Combination treatment of persistent COVID-19 in immunocompromised patients with remdesivir, nirmaltrevir/ritonavir and tixegavimab/cilgavimab. *medRxiv*. 2023;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2023.04.07.23288144v1.

15. Mikulska M, Sepulcri C, Dentone C, et al. Triple combination therapy with two antivirals and monoclonal antibodies for persistent or relapsed SARS-CoV-2 infection in immunocompromised patients. *Clin Infect Dis*. 2023;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36976301.

16. Graziani L, Gori L, Manciulli T, et al. Successful use of nirmatrelvir/ritonavir in immunocompromised patients with persistent and/or relapsing COVID-19. *J Antimicrob Chemother*. 2023;78(2):555-558. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36544352.

17. Trottier CA, Wong B, Kohli R, et al. Dual antiviral therapy for persistent coronavirus disease 2019 and associated organizing pneumonia in an immunocompromised host. *Clin Infect Dis*. 2023;76(5):923-925. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36281907.

18. Food and Drug Administration. Emergency Use Authorization (EUA) for Paxlovid (nirmatrelvir tablets co-packaged with ritonavir tablets): Center for Drug Evaluation and Research (CDER) review. 2021. Available at: https://www.fda.gov/media/155194/download.

19. Charness ME, Gupta K, Stack G, et al. Rebound of SARS-CoV-2 infection after nirmatrelvir-ritonavir treatment. *N Engl J Med*. 2022;387(11):1045-1047. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36069968.

20. Boucau J, Uddin R, Marino C, et al. Characterization of virologic rebound following nirmatrelvir-ritonavir treatment for coronavirus disease 2019 (COVID-19). *Clin Infect Dis*. 2023;76(3):e526-e529. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35737946.

21. Anderson AS, Caubel P, Rusnak JM, EPIC-HR Trial Investigators. Nirmatrelvir-ritonavir and viral load rebound in COVID-19. *N Engl J Med*. 2022;387(11):1047-1049. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36069818.

22. Soares H, Baniecki ML, Cardin R, et al. Viral load rebound in placebo and nirmatrelvir-ritonavir treated COVID-19 patients is not associated with recurrence of severe disease or mutations. *Res Sq*. 2022;Preprint. Available at: https://www.researchsquare.com/article/rs-1720472/v1.

23. Deo R, Choudhary MC, Moser C, et al. Symptom and viral rebound in untreated SARS-CoV-2 infection. *Ann Intern Med*. 2023;176(3):348-354. Available at: https://pubmed.ncbi.nlm.nih.gov/36802755.

24. Ranganath N, O'Horo JC, Challener DW, et al. Rebound phenomenon after nirmatrelvir/ritonavir treatment of coronavirus disease 2019 (COVID-19) in high-risk persons. *Clin Infect Dis*. 2023;76(3):e537-e539. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35698452.

25. Centers for Disease Control and Prevention. COVID-19 rebound after Paxlovid treatment. 2022. Available at: https://emergency.cdc.gov/han/2022/han00467.asp. Accessed July 13, 2023.

26. BC COVID Therapeutics Committee (CTC) COVID Therapy Review and Advisory Working Group (CTRAWG). Therapeutic brief: crushing nirmatrelvir/ritonavir (Paxlovid). 2022. Available at: http://www.bccdc.ca/Health-Professionals-Site/Documents/COVID-treatment/Crushing_Paxlovid.pdf.

27. Hiremath S, Blake PG, Yeung A, et al. Early experience with modified dose nirmatrelvir/ritonavir in dialysis patients with coronavirus disease 2019. *Clin J Am Soc Nephrol*. 2023;18(4):485-490. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36723285.

28. University of Liverpool. Prescribing resources. 2022. Available at: https://covid19-druginteractions.org/prescribing_resources. Accessed July 13, 2023.

29. Ontario Health. COVID-19 supplemental clinical guidance #4: nirmatrelvir/ritonavir (Paxlovid) use in patients with advanced chronic kidney disease and patients on dialysis with COVID-19. 2022. Available at: https://www.ontariohealth.ca/sites/ontariohealth/files/2022-04/PaxlovidClinicalGuide.pdf.

30. Hiremath S, McGuinty M, Argyropoulos C, et al. Prescribing nirmatrelvir/ritonavir for COVID-19 in advanced CKD. *Clin J Am Soc Nephrol*. 2022;17(8):1247-1250. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35680135.

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Document 2A.3

NIH Guidance for Drug-Drug Interactions Between Ritonavir Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications

Document URL

https://files.covid19treatmentguidelines.nih.gov/guidelines/section/section_176.pdf

Reference website URL

https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions/

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Not applicable

Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications

Last Updated: July 21, 2023

Ritonavir, a strong cytochrome P450 (CYP) 3A4 inhibitor and a P-glycoprotein (P-gp) inhibitor, is coadministered with nirmatrelvir to increase the blood concentration of nirmatrelvir, thereby making it effective against SARS-CoV-2. Ritonavir may also increase blood concentrations of certain concomitant medications. The Food and Drug Administration (FDA) prescribing information and Emergency Use Authorization (EUA) fact sheet include a boxed warning about significant drug-drug interactions between ritonavir-boosted nirmatrelvir (Paxlovid) and other medications.

Before prescribing ritonavir-boosted nirmatrelvir to treat patients with mild to moderate COVID-19, carefully review the patient's concomitant medications, including over-the-counter medicines, herbal supplements, and recreational drugs. Clinicians should consider the potential benefits of treatment with ritonavir-boosted nirmatrelvir, the potential risks of drug-drug interactions, and whether any risks related to drug-drug interactions can be safely managed. Clinicians should be aware that many commonly used medications can be safely coadministered with ritonavir-boosted nirmatrelvir despite its drug-drug interaction potential. Box 1 includes commonly prescribed medications that are not expected to have clinically relevant interactions with ritonavir-boosted nirmatrelvir.

Because ritonavir-boosted nirmatrelvir is the only highly effective oral antiviral for the treatment of COVID-19, drug interactions that can be safely managed should not preclude the use of this medication.

Box 1. Select Outpatient Medications Not Expected to Have Clinically Relevant Interactions With Ritonavir-Boosted Nirmatrelvir (Paxlovid)

This list is primarily based on the most common medication searches by U.S. users on the Liverpool COVID-19 Drug Interactions website.

Medications Without Clinically Relevant Interactions

These medications may be coadministered without dose adjustment and without increased monitoring. This list is not inclusive of all noninteracting medications within each drug category.

Acid Reducers
- Famotidine
- Omeprazole
- Pantoprazole

Allergy
- Cetirizine
- Diphenhydramine
- Fexofenadine
- Loratadine

Anti-Infectives
- Azithromycin
- Cidofovir
- Hydroxychloroquine
- Tecovirimat
- Valacyclovir

Cardiovascular
- Aspirin
- Atenolol
- Carvedilol
- Furosemide
- Hydrochlorothiazide
- Irbesartan
- Isosorbide dinitrate
- Lisinopril
- Losartan
- Metoprolol
- Prasugrel

Diabetes
- Empagliflozin
- Insulin
- Metformin
- Pioglitazone

Immunosuppressants
- Abrocitinib
- Baricitinib
- Methotrexate
- Mycophenolate
- Prednisone

Lipid-Modifiers
- Ezetimibe
- Pitavastatin
- Pravastatin

Migraine
- Frovatriptan
- Naratriptan
- Rizatriptan
- Sumatriptan

Neuropsychiatric
- Amitriptyline
- Bupropion
- Citalopram

Neuropsychiatric, continued
- Duloxetine
- Escitalopram
- Fluoxetine
- Gabapentin
- Lorazepam
- Nortriptyline
- Olanzapine
- Paroxetine
- Sertraline
- Venlafaxine

Pain
- Acetaminophen
- Aspirin
- Codeine
- Ibuprofen
- Meloxicam
- Naproxen

Respiratory
- Corticosteroids (inhaled/nasal)
- Formoterol
- Montelukast

Miscellaneous
- Allopurinol
- Contraceptives (PO)[a]
- Cyclobenzaprine
- Donepezil
- Enoxaparin
- Finasteride
- Levothyroxine
- Most mAb products[b]
- Ondansetron

Medications Without Clinically Relevant Interactions, continued

[a] Coadministering contraceptive products that contain ethinyl estradiol with ritonavir-boosted nirmatrelvir may result in lower ethinyl estradiol concentrations. The FDA prescribing information and EUA fact sheet for ritonavir-boosted nirmatrelvir suggest that individuals who use these types of contraceptive products should consider using an additional nonhormonal contraceptive method. However, the lower ethinyl estradiol concentrations are not expected to be clinically significant during the 5 days of therapy. The progestin concentration of a combined hormonal contraceptive is expected to remain similar or increase with coadministration, which would maintain the effectiveness of the PO contraceptive.

[b] Ritonavir-boosted nirmatrelvir interacts with certain conjugated mAbs, such as ado-trastuzumab emtansine, mirvetuximab soravtansine, brentuximab vedotin, enfortumab vedotin, polatuzumab vedotin, and tisotumab vedotin. Before coadministering ritonavir-boosted nirmatrelvir and any of these conjugated mAbs, refer to the drug's FDA prescribing information and consult with the patient's specialist providers as needed.

Key: EUA = Emergency Use Authorization; FDA = Food and Drug Administration; mAb = monoclonal antibody; PO = oral

Medications That Have Clinically Relevant Drug-Drug Interactions With Ritonavir-Boosted Nirmatrelvir

Clinicians should be aware that, in some cases, drug-drug interactions with ritonavir-boosted nirmatrelvir may lead to serious or life-threatening drug toxicities. The recommended treatment course of ritonavir-boosted nirmatrelvir for COVID-19 is 5 days. CYP3A4 inhibition occurs rapidly, with maximum inhibition occurring within 48 hours of ritonavir initiation.[1] After treatment is completed and ritonavir is discontinued, 70% to 90% of CYP3A4 inhibition resolves within 2 to 3 days.[2] The time to resolution of inhibition varies based on factors such as the patient's age; therefore, resolution may take longer in some individuals, such as in adults of advanced age.

Ritonavir is also an inhibitor of CYP2D6, P-gp, and organic anion transporting polypeptide (OATP) 1B1. When used for longer durations or chronically, ritonavir may induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and uridine diphosphate-glucuronyltransferase (UGT). See below for more information.

Nirmatrelvir and ritonavir are CYP3A4 substrates. Ritonavir-boosted nirmatrelvir should not be given within 2 weeks of administering a strong CYP3A4 inducer (e.g., St. John's wort, rifampin). Ritonavir-boosted nirmatrelvir is **contraindicated** in this setting because the delayed offset of enzyme induction may reduce the concentrations of nirmatrelvir and ritonavir, rendering the treatment ineffective against SARS-CoV-2. An alternative treatment for COVID-19 should be prescribed.

Identifying Drug-Drug Interactions

Consult the following resources for information on identifying and managing drug-drug interactions.

- Quick reference lists:
  - Box 1 above lists select outpatient medications that are not expected to have clinically relevant interactions with ritonavir-boosted nirmatrelvir.
  - Box 2 below lists select outpatient medications that have clinically relevant drug-drug interactions with ritonavir-boosted nirmatrelvir.
- Web-based drug-drug interaction checker:
  - The Liverpool COVID-19 Drug Interactions website
- Tables with guidance on managing specific drug-drug interactions:
  - The University of Waterloo/University of Toronto drug interaction guide

- The FDA prescribing information and EUA fact sheet and checklist for ritonavir-boosted nirmatrelvir

Management Strategies for Drug-Drug Interactions

Consider the magnitude and significance of the potential drug-drug interaction when choosing management strategies for patients who will be receiving ritonavir-boosted nirmatrelvir. Potential strategies include:

- Increasing monitoring for potential adverse events to the concomitant medication.
- Adjusting the dose of the concomitant medication.
- Temporarily withholding the concomitant medication.
- Using an alternative to the concomitant medication.
- Using alternative COVID-19 therapies (see Therapeutic Management of Nonhospitalized Adults With COVID-19).

Use the chosen strategy for the 5-day duration of ritonavir-boosted nirmatrelvir treatment and for at least 2 to 3 days after treatment completion. The strategy may need to continue for a longer duration if ritonavir-boosted nirmatrelvir is initiated in an adult of advanced age or if the interacting medication has a long half-life.

Consider consulting with an expert (e.g., a pharmacist or the patient's specialist providers) when treating patients who are receiving highly specialized therapies or drugs that are prone to concentration-dependent toxicities, such as certain anticonvulsant, anticoagulant, immunosuppressant, antiarrhythmic, chemotherapeutic, and neuropsychiatric drugs.

The decision to prescribe ritonavir-boosted nirmatrelvir to patients who are receiving calcineurin and mammalian target of rapamycin inhibitors should always be made in consultation with the patient's specialist providers. Among reports submitted to the FDA Adverse Events Reporting System, the most commonly reported concomitant medications resulting in serious adverse reactions, including fatal events, were calcineurin inhibitors (e.g., tacrolimus).[3] Ritonavir-boosted nirmatrelvir may be prescribed to select patients who are receiving these medications if an expert in managing the interaction is available and close therapeutic drug monitoring is logistically feasible. Otherwise, an alternative therapy for COVID-19 should be considered. See the American Society of Transplantation statement for more information.

Interactions between ritonavir-boosted nirmatrelvir and chemotherapeutic agents should also be managed in consultation with the patient's specialist providers. For guidance on managing these interactions, refer to the FDA prescribing information or EUA fact sheet for ritonavir-boosted nirmatrelvir and the prescribing information for the chemotherapeutic agent. The University Health Network/Kingston Health Sciences Centre provides an additional resource for evaluating drug-drug interactions between ritonavir-boosted nirmatrelvir and chemotherapeutic agents.

Patients should be counseled about ritonavir-boosted nirmatrelvir's drug-drug interaction potential and the signs and symptoms of potential adverse effects. If ritonavir-boosted nirmatrelvir is prescribed to patients who take certain recreational drugs, those patients will require counseling and careful monitoring for adverse effects.

Box 2. Select Outpatient Medications That Have Clinically Relevant Drug-Drug Interactions With Ritonavir-Boosted Nirmatrelvir (Paxlovid)

The guidance in Box 2 is based on the drug-drug interaction potential of the FDA-authorized 5-day course of ritonavir-boosted nirmatrelvir.

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Not all medications that may interact with ritonavir-boosted nirmatrelvir are included in Box 2. Deviation from the recommended strategies may be appropriate in certain clinical scenarios.

Prescribe Alternative COVID-19 Therapy

For these medications, management strategies are not possible or feasible, or the risks outweigh the potential benefits.

Anticonvulsants
- Carbamazepine
- Phenobarbital
- Phenytoin
- Primidone

Anti-Infectives
- Glecaprevir/pibrentasvir
- Rifampin
- Rifapentine

Immunosuppressants
- Voclosporin

Cardiovascular
- Amiodarone
- Clopidogrel[a,b]
- Disopyramide
- Dofetilide
- Dronedarone
- Eplerenone
- Flecainide
- Ivabradine
- Propafenone
- Quinidine

Neuropsychiatric
- Clozapine
- Lurasidone
- Midazolam (PO)
- Pimozide

Pulmonary Hypertension[c]
- Sildenafil
- Tadalafil
- Vardenafil

Miscellaneous
- Bosentan
- Certain chemotherapeutic agents[d]
- Ergot derivatives
- Lumacaftor/ivacaftor
- St. John's wort
- Tolvaptan

Temporarily Withhold Concomitant Medication, if Clinically Appropriate

Withhold these medications during ritonavir-boosted nirmatrelvir treatment and for at least 2–3 days after treatment completion. They may need to be withheld for longer if the patient is an adult of advanced age or if the interacting medication has a long half-life. If withholding is not clinically appropriate, use an alternative concomitant medication or COVID-19 therapy.

Anticoagulants
- Rivaroxaban[e]

Anti-Infectives
- Erythromycin

BPH
- Alfuzosin
- Silodosin

Cardiovascular
- Aliskiren
- Ranolazine
- Ticagrelor[b]
- Vorapaxar

Immunosuppressants[f]
- Everolimus
- Sirolimus
- Tacrolimus

Lipid-modifiers
- Atorvastatin[g]
- Lomitapide
- Lovastatin[g]
- Rosuvastatin[g]
- Simvastatin[g]

Migraine
- Eletriptan
- Rimegepant
- Ubrogepant

Neuropsychiatric
- Suvorexant
- Triazolam[h]

Erectile Dysfunction
- Avanafil

Respiratory
- Salmeterol

Miscellaneous
- Certain chemotherapeutic agents[d]
- Colchicine[i]
- Finerenone
- Flibanserin
- Naloxegol

Adjust Concomitant Medication Dose and Monitor for Adverse Effects

Reduce the dose and/or extend the dosing interval of the concomitant medication. Consult the Liverpool COVID-19 Drug Interactions website or the University of Waterloo/University of Toronto drug interaction guide for specific dosing recommendations.[j] If the dose of the concomitant medication cannot be adjusted, withhold the medication (if clinically appropriate) or use an alternative concomitant medication or COVID-19 therapy.

Anticoagulants
- Apixaban
- Dabigatran
- Edoxaban

Anti-Infectives
- Clarithromycin
- Itraconazole
- Ketoconazole
- Maraviroc
- Rifabutin

BPH
- Tamsulosin

Cardiovascular
- Amlodipine
- Cilostazol
- Digoxin
- Diltiazem
- Felodipine
- Nifedipine
- Verapamil

Diabetes
- Saxagliptin

Erectile Dysfunction[c]
- Sildenafil
- Tadalafil
- Vardenafil

Immunosuppressants
- Cyclosporine[f]
- Dexamethasone[k]
- Fedratinib
- Ruxolitinib
- Tofacitinib
- Upadacitinib

Migraine
- Almotriptan[i]

Neuropsychiatric
- Alprazolam[h]
- Aripiprazole
- Brexpiprazole

Neuropsychiatric, cont'd
- Buspirone
- Cariprazine
- Chlordiazepoxide[h]
- Clobazam[h]
- Clonazepam[h]
- Clorazepate[h]
- Diazepam[h]
- Estazolam[h]
- Flurazepam[h]
- Iloperidone
- Lumateperone
- Pimavanserin
- Quetiapine
- Trazodone

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Adjust Concomitant Medication Dose and Monitor for Adverse Effects, continued			
Pain • Fentanyl • Hydrocodone • Oxycodone **Pulmonary Hypertension** • Riociguat	**Miscellaneous** • Certain chemotherapeutic agents[d] • Darifenacin	**Miscellaneous**, cont'd • Elexacaftor/ tezacaftor/ivacaftor • Eluxadoline • Ivacaftor	**Miscellaneous**, cont'd • Solifenacin • Tezacaftor/ivacaftor
Continue Concomitant Medication and Monitor for Adverse Effects			
Pre-emptive dose adjustment is not required but may be considered based on an individualized assessment of the patient's risk for AEs. Educate patients about potential AEs. Consult the Liverpool COVID-19 Drug Interactions website or the University of Waterloo/University of Toronto drug interaction guide for monitoring guidance and dose adjustment information as needed.[j]			
Anticoagulants • Warfarin **Anti-Infectives** • Brincidofovir[l] • Cobicistat- or ritonavir-boosted ARV drugs • Isavuconazole • Posaconazole • Voriconazole	**BPH** • Doxazosin • Terazosin **Diabetes** • Glyburide **Cardiovascular** • Mexiletine • Sacubitril • Valsartan	**Migraine** • Zolmitriptan **Neuropsychiatric** • Haloperidol • Hydroxyzine • Mirtazapine • Risperidone • Ziprasidone • Zolpidem	**Pain** • Buprenorphine • Hydromorphone • Methadone • Morphine • Tramadol **Miscellaneous** • Certain chemotherapeutic agents[d] • Certain conjugated mAbs[m] • Oxybutynin

[a] Reduced effectiveness of clopidogrel is likely. It may be acceptable to continue clopidogrel if the benefits of using ritonavir-boosted nirmatrelvir outweigh the risk of reduced clopidogrel effectiveness.

[b] For patients at very high risk of thrombosis (e.g., those who received a coronary stent within the past 6 weeks), consider prescribing an alternative antiplatelet (e.g., prasugrel, if clinically appropriate) or an alternative COVID-19 therapy.

[c] Some PDE5 inhibitors are used to treat both PAH and erectile dysfunction; however, the doses used to treat PAH are higher than those used for erectile dysfunction. Because of this, and because PDE5 inhibitors are used chronically in patients with PAH, coadministration with ritonavir-boosted nirmatrelvir is **contraindicated** in these patients. PDE5 inhibitors can be coadministered with ritonavir-boosted nirmatrelvir in patients with erectile dysfunction, though the dose of the PDE5 inhibitor should be adjusted.

[d] Ritonavir-boosted nirmatrelvir may increase concentrations of some chemotherapeutic agents, leading to an increased potential for drug toxicities. Some chemotherapeutic agents may decrease the effectiveness of ritonavir-boosted nirmatrelvir. Please refer to the FDA prescribing information and EUA fact sheet for ritonavir-boosted nirmatrelvir and the prescribing information for the chemotherapeutic agent and consult the patient's specialist provider. The University Health Network/Kingston Health Sciences Centre is an additional resource for evaluating drug-drug interactions for chemotherapeutic agents.

[e] For patients who are at high risk of arterial or venous thrombosis (e.g., those who had a stroke within the past 3 months with a CHA_2DS_2-VASc score of 7–9 or a pulmonary embolism within the past month), consult the primary or specialty provider and consider using an alternative anticoagulant (e.g., LMWH) or an alternative COVID-19 therapy. For patients with a lower risk of arterial or venous thrombosis, clinicians may consider administering low-dose aspirin while rivaroxaban is being withheld.

[f] The use of another COVID-19 therapy may need to be considered. These immunosuppressants have significant drug-drug interaction potential with ritonavir, and they **should not be used** if close monitoring, including therapeutic drug monitoring (i.e., measuring drug concentrations), is not feasible. Consult a patient's specialist providers before coadministering these immunosuppressants with ritonavir-boosted nirmatrelvir. See the American Society of Transplantation statement for more information.

[g] Withhold lovastatin and simvastatin for at least 12 hours before initiating ritonavir-boosted nirmatrelvir, during treatment, and for 5 days after treatment completion. Withhold atorvastatin and rosuvastatin at the beginning of treatment with ritonavir-boosted nirmatrelvir and resume after completing the 5-day course. If withholding a statin is not clinically appropriate (e.g., because the patient recently had a myocardial infarction), clinicians can reduce the doses of

Continue Concomitant Medication and Monitor for Adverse Effects, continued

atorvastatin and rosuvastatin and continue treatment. However, lovastatin and simvastatin should be switched to an alternative statin.

[h] The guidance on managing drug-drug interactions between certain benzodiazepines and ritonavir-boosted nirmatrelvir can vary significantly between product information resources. Note that abrupt discontinuation or rapid dose reduction of benzodiazepines may precipitate an acute withdrawal reaction.[4] The risk is greatest for patients who have been using high doses of benzodiazepines over an extended period.

[i] Do not coadminister this medication with ritonavir-boosted nirmatrelvir in patients with hepatic or renal impairment.

[j] For medications that are not included on the Liverpool COVID-19 Drug Interactions website or in the University of Waterloo/University of Toronto drug interaction guide, refer to the FDA labels for information on coadministering these medications with ritonavir or other strong CYP3A4 and/or P-gp inhibitors (e.g., ketoconazole).

[k] Dexamethasone exposure is expected to increase 2.60-fold when dexamethasone is coadministered with ritonavir-boosted nirmatrelvir.[5] Clinicians should weigh the risks and benefits of continuing the patient's normal dose of dexamethasone (while monitoring for AEs) against the risks and benefits of decreasing the dose. Patients who are receiving higher doses of dexamethasone will be at a greater risk of AEs.

[l] Patients should take ritonavir-boosted nirmatrelvir at least 3 hours after taking brincidofovir.

[m] Ritonavir-boosted nirmatrelvir interacts with certain conjugated mAbs, such as ado-trastuzumab emtansine, mirvetuximab soravtansine, brentuximab vedotin, enfortumab vedotin, polatuzumab vedotin, and tisotumab vedotin. Before coadministering ritonavir-boosted nirmatrelvir and any of these conjugated mAbs, refer to the drug's FDA prescribing information and consult with the patient's specialist providers as needed.

Key: AE = adverse effect; ARV = antiretroviral; BPH = benign prostatic hyperplasia; CHA_2DS_2-VASc = congestive heart failure, hypertension, age, diabetes, stroke, vascular disease; CYP = cytochrome P450; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; LMWH = low-molecular-weight heparin; mAb = monoclonal antibody; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase 5; P-gp = P-glycoprotein; PO = oral

Drug-Drug Interaction Considerations When Using Extended Courses of Ritonavir-Boosted Nirmatrelvir (Paxlovid)

The guidance in this document is based on the drug-drug interaction potential of the FDA-authorized 5-day course of ritonavir-boosted nirmatrelvir. Longer treatment courses of ritonavir-boosted nirmatrelvir are not authorized by the current FDA EUA, and there are insufficient data on the efficacy of administering a second treatment course in cases where SARS-CoV-2 viral rebound is suspected.

Longer treatment courses may be utilized in certain cases (see Special Considerations in People Who Are Immunocompromised). Clinicians should be aware that the drug-drug interaction potential of ritonavir may change based on duration of treatment. Clinicians should be aware that:

- Induction properties[6] may become clinically relevant when ritonavir is used for longer durations (i.e., ≥10 days) or chronically (e.g., in people who take HIV protease inhibitors).[7] For example, induction of CYP2C9 and CYP2C19 may decrease warfarin and voriconazole concentrations, and induction of glucuronidation may decrease lamotrigine or valproic acid concentrations.
- The management strategies listed in Box 2 are based on the drug-drug interaction potential of a 5-day treatment course of ritonavir-boosted nirmatrelvir. These strategies may need to be modified when using extended courses. For example, clinicians may need to decide whether to hold or reduce the dose of corticosteroids instead of continuing them as suggested in Box 2. Clinicians may need to adjust monitoring plans for adverse effects or therapeutic drug monitoring in certain patients (e.g., in those who are receiving tacrolimus). In other cases, the potential risks of holding certain agents (e.g., chemotherapeutic agents or statins in high-risk individuals) for extended periods to allow for safe coadministration of ritonavir-boosted nirmatrelvir may outweigh the

potential benefits of treatment.

- After discontinuing longer courses of ritonavir-boosted nirmatrelvir, drug-drug interactions caused by CYP3A4 inhibition largely resolve within 2 to 3 days.[2] Drug-drug interactions caused by induction (e.g., CYP2C9, CYP2C19, UGT) resolve gradually and variably.[8,9]

Clinicians should consult with an expert (e.g., pharmacists and physicians with HIV expertise) when using extended courses of ritonavir-boosted nirmatrelvir. The Liverpool COVID-19 Drug Interactions website also provides guidance for managing drug-drug interactions for extended courses (i.e., ≥10 days) of ritonavir-boosted nirmatrelvir.

References

1. Katzenmaier S, Markert C, Riedel KD, et al. Determining the time course of CYP3A inhibition by potent reversible and irreversible CYP3A inhibitors using a limited sampling strategy. *Clin Pharmacol Ther*. 2011;90(5):666-73. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21937987.
2. Stader F, Khoo S, Stoeckle M, et al. Stopping lopinavir/ritonavir in COVID-19 patients: duration of the drug interacting effect. *J Antimicrob Chemother*. 2020;75(10):3084-3086. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32556272.
3. Food and Drug Administration Center for Drug Evaluation and Research. Antimicrobial drugs advisory committee meeting. 2023. Available at: https://www.fda.gov/media/168508/download.
4. Food and Drug Administration. FDA requiring Boxed Warning updated to improve safe use of benzodiazepine drug class. 2020. Available at: https://www.fda.gov/media/142368/download.
5. Li M, Zhu L, Chen L, Li N, Qi F. Assessment of drug-drug interactions between voriconazole and glucocorticoids. *J Chemother*. 2018;30(5):296-303. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30843777.
6. Foisy MM, Yakiwchuk EM, Hughes CA. Induction effects on ritonavir: implications for drug interactions. *Ann Pharmacother*. 2008;42(7):1048-1059. Available at: https://pubmed.ncbi.nlm.nih.gov/18577765.
7. University of Liverpool. Evaluating the interaction risk of COVID-19 therapies. 2022. Available at: https://covid19-druginteractions.org/prescribing_resources. Accessed July 20, 2023.
8. Ramsden D, Fung C, Hariparsad N, et al. Perspectives from the innovation and quality consortium induction working group on factors impacting clinical drug-drug interactions resulting from induction: focus on cytochrome 3A substrates. *Drug Metab Dispos*. 2019;47(10):1206-1221. Available at: https://pubmed.ncbi.nlm.nih.gov/31439574/.
9. Marzolini C, Kuritzkes DR, Marra F, et al. Recommendations for the management of drug-drug interactions between the COVID-19 antiviral nirmatrelvir/ritonavir (Paxlovid) and comedications. *Clin Pharmacol Ther*. 2022;112(6):1191-1200. Available at: https://pubmed.ncbi.nlm.nih.gov/35567754.

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Document 2A.4

Liverpool Drug Interactions Group Drug-Drug Interactions with Outpatient Medicines & Nirmatrelvir/ritonavir (NMV/r)

Document URL

www.covid19-druginteractions.org/prescribing_resources/paxlovid-outpatient-medicines

Reference website URL

https://www.covid19-druginteractions.org/prescribing_resources

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Document 2A.5

Liverpool Drug Interactions Group Drug-Drug Interactions with Essential Medicines & Nirmatrelvir/ritonavir (NMV/r)

Document URL

www.covid19-druginteractions.org/prescribing_resources/paxlovid-essential-medicines

Reference website URL

https://www.covid19-druginteractions.org/prescribing_resources

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Document 2A.6

EMA European Public Assessment Report of Paxlovid (updated February 24, 2022)

Document URL

https://www.ema.europa.eu/en/documents/assessment-report/paxlovid-epar-public-assessment-report_en.pdf

Reference website URL

https://www.ema.europa.eu/en/medicines/human/EPAR/paxlovid

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Not applicable

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27 January 2022
EMA/95110/2022 – Rev.[1]
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Paxlovid

Chemical name / International non-proprietary name: (1R,2S,5S)-N-((1S)-1-Cyano-2-((3S)-2-oxopyrrolidin-3-yl)ethyl)-3-((2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido) butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (PF-07321332) / ritonavir

Procedure No. EMEA/H/C/005973/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

[1] The amendment concerns the editorial correction of a factual mistake in relation to an excipient contained in the product.

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List of abbreviations

3CL	3C-like
3CLpro	3C-like protease
5d	5-day
10d	10-day
19F	fluorine-19
Ω	inter-individual variance
%RSE	Percent relative standard error
ACE-2	angiotensin-converting enzyme 2
ADE	antibody-dependent enhancement
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
Ae	amount of unchanged drug excreted in urine
AESI	adverse events of special interest
Al	Aluminium
ALB	Albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
API	active pharmaceutical ingredient
APTT (aPTT)	activated partial thromboplastin time
AS	Active substance
ASMF	Active Substance Master File
AST	aspartate aminotransferase
AUC	area under concentration-time curve
AUC24	area under the concentration-time curve from time zero to 24 hours
AUCinf	area under the serum concentration-time profile from time zero extrapolated to infinite time
AUCinf (dn)	Dose normalised AUCinf
AUClast	area under the serum concentration-time profile from time zero to the time of the last quantifiable concentration
AUClast (dn)	area under the serum concentration-time profile from time zero to the time of the last quantifiable concentration, dose normalised
AUCtau/AUCt	area under the plasma concentration-time profile from time zero to time tau (τ), the dosing interval
ACE2	angiotensin converting enzyme 2 receptor
ADR	adverse drug reaction
BCRP	breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BID	twice daily
BiPAP	Bilevel positive airway pressure
BMI	body mass index
BP	blood pressure
BSA	Body surface area
BUN	blood urea nitrogen
C12	plasma concentration at 12 hours post dose
C24	plasma concentration at 24 hours post dose
Caco-2	human colonic adenocarcinoma cells
CC50	cytotoxicity concentration 50%
Cav	average free concentration
Cb/Cp	concentration in blood/concentration in plasma
Ceff	efficacious concentration
CHOL	Cholesterol
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
CL	clearance
CL/F	apparent clearance
Clbile	biliary intrinsic clearance of drug from eg, plasma
CLr	renal clearance
CMA	conditional marketing authorisation
CMC	Chemistry Manufacturing and Controls

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Cmax	the observed maximum concentration
Cmax.ss	Cmax at steady-state
Cmin	minimal concentration (Ctrough)
CO	Clinical Overview
CoA	Certificate of analysis
CoV	Coronavirus
COVID-19	coronavirus disease 2019
CPE	cytopathic effect
C-QTc	concentration-QTc
QTc	corrected QT interval
CRP	C-reactive protein
CSR	clinical study report
CT	Connecticut; Computerised tomogram
CTA	clinical trials application
Ctrough	drug concentration observed at the last planned timepoint prior to dosing
CV	coefficient of variation; cardiovascular
CYP	cytochrome P450
CYP1A2	cytochrome P450 1A2
CYP3A4	cytochrome P450 3A4
CYP2B6	cytochrome P450 2B6
CYP2C9	cytochrome P450 2C9
DAIDS	Division of AIDS
DDI	drug-drug interaction
DBP	diastolic blood pressure
dNHBE	differentiated normal human bronchial epithelial cells
+dP/dT	cardiac contractility
EC50	drug concentration at which 50% inhibition of viral replication is observed; Concentration required for 50% effect
EC90	drug concentration at which 90% inhibition of viral replication is observed; Concentration required for 90% effect
ECG	Electrocardiogram
E-DMC	external data monitoring committee
ED	Emergency department
EFD	embryo-fetal development
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EoT	end of therapy
EPIC-HR	evaluation of protease inhibition for COVID-19 high-risk
ER	Emergency room
EU	European Union
EUA	Emergency Use Authorisation
EV71	Enterovirus 71
F1	relative bioavailability
f2	similarity factor
FC	food consumption
FDA	Food and Drug Administration
FE	food effect
FIB	Fibrinogen
FIH	first-in-human
fm	fraction metabolised
FOB	functional observational battery
FRET	fluorescence resonance energy transfer
FTIR	Fourier transform infrared spectroscopy
fu	fraction unbound
GC(-MS)	Gas chromatography (tandem mass spectrometry)
GCP	Good Clinical Practice
GD	gestation days
GeoMean	geometric mean
GFR	Glomerular filtration rate
GFR CKD-EPI	Glomerular Filtration Rate Chronic Kidney Disease Epidemiology
Equat	Collaboration equation
GI	Gastrointestinal
GISAID	global initiative on sharing avian influenza data

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GLOB	Globulin
GMP	Good Manufacturing Practice
HCl	hydrochloric acid
HCV	Hepatitis C virus
HCoV	human coronavirus
HDPE	High Density Polyethylene
HEK	human embryonic kidney
HHS	Department of Health and Human Services
HIV	human immunodeficiency virus
HRMS	High Resolution Mass Spectrometry
HPD	hours post-dose
HPLC(/MS)	high-performance liquid chromatography (tandem mass spectrometry)
HRV1B	Human rhinovirus 1B
HR	heart rate
IB	Investigator's Brochure
IC50	the drug concentration at which 50% inhibition of the 3CL protease enzyme is observed
ICH	International Council for Harmonisation
ICU	intensive care unit
IgG	Immunoglobulin G
IIV	inter-individual variability
IND	Investigational New Drug
INR	International normalised ratio
IOV	inter-occasion variability
IPPV	Intermittent positive pressure ventilation
IR	immediate release
IR	Infrared spectroscopy
IUPAC	International Union of Pure and Applied Chemistry
IV	Intravenous
Ka	absorption rate constant
KF	Karl-Fischer titration
Ki	inhibition constant
KI	concentration at 50% kinact
Kiapp	apparent inhibition constant
Kinact	maximal rate of enzyme activation
kp,uu	unbound partition coefficient
LC-MS/MS	liquid chromatography tandem mass spectrometry
(L)LDPE	(Linear) Low Density Polyethylene
LLN	Lower limit of normal
LOQ	limit of quantification
LS	least-squares
LV +dP/dt max	maximum positive slope of the left ventricular pressure wave; an index of cardiac contractility
M	male; metabolite
M&E/ME	metabolism and excretion
MA	marketing authorisation
MAA	Marketing Authorisation Application
mAb	monoclonal antibody
MAD	multiple ascending dose
MATE	multidrug and toxic compound extrusion
MDCK	Madin-Darby canine kidney cell line
MDR1	multidrug resistance 1
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
Mfg	Manufacturing
MHV	mouse hepatitis virus
min	Minute
mITT	modified intent-to-treat
mITT1	modified intent-to-treat 1
mITT2	modified intent-to-treat 2
MO	Major Objection
Mpro	main protease
MRC-5	human lung epithelial cells-5
mRNA	messenger ribonucleic acid

msec	Milliseconds
MT	mid-turbinate
N	Number (N = Number of participants; n = Number in tables for sample; No. = Number, when adjective)
ND	not determined
NDA	New Drug Application
NF	US national formulary
NI	non-inferiority
NMR	nuclear magnetic resonance
NOAEL	no-observed-adverse-effect-level
NP	Nasopharyngeal
NR	not reported
NTCP	sodium taurocholate cotransporting polypeptide
OAT	organic anion transporter
OATP	organic anion-transporting polypeptide
OATP1B	organic anion-transporting polypeptide 1B
OCT	organic cation transporter
OPA	Oriented PolyAmide
PAH	Pulmonary arterial hypertension
Papp	apparent permeability coefficient
PBO	Placebo
PBPK	physiological based pharmacokinetic modelling and simulation
pcVPC	prediction corrected visual predictive check
PD	pharmacodynamic(s)
PDE	Phosphodiesterase
PE	polyethylene
PEPT	peptide transporter 1
P-gp	p-glycoprotein
Ph. Eur.	European Pharmacopoeia
PI	prediction interval
PK	pharmacokinetic(s)
PMAR	Population Modeling Analysis Report
PO	by mouth
POC	proof of concept
popPK	population pharmacokinetics
PR	time from the onset of the P wave to the start of the QRS complex in the electrocardiogram
PRO	patient reported outcomes
PSD	Particle size distribution
PT	Preferred Term; prothrombin time
PTR	peak to trough ratio
PVC	Polyvinylchloride
PXRD	Solid state X-Ray diffraction
q12h	every 12 hours
q24h	every 24 hours
QC'd	quality controlled
QD	once daily
QRS	Deflections in the tracing of the electrocardiogram comprising the Q, R, and S waves, representing the depolarisation of the ventricles
QSP	quantitative systems pharmacology
QT	time from the beginning of the QRS complex to the end of the T wave in the electrocardiogram
QTc	QT interval corrected for heart rate
QTcF	QTc corrected using Fridericia's formula
(Q)SAR	quantitative structure activity relationship
QTPP	quality target product profile
Rac	observed accumulation ratio for AUC_T
Rac,Cmax	observed accumulation ratio for Cmax
rBA	relative bioavailability
RdRp	RNA-dependent RNA polymerase
REC	Recommendation
RH	relative humidity
RNA	Ribonucleic acid
ROW	Rest of the World

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rpm	rotations per minute
RT-PCR	reverse transcriptase–polymerase chain reaction
RTV	Ritonavir
RR	respiratory rate
SAD	single ascending dose
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-1	severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SARS-CoV-2-MA10	Severe acute respiratory syndrome coronavirus 2 (mouse-adapted virus)
SBP	systolic blood pressure
SC	Subcutaneous
SD	standard deviation
SE	supratherapeutic exposure / standard error
SM	Starting material
SmPC	summary of product characteristics
SO	Specific obligation
SoA	schedule of activities
SoC	standard of care
SOC	System Organ Class
t½	terminal elimination half-life
TBD	To be determined
TDI	time-dependent inhibitor / inhibition
TEAE	treatment-emergent adverse event
TI	therapeutic index
T/R	test/reference ratio
Tmax	the time to reach Cmax
TMPRSS2	transmembrane serine protease 2
TSH	thyroid stimulating hormone
UFLC-MS	ultra-fast liquid chromatography tandem mass spectrometry
UGT	uridine diphosphate-glucuronosyltransferase
UHPLC-HRMS	ultra-high-performance liquid chromatography - high resolution mass spectrometry
UK	United Kingdom
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
UV(VIS)	Ultraviolet (visible) spectroscopy
VeroE6	monkey kidney cells E6
VOC	variant of concern
VOI	variant of interest
Vss	volume of distribution at steady state
v/v	volume per volume
V/F	apparent volume of distribution
WOCBP	woman of child-bearing potential
WHO	World Health Organization
WT	wild type
w/v	weight per volume
w/w	weight per weight
XRD	X-Ray diffraction

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Europe MA EEIG submitted on 7 January 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Paxlovid, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 July 2021.

A combination pack request was submitted to the Agency on 31st May 2021. In accordance with Eudralex, Notice to Applicants, Volume 2A, Chapter 1, Section 5.5, "In very exceptional circumstances, which must be considered on a case by case basis, the marketing of distinct medicinal products in the same package may be indispensable for public health reasons. Such reasons cannot be related to convenience or commercial purposes". Further to consultation with ETF on 6th July 2021, the CHMP endorsed via written procedure the outcome of the review process that the proposed combination pack was considered indispensable for public health, in order to facilitate patient access to the medicinal product in the current pandemic situation. The European Commission has been informed of this outcome and endorsed the acceptance of the combination pack in the context of the Covid-19 emergency situation, stressing that the studies to support co-formulation shall be accelerated, and the progress of these ongoing studies must be reported to the EMA.

The applicant applied for the following indication:

"PAXLOVID is indicated for the treatment of mild-to-moderate Coronavirus Disease 2019 (COVID 19) in adult and adolescent patients (12 years of age and older weighing at least 40 kg) and who are at high risk for progression to severe COVID 19 (see section 5.1)".

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0566/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0566/2021 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No

847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation.

1.5.2. New active substance status

The applicant requested the active substance (1R,2S,5S)-N-((1S)-1-Cyano-2-((3S)-2-oxopyrrolidin-3-yl)ethyl)-3-((2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido) butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
9 July 2021	EMA/SA/0000061585	*EMA staff*

The scientific advice pertained to the following quality, non-clinical and clinical aspects:

a) Justification for co-packaging PF-07321332 with RTV
b) Non-clinical safety strategy
c) Clinical pharmacology programme
d) Strategy regarding the investigation of human ADME
e) Dose regimen selection
f) Adequacy of the phase 3 outpatient study (C4671005) to support a conditional MAA for treatment of adult patients with symptomatic COVID-19
g) Acceptance of non-EU data to support a CMA
h) Options for EUA in the EU and appropriate communication channels to request additional guidance

Scientific advice compliance

Overall, there is some degree of fulfilment to the CHMP advice given to the applicant's questions raised in the request of scientific advice.

However, some issues deserve to be underlined.

- It was clearly identified by the CHMP that it was difficult to predict whether the DDI potential of PF 07321332/ritonavir 300/100 mg BID would be similar to that of ritonavir 100 mg BID. As part of the response the CHMP underline the contributory value of PBPK simulations. However as a particular caveat, the applicant during the procedure was not able to provide a relevant PBPK model of simulation insofar that this model was only based on data from Healthy

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volunteers and not from patients while PK data were collected in adult patient in the C467-1005 (EPIC-HR) study.

- Finally, the applicant's questions on the clinical development of the drugs were too broad to enable the Committee to elaborate an advice.

1.7. COVID-19 EMA pandemic Task Force (COVID-ETF)

In line with their mandate as per the EMA Emerging Health Threats Plan, the ETF undertook the following activities in the context of this conditional marketing authorisation application:

The ETF endorsed the Scientific Advice letter, confirmed eligibility to the rolling review procedure based on the information provided by the applicant and agreed the start of the rolling review procedure.

Furthermore, the ETF discussed the (Co-)Rapporteur's assessment reports overviews and provided their recommendation to the CHMP.

For the exact steps taken at ETF, please refer to section 1.8.

1.8. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jean-Michel Race Co-Rapporteur: Fátima Ventura

The Rapporteur appointed by the PRAC was: PRAC Rapporteur: Martin Huber

ETF discussion on Scientific Advice on	6 July 2021
The CHMP confirmed eligibility to the centralised procedure on	22 July 2021
Agreement by ETF to start the rolling review procedure on	10 December 2021
The application was received by the EMA on	7 January 2022
The procedure started on	10 January 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	14 January 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 January 2022
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 January 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	20 January 2022
ETF discussions took place on	21 January 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	21 January 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	26 January 2022

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The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Paxlovid on	27 January 2022
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	27 January 2022

Paxlovid was evaluated as part of 'OPEN', an initiative started in December 2020 with the aim of increasing international collaboration in the EU review of COVID-19 vaccines and therapeutics. More information can be found on the EMA website.

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2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

In December 2019, the World Health Organization (WHO) was informed about a cluster of cases of viral pneumonia of unknown cause in Wuhan, China. In mid-January 2020, the pathogen causing this atypical pneumonia was identified as a novel coronavirus, severe acute respiratory coronavirus 2 (SARS-CoV-2) and genome sequence data were published. Since then, the virus has spread globally, on 30 January 2020 the WHO declared the outbreak a Public Health Emergency of International Concern and on 11 March 2020 a pandemic. The pandemic is ongoing despite unprecedented efforts to control the outbreak.

According to European Centre for Disease Prevention and Control (ECDC), histologic findings from the lungs include diffuse alveolar damage similar to lung injury caused by other respiratory viruses, such as MERS-CoV and influenza virus. A distinctive characteristic of SARS-CoV-2 infection is vascular damage, with severe endothelial injury, widespread thrombosis, microangiopathy and angiogenesis.

2.1.2. Epidemiology and risk factors

As of 24 January 2022, there have been over 349 million confirmed cases of SARS-CoV-2 infection globally with approximately 5.59 million deaths resulting from infection and subsequent coronavirus disease (COVID-19) as registered by WHO (https://covid19.who.int/). The majority of infections result in asymptomatic or mild disease with full recovery.

Underlying health conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, chronic kidney disease, immune compromised status, cancer and obesity are considered risk factors for developing severe COVID-19. Other risk factors include organ transplantation and chromosomal abnormalities. Increasing age is another risk factor for severe disease and death due to COVID-19.

2.1.3. Aetiology and pathogenesis

SARS-CoV-2 is a positive-sense single-stranded RNA (+ssRNA) virus, with a single linear RNA segment. It is enveloped and the virions are 50–200 nanometres in diameter. Like other coronaviruses, SARS-CoV-2 has four structural proteins, known as the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins.

The spike protein contains a polybasic cleavage site, a characteristic known to increase pathogenicity and transmissibility in other viruses. The Spike is responsible for allowing the virus to attach to and fuse with the membrane of a host cell. The S1 subunit catalyses attachment to the angiotensin converting enzyme 2 (ACE-2) receptor present on cells of the respiratory tract, while the S2 subunit facilitates fusion with the cell membrane. The spike protein is considered a relevant antigen for vaccine development because it was shown that antibodies directed against it neutralise the virus and it elicits an immune response that prevents infection in animals.

It is believed that SARS-CoV-2 has zoonotic origins and it has close genetic similarity to bat coronaviruses. Its gene sequence was published mid-January 2020 and the virus belongs to the beta-coronaviruses.

Human-to-human transmission of SARS-CoV-2 was confirmed in January 2020. Transmission occurs primarily via respiratory droplets from coughs and sneezes and through aerosols. The median incubation period after infection to the development of symptoms is four to five days. Most symptomatic individuals experience symptoms within two to seven days after exposure, and almost all symptomatic individuals will experience one or more symptoms before day twelve. Common symptoms include fever, cough, fatigue, breathing difficulties, and loss of smell and taste and symptoms may change over time.

The major complication of severe COVID-19 is acute respiratory distress syndrome (ARDS) presenting with dyspnoea and acute respiratory failure that requires mechanical ventilation. In addition to respiratory sequelae, severe COVID-19 has been linked to cardiovascular sequelae, such as myocardial injury, arrhythmias, cardiomyopathy and heart failure, acute kidney injury often requiring renal replacement therapy, neurological complications such as encephalopathy, and acute ischemic stroke.

2.1.4. Clinical presentation, diagnosis

The severity of COVID-19 disease varies. The disease may take a mild course with few or no symptoms, resembling other common upper respiratory diseases such as the common cold. Mild cases typically recover within two weeks, while those with severe or critical disease may take three to six weeks to recover. Among those who have died, the time from symptom onset to death has ranged from two to eight weeks.

Studies among hospitalised patients have found that high SARS-CoV-2 viral load is associated with worse outcomes, including increased mortality rates (Magleby, 2020) (Westblade, 2020). Community-based studies in non-hospitalised patients show symptomatic patients have higher viral load across both adults and children compared to asymptomatic individuals (Chung, 2021).

The gold standard method of testing for presence of SARS-CoV-2 is the reverse transcription polymerase chain reaction (RT-PCR), which detects the presence of viral RNA fragments. As this test detects RNA but not infectious virus, its ability to determine duration of infectivity of patients is limited. The test is typically done on respiratory samples obtained by a nasopharyngeal swab, a nasal swab or sputum sample.

2.1.5. Management

The management of COVID-19 cases has developed during 2020 and 2021, and includes supportive care, which may include fluid therapy, oxygen support, and supporting other affected vital organs.

Treatment of hospitalised patients encompass anti-inflammatory agents such as dexamethasone, targeted immunomodulatory agents and anticoagulants as well as antiviral therapy which at this stage are only registered via IV administration (e.g. Veklury (EMEA/H/C/005622)).

Monoclonal antibodies and notably bi-therapies to overcome potential escape by VOC with mutations on spike are perceived as of potential value. This was particularly true for immunocompromised individuals especially where vaccines might not induce adequate immune response in those patients of particular medical need. Thurs, recently, three monoclonal antibodies Ronapreve (casirivimab/imdevimab, EMEA/H/C/005814), Regkirona (regdanvimab, EMEA/H/C/005854) and Xevudy (sotrovimab, EMEA/H/C/005676) have been authorised for the treatment of COVID-19 disease in adult. In the case of Ronapreve also adolescents (from 12 years of age and weighing at least 40 kilograms), who do not require supplemental oxygen and who are at increased risk of their disease becoming severe.

Ronapreve is also approved for prevention of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kilograms.

Other products have been repurposed to be used for the treatment of COVID-19, such as Kineret (anakinra, EMEA/H/C/000363) in adult patients with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure determined by plasma concentration of soluble urokinase plasminogen activator receptor (suPAR)≥6 ng/ml, and RoActmera (tocilizumab, EMEA/H/C/000955) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.

Additionally, there are 5 approved vaccines for active immunisation against SARS-CoV-2 aiming to prevent COVID-19 disease: Comirnaty (EMEA/H/C/005735), Spikevax (EMEA/H/C/005791), Vaxzevria (EMEA/H/C/005675), COVID-19 vaccine Janssen (EMEA/H/C/005737) and Nuvaxovid (EMEA/H/C/005808).

While care for individuals with COVID-19 has improved with clinical experience, there remains an urgent need for vaccines and therapeutics able to prevent, mitigate and treat COVID-19 infections during the ongoing pandemic. Especially protection of vulnerable groups and mitigating the effects of the pandemic on a population level are desired. In addition, some studies have shown that patients might experience potential sequelae, including chronic fatigue, thrombotic events post infection, non-reversible lung disease, etc; although these aspects have not been fully determined yet.

2.2. About the product

Paxlovid is a combination pack medicinal product containing two active substances in separate pharmaceutical forms: PF-07321332 and ritonavir. PF-07321332 is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (Mpro). Inhibition of the SARS-CoV-2 Mpro renders the protein incapable of processing polyprotein precursors which leads to the prevention of viral replication. Ritonavir inhibits the CYP3A-mediated metabolism of PF-07321332, thereby providing increased plasma concentrations of PF-07321332.

The recommended dosage is 300 mg PF-07321332 (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) orally every 12 hours for 5 days.

The combination pack has been considered indispensable for public health by the CHMP and the European Commission, in order to facilitate patient access to the medicinal product in the current pandemic situation.

The applicant applied for the following indication: "PAXLOVID is indicated for the treatment of mild-to-moderate Coronavirus Disease 2019 (COVID-19) in adult and adolescent patients (12 years of age and older weighing at least 40 kg) and who are at high risk for progression to severe COVID-19 (see section 5.1)".

2.3. Type of application and aspects on development

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of Regulation (EC) No 726/2004, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide clinical comprehensive data.
- Unmet medical needs will be addressed, as in the framework of the ongoing COVID-19 pandemic there is an urgent need for safe and effective therapeutic interventions that can reduce viral

transmission, improve time to clinical recovery and prevent the progression of infection to more severe disease, hospitalisation and death. Such a therapeutic would also have the potential as an effective treatment for future coronavirus epidemics. Thus, development of pan-coronavirus treatments has a critical role in global health protection to prevent potential future pandemics.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. The applicant is providing data from their Phase 2/3 study C4671005 (EPIC-HR), which achieved overwhelming efficacy at the predefined interim analysis (based on 45% of the targeted sample size of around 3000 patients). Study C4671005 was conducted in the high-risk population. According to the applicant, the scheduled interim analysis showed an 89% reduction in risk of COVID-19-related hospitalisation or death from any cause compared to placebo in patients treated within three days of symptom onset (primary endpoint). In the overall study population through Day 28, no deaths were reported in patients who received PF-07321332/ritonavir compared to 10 (1.6%) deaths in patients who received placebo. Therefore, the benefits to public health of the immediate availability of the product outweigh the risks of further additional data requirement.

2.4. Quality aspects

2.4.1. Introduction

The finished product Paxlovid consists of two separately manufactured dosage forms both presented as film-coated tablets of pink and white colour, which are co-packaged together. Pink tablets contain the active substance (1R,2S,5S)-N-((1S)-1-Cyano-2-((3S)-2-oxopyrrolidin-3-yl)ethyl)-3-((2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido) butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide, hereafter referred as PF-07321332; white tablets contain ritonavir.

The PF-07321332 immediate release film-coated tablet (pink) contains 150 mg of PF-07321332 as active substance. Other ingredients are:

Tablet core: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, colloidal silicon dioxide and sodium stearyl fumarate;

Film-coating: hydroxy propyl methylcellulose, titanium dioxide, polyethylene glycol and iron oxide red.

The ritonavir immediate release film-coated tablet (white) contains 100 mg of the active substance ritonavir. Other ingredients are:

Tablet core: copovidone, sorbitan laureate, anhydrous colloidal silica, calcium hydrogen phosphate, anhydrous and sodium stearyl fumarate;

Film-coating: hypromellose, titanium dioxide, macrogol, hydroxy propyl cellulose, talc, anhydrous colloidal silica and polysorbate 80.

The ritonavir 100 mg film-coated tablets co-packaged in Paxlovid have been approved in EU countries as a generic product since 2015. The reference product Norvir has been approved since 25/08/1996 via the centralised procedure EU/1/96/016/005.

The finished product Paxlovid is packaged into a composite "Oriented PolyAmide/Aluminum Foil/Polyvinylchloride foil blister" (OPA/Alu/PVC) with aluminium foil lidding; each tablet is placed into an individual blister cavity.

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The blister packaging configuration provides the recommended dosage which is 300 mg PF-07321332 (two 150 mg tablets) and 100 mg ritonavir (one 100 mg tablet) to be taken together, orally, twice daily for 5 days. The blister configuration is depicted in Figure 1:

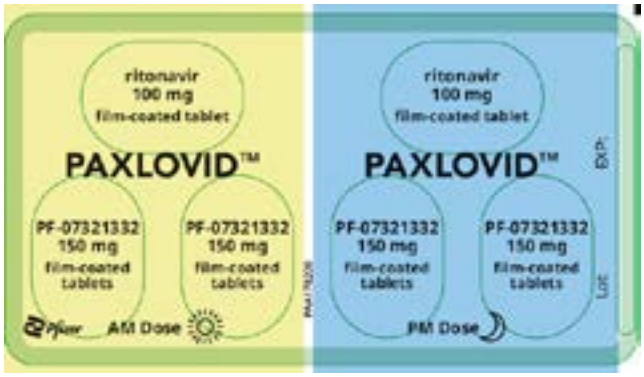

Figure 1. Blister configuration of Paxlovid

Five blister cards are packed in an outer carton, providing 5 days treatment.

2.4.2. Active Substance PF-07321332

2.4.2.1. General Information

The chemical name (IUPAC) of PF-07321332 is (1R,2S,5S)-N-((1S)-1-Cyano-2-((3S)-2-oxopyrrolidin-3-yl)ethyl)-3-((2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide, corresponding to the molecular formula $C_{23}H_{32}F_3N_5O_4$. It has a molecular mass of 499.54 g/mol and the following structure (Figure 2):

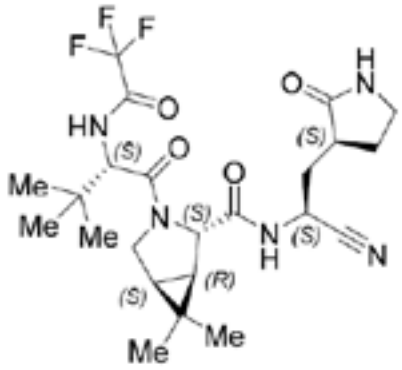

Figure 2. Chemical structure of PF-07321332 active substance

The structure of the active substance (AS) PF-07321332 was elucidated by a combination of analytical methods, including 1H-NMR, 13C-NMR, High Resolution Mass Spectrometry (HRMS), UV-VIS spectroscopy and attenuated total reflectance (ATR) FTIR spectroscopy. The molecular structure and absolute configuration of PF-07321332 was independently confirmed using single crystal X-ray diffraction technique.

PF-07321332 is a non hygroscopic, white to pale coloured crystalline powder. It has low solubility in (unbuffered) water and buffered aqueous media with pH from 1.97 to 6.96 ranging between 0.98 and 1.15 mg/mL.

PF-07321332 has 6 asymmetric centres, giving 32 possible stereoisomers (azabicyclo[3.1.0]hexane moiety can only exist in the syn configuration) as could be derived from Figure 2, which shows the absolute configuration.

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As an additional element of the chiral control strategy, chiral identification assays have been developed for each of the starting materials (SMs) to ensure that the correct enantiomer of each is used in the active substance synthesis.

PF-07321332 manufactured by the manufacturing process is isolated as crystalline polymorphic form 1 (anhydrous form) as confirmed by powder X-ray diffraction (XRPD). Form 2 and Form 3 are further possible polymorphic forms. Form 1 is the thermodynamically most stable form at relevant temperatures and humidities. As the AS is poorly soluble, the polymorphic form could have an influence on the performance of the product, and thus it should be demonstrated that the polymorphic form does not change during storage of the AS **(REC3)**.

Overall, the provided general information on the active substance is sufficient.

2.4.2.1. Manufacture, characterisation and process controls

The manufacturing process consists of several chemical transformation steps. A brief description of the manufacturing process is given including reagents and solvents, some in-process controls, and batch scale sizes. The projected commercial manufacturing scale for PF-07321332.

The manufacturing process proposed for commercial supply has been described, however some further details of the manufacturing process and aspects of its control strategy should be provided; this was raised initially as a Major Objection (MO). Specifically, amounts or ratios for all compounds, reagents, catalysts, and solvents should be described; process conditions and parameters (like temperature, reaction time, pH, etc.) should be established and described; it should be clearly defined in which of the steps processing aids are used; conditions of reprocessing should be described and the effect on the impurity profile should be investigated. Since different process conditions may lead to a different impurity profile, it is requested that in order to improve the control strategy description and to confirm a consistent impurity profile, additional details should be included in the manufacturing process proposed for PF-07321332 commercial supply. In the context of a CMA this issue can be classified as a Specific Obligation (SO) and the data will be provided post-approval **(SO1)** at latest in June 2022 as committed by the applicant.

The proposed choice of starting materials (SMs) are considered acceptable. Adequate justification to support the definition of the SMs according to ICH Q11 guideline have been provided. All three SMs are significant structural fragments of the active substance and there are sufficient chemical steps, and a form conversion step, between them and the final active substance. The synthesis routes for each of the SMs used by each of the suppliers are sufficiently described. However, some of the synthesis routes of the SM are still being optimised which could result in changes in the synthesis routes. Therefore, the final synthesis routes for the starting materials should be provided as soon as possible, at latest in June 2022 **(REC2)**. Names and addresses for the SM manufacturers were provided in the responses but the dossier needs to be updated accordingly with this information **(REC2)**. Provisional SM specifications, analytical procedures and summary of validation data were provided. However, the provisional SM specifications are not yet completely finalised. The SM specifications should be clearly updated based on historical batch data and comparative data should be presented **(REC2)**. Appropriate acceptance limits for impurities, including chiral impurities, should be included in the starting material specifications. See discussion below concerning the control strategy for impurities **(SO2)**.

A list of the reagents, solvents and catalysts used in the manufacturing process with identification of ICH classification for solvents as well as the respective specifications has been submitted. The specifications for raw materials are acceptable.

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Three intermediates are isolated. Provisional specifications have been established for the intermediates PF-07336591-01 and PF-07320267 in the manufacturing process of PF-07321332 active substance. The provisional intermediate specifications are not yet completely finalised, but the provided information submitted suffices in the context of the current emergency situation. However, in order ensure comprehensive control of impurities throughout the lifecycle of the product, for each of the isolated intermediates, intermediate specifications should be clearly established including at least the test parameters description, assay/purity, limits of identified, unidentified and total impurities. See discussion below concerning the control strategy for impurities **(SO2)**.

A short discussion on inorganic and organic impurities (including elemental, genotoxic and chiral impurities) was provided. The applicant stated that the active substance control strategy for the impurities has not yet been fully established. The control strategy for the impurities, including chiral impurities, in the AS should be clearly defined. The carry-over of impurities arising from the synthesis of the starting materials and the proposed manufacturing process of the AS for commercial supply should be investigated on three pilot-or production batches. More information about the potential formation of other chiral impurities and their control strategy should be provided. Based on these data appropriate methods for control and acceptance criteria for impurities, including chiral impurities, should be included in the SMs and intermediates specifications. If necessary, toxicological qualified limits for additional impurities should be included in the AS specification. The applicant has committed to continue to re-evaluate the specifications and limits as additional manufacturing experience becomes available and as part of validation, currently scheduled to complete in June 2022.
This issue of the control strategy for the impurities in the AS was raised initially as major objection. In the context of a CMA this issue can be classified as a Specific Obligation **(SO2)**. The data should be provided at latest in June 2022 as proposed by the applicant.
The residual solvents used in the final manufacturing step are specified in the active substance specifications with adequate limits according to ICH Q3C guideline. Purge factors for the residual solvents have been calculated. However, as the control strategy of the manufacturing process has not been completely finalised, the calculation of the purge factors cannot be concluded as final.
Therefore, the carry-over of residual solvents used in the manufacturing steps before the final step should be also investigated on three consecutive production batches **(REC3)**.

The provided risk assessment concerning the potential presence of nitrosamines in the active substance is sufficient. Potential sources of nitrosamine impurities currently listed in EMA guidance were addressed. No risks are identified.
A short description of the manufacturing process development is provided. The proposed and current manufacturing process is mainly similar to the earlier processes reported. Changes from process to process have been adequately described. The earlier routes were used to provide earlier development, pre-clinical and clinical batches. The applicant stated that at this stage of development Quality Risk Management is in-progress, an enhanced synthetic Route is being developed, and validation is ongoing consistent with ICH Q7 and ICH Q11 for active substance. A commitment has also been given to submit the enhanced control strategy for the current Route and the enhanced Route for Agency review and approval by variation as applicable **(REC2)**.

PF-07321332 is packaged in two sealed, low density polyethylene (LDPE) anti-static liners, which is then inserted in a high-density polyethylene (HDPE) drum or equivalent secondary container. A representative IR spectrum for the low-density polyethylene liner is provided as well as the corresponding specification. The provided information is acceptable.

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2.4.2.2. Specification

The active substance specification includes tests for assay (HPLC), appearance, identification (IR, HPLC), impurities (HPLC), residual solvents (GC), water content (Ph. Eur.), solid state polymorphic form (PXRD), residue on ignition (Ph. Eur.), and particle size distribution (laser diffraction).

The active substance specification contains all relevant test parameters. The justifications for the specifications, including individual specified organic impurities, qualified at toxicological levels or in line with ICH Q3A (R2), are acceptable in the context of this procedure. However, this provisional active substance specification should be revised in line with CHMP recommendations (RECs) and a final specification should be established for commercial supply.

As the control strategy for the impurities will be finalised at the latest in 2Q 2022 (SOB2) if necessary, additional impurities should be specified in the AS specification. In addition, the structure of one of the impurities should be stated and it should be classified according to ICH M7 **(REC3)**. Acceptance criteria for particle size distribution (PSD) have been set but should be tightened taking into account clinical batches, unless it could be show on PK or bioavailability data that the set upper limits of the PSD have no impact on the performance of the finished product **(REC4)**. With regard to the omission of testing for microbial enumeration it is stated that microbiological quality will be evaluated for three primary stability lots at initial release and when stored under the proposed long-term storage conditions and results will be reported **(REC4)**.

The absence of elemental impurities of class 1 and class 2a has been shown on six batches of active substance for Class 1/2A and two batches for Class 3 Element. All of these elemental impurities were <30% of ICHQ3D option 1 limit. It is stated that the Class 1/2A elemental impurities, will continue to be monitored in the active substance and an appropriate control strategy will be established; this is acknowledged. The data should be provided at the latest in 2Q 2022 **(REC3).**

The descriptions of the analytical procedures are acceptable in the context of the present conditional marketing authorisation in an emergency situation. The results of methods validation studies have been conducted and some validation data for the in-house methods were provided. However, not all validation parameters required according to ICH Q2(R) guideline have been investigated and will be provided later. A MO was initially raised requesting complete validation data for the HPLC method for assay and impurity testing and for the residual solvent method to be provided in order ensure comprehensive control of impurities throughout the lifecycle of the product. In the context of a CMA this data can be provided post-approval by June 2022 as a specific obligation (**SO3).** In addition, section 3.2.S.4.2 should be updated with the description of the residual solvent methods and the description and validation of the XRPD method **(REC4).**

The quality of the reference standard for the active substance is sufficiently proven.

Satisfactory batch analysis data are given for active substance batches used for toxicological batch and clinical batches. The batch data covers all synthesis routes used in the manufacturing development. Batch analysis data for three production batches of the current process are within set specifications.

2.4.2.3. Stability

Stability data for two active substance batches produced by earlier manufacturing processes for up to 6 months under long term conditions at 25°C/60% and under accelerated conditions at 40°C/ 75% RH were given showing compliance with specifications. The stability batches were packaged in double LDPE bags which are placed in HDPE drums.

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No significant changes were observed. The stability of the active substance batches produced by earlier synthetic routes are supportive for proposed synthetic route as all synthetic routes have the same polymorphic form, similar synthetic chemistry and same final solvents. Differences in purity profile at release are not expected to impact stability. However, the applicant should provide further stability data for batches of PF-07321322 AS manufactured by the current route and from previous routes **(REC5)**.

A photostability study was completed under ICH conditions using light source option 2 two batches from earlier routes. No changes were observed in the photostability studies. The applicant has demonstrated that the active substance is photostable.

Samples of PF-07321332 from earlier synthetic routes were subjected to forced degradation conditions to confirm the suitability of the assay and purity method and to identify potential primary degradation products. Forced degradation data on a batch of PF-07321332 AS manufactured by the commercial synthetic route should also be provided **(REC5).**

Taking into account the requirements of the ICH Q1E guideline the proposed re-test period and storage conditions can be accepted. A commitment was given that the first three batches from route F will be placed on stability under long-term conditions at 30°C/75% RH for 36 months and under accelerated conditions at 40°C/75% RH over 6 months **(REC5)**.

2.4.3. Active substance ritonavir

Ritonavir is an established active substance described in the Ph. Eur. The supplier of ritonavir used in the manufacture of Paxlovid is Hetero Drugs Limited. Ritonavir from Hetero is already approved for use in other medicinal products in the EU, using the AMSF procedure.

2.4.3.1. General information

The chemical name (Ph. Eur.) of ritonavir is Thiazol-5-ylmethyl[(1S,2S,4S)-1-benzyl-2-hydroxy-4-[[(2S)-3- methyl-2-[[methyl[[2-(1 metylethyl)thiazol-4-yl] methyl] carbamoyl] amino] butanoyl] amino]-5-phenylpentyl]carbamate, corresponding to the molecular formula C37H48N6O5S2. It has a molecular mass of 720.94 g/mol and the following structure (Figure 3):

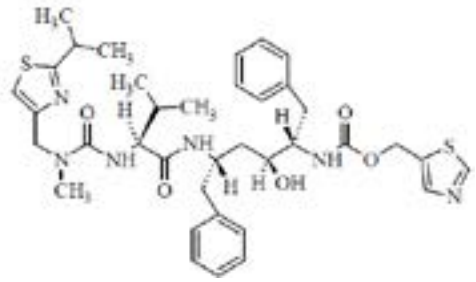

Figure 3. Chemical structure of ritonavir active substance

The molecular structure of ritonavir was investigated and confirmed by the 1H and 13C NMR spectroscopy, mass spectrometry, UV spectroscopy, and InfraRed spectroscopy.

Ritonavir is a white or almost-white, non-hygroscopic, crystalline powder, practically insoluble in water, freely soluble in methanol and sparingly soluble in acetonitrile.

Ritonavir exhibits isomerism. It contains 4 chiral centres which are introduced selectively in the synthetic process. Enantiopurity is determined by a chiral HPLC method in the active substance

specification. It also exhibits polymorphism; Hetero consistently produces polymorphic Form-I, characterised by a XRD pattern, and tested in the active substance specification.

2.4.3.1. Manufacture, process controls, characterisation and container closure

Ritonavir from Hetero is already approved in the EU using the AMSF procedure. A Letter of Access specifying the ASMF version (applicant's and Restricted Part of the ASMF) has been submitted.

The chemical synthesis and a brief description of manufacturing process of intermediate and final active substance were provided. The manufacturing process consists of four chemical reaction steps followed by a purification and drying step. The 4 starting materials are well defined, have been justified are controlled by acceptable specifications and are acceptable.

Information on possible impurities is provided covering Ph. Eur. impurities, additional non-Ph. Eur. impurities, residual solvents, genotoxic impurities, and elemental impurities.

Details of the impurity studies carried out considering all the above impurities and the residual solvents of ritonavir (Form-I) were enclosed. Studies have been carried out to check the presence of the other possible impurities from the manufacturing process of ritonavir and its starting materials.

A study has been conducted to check the possible presence of Class-I solvents in ritonavir with a validated method. From the study results it was concluded that all Class-I solvents are absent in the batches tested and therefore do not need to be controlled at the level of active substance.

Based on the evaluation of the process, three impurities were identified as potential genotoxic impurities. Studies have been carried out to check their presence in final AS with a validated method. From the studies it was clear that these compounds are below detection limit in all the batches being tested.

A risk assessment for the following Class 1, 2A, 2B and 3 elemental impurities as per ICH Q3D requirement was carried out for ritonavir production scale batches. Results from batch analysis obtained demonstrate that Class 1 and 2A along with intentionally added Class 2B and class 3 elemental impurities were found to be insignificant levels in ritonavir production scale batches. Considering the manufacturing process, the potential presence of Class 1 and 2A and intentionally added Class 2B and Class 3 elemental impurities in ritonavir are highly remote. It is concluded that the active substance complies with ICH Q3D and that no further controls are required.

The active substance is packaged in transparent polyethylene bag, tied with a plastic tag. This bag is placed in a black bag tied using another plastic tag. The polyethylene bags are made from LDPE (Low Density Polyethylene) and LLDPE (Linear Low-Density Polyethylene) respectively. The bags are placed in an HDPE drum. The packaging materials complies with relevant EU regulations and Ph. Eur. requirements.

Specifications and test procedures for packing materials, IR spectrums of the polythene bags, in-house and supplier certificates of analysis for packing material and compliance certificate of packing material have been provided.

2.4.3.2. Specification analytical procedures, reference standards, batch analysis

The proposed active substance specifications includes tests for appearance, solubility, identification (IR, HPLC), polymorphic form (XRD), related substances (HPLC), water content (Ph. Eur.), sulfated ash (Ph. Eur.), assay (HPLC), specific rotation (Ph. Eur.) and residual solvents (GC). 4-Nitrophenyl chloroformate and [(5-Thiazolyl)methyl]- (4-nitrophenyl)carbonate content (UFLC-MS) and 1,3-

Dichloroacetone (GC-MS) content are not part of the release specifications but are going to be monitored on the first batch of every year and multiple of every 10th batch.

The active substance specification contains all the requirements of the Ph. Eur. with additional requirements for polymorphic form, specific optical rotation, residual solvents, and additional non-Ph. Eur. impurities. The limits for impurities are in compliance with Ph. Eur., ICH Q3A, ICH Q3C, ICH Q3D, and ICH M7. The active substance complies with relevant EMA and ICH guidelines where appropriate.

The applicant provided an acceptable active substance specification as applied by the ASMF holder. It is also noted that the AS is converted to the *premix* and shipped to the ritonavir finished product manufacturer. The *ritonavir premix* specification applied by the finished product manufacturer has been provided in dossier section 3.2.P.3.4. This is acceptable, however the applicant's own specification for ritonavir AS should also be provided **(REC1).**

The analytical procedures are described, and their suitability was demonstrated by validation data. The reference standards are sufficiently characterised.

The provided batch data of three ritonavir batches demonstrate compliance with the active substance specification. No significant differences between the batches was observable.

2.4.3.3. Stability

Stability studies were initiated for the first three ritonavir AS validation batches, as per the ICH Q1A guideline at accelerated (40±2°C/ 75±5% RH), intermediate (30±2°C/ 65±5% RH), and long term conditions 25±2°C/ 60±5% RH. The batches were stored in the specified container closure system for 60, 12 and 6 months under long term, intermediate and accelerated conditions respectively. The methods adopted for conducting the stability studies are stability indicating which were established based on the degradation studies performed. The available stability data have been evaluated and no significant changes were observed in any of the stability batches. It has also been demonstrated that the active substance is photostable.

A forced degradation study has been performed under various stress conditions. The summary report on appearance, identification by IR and HPLC, P-XRD, related substances by HPLC, water and assay by HPLC is provided demonstrating that the methods adopted for conducting the stability studies are stability indicating.

Based on the evaluation of stability data, the claimed retest period and storage condition is endorsed.

2.4.4. Paxlovid finished medicinal product

The proposed medicinal product Paxlovid consists of PF-07321332 150 mg film-coated tablets and ritonavir 100 mg film-coated tablets, which are separately manufactured, but co-packaged on the same blister for ease of daily co-administration.

2.4.5. PF-07321332 film-coated tablets

2 . 4 . 5 . 1 . Description of the product and pharmaceutical development

Description of PF-07321332 film-coated tablets

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The PF-07321332 tablets are described as an oval, pink, film-coated tablet, with the dimensions of approx. 8.5 x 17.5 mm, debossed with "PFE" on one tablet side and with "3CL" on the opposite side.

PF-07321332 finished product was designed as an immediate release (IR) dosage form, containing 150 mg PF-07321332 as active substance.

Excipients used for manufacturing the PF-07321332 tablet are listed in section 2.4.1 of this report and in section 6.1 of the SmPC. All excipients are confirmed to comply with Ph. Eur, with exception of the film coat Opadry Pink, though all of its components are compendial, Ph. Eur. and NF, respectively).

Pharmaceutical development

The objective of pharmaceutical development was to rapidly develop a physically and chemically stable solid oral dosage form with the appropriate biopharmaceutical properties and quality attributes according to the quality target product profile (QTPP).

A Quality Target Product Profile (QTPP), in accordance with ICH Q8 was established to guide formulation and process development activities. Oriented towards this QTPP, quality attributes were derived as basis for the prospective finished product specification. Through a combination of experimental studies, risk assessments, and manufacturing experience across a range of scales and equipment types, an accelerated understanding of the formulation and process conditions and their impact on the quality attributes of the finished product was obtained.

The active substance PF-07321332 is a non-hygroscopic and white to off-white crystalline compound with low aqueous solubility across the physiologically relevant pH range. The solubility is pH independent, as it is a non-ionisable compound. PF-07321332 is tentatively classified as BCS II/IV (low solubility with permeability to-be-determined) compound. A definite BCS classification for the active substance PF-07321332 on the basis of sound analytical data should be provided **(REC6).**

Different polymorphic forms have been identified for PF-07321332. The polymorphic Form claimed to be the thermodynamically most stable form under relevant manufacturing and storage conditions and has been used for all drug product development and clinical manufacture activities. In addition, it should be investigated, and data should be presented whether the polymorphic form selected for PF-07321332 finished product manufacture can remain stable under the proposed manufacturing conditions and during shelf life **(REC6)**.

For registration stability and clinical product batches manufactured to date the AS PSD had been stated. It is stated that particle size of all batches would continue to be monitored using a validated laser diffraction method with dry dispersion. As the data set in terms of PSD is premature, the stated PSD ranges used for producing clinical and registration stability batches is regarded as the provisional PSD specification, unless/until new PK data can justify wider PSD ranges. Considering that the active substance PSD, may impact the finished product characteristics and performance, an in-depth discussion with respect to potential PSD impact on manufacturability and bio-performance of the PF-07321332 IR film-coated tablets should be provided **(REC6)**.

All excipients and corresponding quantities chosen are typically used for oral solid dose products such as the film-coated tablets in question, thus acceptable. All excipients are confirmed to comply with Ph. Eur, with exception of the film coat Opadry Pink, though all of its components are compendial, Ph. Eur. and NF, respectively).Section 3.2.P.4 for the dossier for PF-07321332 tablets should be updated to include compendial and non-compendial excipients used for the manufacture of PF-07321332 150 mg film-coated tablets and their function. In addition, the same section should be updated with an adequately compiled specification for the film coat system Opadry Pink, with a confirmation of compliance with the EU regulation 231/2012 for red iron oxide and with exemplary CoAs for the non-compendial excipient Opadry **(REC8).**

Concerning compatibility, no experimental data of the PF-07321332 with each of the selected excipients are available. Instead, reference is made to the finished product stability study at ICH storage conditions. Based on stability data available to date, no active substance-excipient incompatibility has been observed.

During formulation development, some formulations were tested in terms of desired quality attributes and bio-performance. For the first-in-human study an oral suspension formulation was developed.

The different formulations used for different Phase of clinical development have been adequately described. The development core tablet formulations have very similar compositions with one difference (in the 150 mg formulation the disintegrant was replaced). Both formulations were manufactured with the same process, applying dry granulation, followed by tablet compression and film coating.

The dissolution performance of representative PF-07321332 150 mg immediate release film-coated tablet batches was investigated in dissolution media over the physiological range. The dissolution conditions were satisfactorily justified and were found to be most suitable and thus are proposed for the routine quality control (QC).

The discriminatory power of the dissolution method was studied by testing diverse "bad" batches and is considered appropriately addressed. Following a request during the rolling review, a revised dissolution specification has been provided for 150 mg PF-07321332 film-coated tablets and is accepted. Based on the dissolution results provided, the discriminating capability of the proposed dissolution method is considered demonstrated, with regard to the timepoint set for routine QC testing.

The manufacturing process development of PF-07321332 150 mg immediate release film-coated tablets comprises a conventional dry granulation process including the following steps: blending, screening, lubrication, dry granulation, milling, blending, followed by tablet compression and film coating.

A risk assessment considering requirements from the QTPP was conducted to identify the potential relationships between the process parameters and quality attributes. Based on this assessment, quality attributes including assay, content uniformity, dissolution, disintegration and tablet appearance were determined to be potentially impacted by the process parameters.

As next step, based on the outcome of this risk assessment, statistically designed experiments were conducted at laboratory scale, with additional learnings gained during manufacture of clinical, technical transfer and registration stability batches to collect more manufacturing process understanding and to recommend acceptable operating ranges for finished product manufacture. The operating ranges studied for the process parameters at laboratory and large manufacturing scales were shown to be robust for all quality attributes studied. It is stated that parameters would continue to be evaluated to further refine the control strategy of finished product manufacturing for commercial supplies. Impact on manufacturability and dissolution of the finished product of certain steps needs to be addressed in further detail **(REC6)**.

Overall, the manufacturing process development experiments have defined operating ranges for the proposed unit operations, which are considered appropriate for manufacturing PF-07321332 finished product of acceptable quality. However, the control strategy with respect to unit operations should be substantially amended (see below in *Manufacture of the product and process controls)*.

The container closure system including the microbiological attributes has been adequately justified. For further details refer below to *Co-packed medicinal product Paxlovid.*

2.4.5.1. Manufacture of the product and process controls

The respective manufacturing sites along with their corresponding responsibilities are clearly specified. Confirmations are available stating that the manufacturers operate under GMP.

A brief description is provided for the developed manufacturing process consisting of the following steps: initial blending, screening, lubrication, dry granulation followed by milling, blending and lubrication, followed by tablet compression and film coating.

The 150 mg film-coated tablets use compendial excipients and are manufactured using conventional processing equipment. The narrative description of the manufacturing process is presented with an acceptable level of detail in the context of this procedure, with regard to process parameters limits and hold times. However the following updates in the process description should be made: the individual process steps should be numerated in line with the corresponding numeration indicated in the flow chart; the term „Package" currently stated at Step 10 needs to be replaced with „Co-package" or similar to adequately reflect the co-packaging of PF-07321332 with ritonavir film-coated tablets in the same blister **(REC7)**.

In addition it has been clarified that there are no intermediates in the manufacturing process but more details on the process description, fully reflecting the information level required in the Guideline on Manufacture of the Finished Dosage Form (EMA/CHMP/QWP/245074/2015) (e.g. the operating ranges defined within the process development) should be sufficiently considered in the process narrative and will be added once validation is complete **(REC7)**. The applicant has noted that based on available batch data at the commercial site, including tech transfer, ICH registration stability, clinical, and commercial manufacture, there is no indication of criticality associated with any hold time between the manufacturing steps; all unit operations, have shown to be robust enough and in-process testing as well as enhanced analytical testing are in place to ensure appropriate quality of each released batch. However, it should be further clarified whether hold times are intended to be applied for the PF-07321332 finished product manufacture and, if so, relevant supportive stability data should be provided **(REC7)**. As manufacturing experience will be accumulated appropriate controls will be implemented, if needed, and critical process steps and parameters should be described **(REC7)**. Considering the presented information and commitments made, in the context of this procedure, the level of detail of the narrative description of the manufacturing process is acceptable. Batch formulae for batch sizes are provided.

With respect to process validation data, the applicant provided some batch data from recent commercial batches and responded that the requested validation scheme will be available in April 2022 and validation data be provided in June 2022. The few data provided suggest high reproducibility and may be regarded as supportive only, but they cannot adequately replace a full process validation data. Therefore, full process validation data, considering all requirements specified in the Guideline on Process Validation for Finished Products (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1), should be provided **(REC7)**.

2.4.5.2. Product specification analytical procedures, batch analysis, reference standards

PF-07321332 150 mg film-coated tablets specifications include appropriate tests for this kind of dosage form including for appearance, identity (HPLC and IR), assay (HPLC), degradation products (HPLC), dissolution (Ph. Eur., HPLC), content uniformity (Ph. Eur.) and microbial limits (Ph. Eur.). During stability, only appearance, assay, degradation products, dissolution and microbial purity are performed.

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Sufficient information on specifications has been provided. However, some additional testing parameters like content uniformity, tablet thickness, and tablet weight should be included in the release specifications **(REC9)**.

The impurities and degradation products have been sufficiently discussed. There are no impurities in the finished product that are different from those present in the active substance. However, to complete the discussion on degradation products, the degradation pathway of the possible degradation products should be highlighted under the section 3.2.P.5.5 and linked sufficiently to 3.2.S.3.2 **(REC9)**. The finished product contains no Class 1 or Class 2 mutagenic impurities or degradation products.

The dissolution limit has been satisfactorily justified. An elemental impurities risk assessment was completed in line with ICH Q3D. The risk of the mentioned elemental impurities in each of the key sources, including the AS, excipients, container closure system, manufacturing equipment, and utilities were assessed. Batch data from testing representative lots of the in-going AS and film coating were considered in the risk assessment, as well as data from the Lhasa Elemental Impurities Excipients Database. The data showed that the risk of the Class 1, Class 2A elemental impurities exceeding the 30% Control Threshold of the Option 2 concentration limits and associated Oral PDEs were low to negligible. Testing by sufficiently validated Inductively Coupled Plasma- Mass Spectrometry (ICP-MS) on representative lots of the finished product confirmed the overall low - negligible risks for Class 1 and Class 2A elemental impurities and Li exceeding their PDEs in the finished product. Based on the risk assessment and on the discussion presented it can be concluded that no elemental impurities testing and no additional EI controls are needed for the PF-07321332 IR tablets.

A risk assessment on the potential presence and formation of nitrosamine in the finished product was completed, considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). The applicant states, that no vulnerable amines have been identified in AS or excipients, as well as no nitrosamine risk have been identified from the packaging material used. To support this risk assessment, the limit for any N-nitrosamine without specific toxicological information has been calculated as 30 ppb, using the acceptable lifetime intake of 18 ng/day recommended by EMA in "Nitrosamine impurities in human medicinal products" (09-Jul- 2020), in combination with the maximum daily dose of PF-07321332 of 600 mg and a conservative 10 year to lifetime treatment duration. The limit for DIPNA is 44 ppb, using the acceptable intake of 26.5 ng/day in combination with the maximum daily dose of PF-07321332 of 600 mg.

Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Overall, the specification limits have been sufficiently justified. In addition, justification has been provided concerning exclusion of tests on water content, nitrosamines, chiral purity, elemental impurities. Further information on justification of the limit for assay during shelf life should be provided **(REC9)**.

The descriptions of the analytical procedures and their validations provided are acceptable. Some additional information concerning some validation parameters for the three methods used for identity, assay degradation products and content uniformity should be provided **(REC9)**. Satisfactory information regarding the reference standards has been provided during the procedure.

Batch analysis data were provided for seven batches of PF-07321332 150 mg film-coated tablets. These batches were manufactured according to the details described in Section P.3.3 Description of Manufacturing Process and Process Controls and tested by the methods described in Section P.5.2 Analytical Procedures. Some of the data presented were evaluated against specifications that differ from those described in Section P.5.1. Specification(s) but all data were within the specifications at the time.

Adventitious agents

PF-07321332 150 mg film-coated tablets contain lactose monohydrate, which is the only excipient in PF-07321332 150 mg tablets that is of animal origin. It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.4.6. Ritonavir film-coated tablets

2.4.6.1. Description of the product and pharmaceutical development

Ritonavir 100 mg film-coated tablets are described as white to off white, capsule shaped, film-coated tablet, debossed with 'H' on one side and 'R9' on other side. Its approximate dimensions are 17.14 mm x 9.13 mm.

Pharmaceutical development

The finished product has been developed as a generic to the reference product Norvir, which is authorised in the EU by AbbVie Deutschland GmbH & Co. Its qualitative composition is essentially similar to the reference product.

Ritonavir active substance is a white to light tan powder. Due to its low solubility and permeability properties, it has been assigned to BCS Class IVa.

Excipients matching those of the EU reference product were chosen, all of which complying with Ph. Eur. monographs, including those contained in the non-compendial coating mixture. All excipients are common ingredients for this product type. Their compatibility with the ritonavir premix was confirmed by stability data. Minor amendments should be made to the composition table as to specify the active ingredient at the declared amount (100 mg) along with one total amount of each excipient used **(REC12)**.

Pharmaceutical development started with pre-formulation studies based on published information, physicochemical characterisation and *in-vitro* dissolution data of the US and EU reference products. Formulation development was driven by ritonavir's key physicochemical characteristics and reference product's *in-vitro* dissolution characteristics., additional information is required on the stability of the polymorph form during storage and manufacturing conditions **(REC13)**.

Following several trial formulations, a manufacturing process was chosen which resulted in tablets with acceptable *in vitro* dissolution data. The manufacturing process development was described. A process robustness study was conducted, identifying the possible variables during various stages of the

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manufacturing process and their effect on the *in vitro* dissolution performance of the formulation. Optimisation studies of different steps of the process were conducted. Nevertheless, little information on the development of the manufacturing process is provided. Critical process parameters during manufacture are identified with specified set points. However, justification based on development data is awaited for CPPs during dry mixing, lubrication, compression, and film-coating **(REC13)**.

The proposed dissolution method for routine QC testing is paddles, 75 rpm 900 ml water with 60 mM Polyoxyethylene 10 Laurylether. As the requirements of Reflection Paper EMA/CHMP/CVMP/QWP/336031/2017 apply to ritonavir film-coated tablets as part of the CMA for Paxlovid, justification of the dissolution conditions are awaited, particularly the choice of media (water with surfactant at a specific concentration), and the agitation speed (75 rpm) **(REC13)**.

For commercial batches used in the bioequivalence study, *in vitro* dissolution studies were conducted and compared to the results obtained with the EU reference product. The dissolution profiles were found similar in all media when compared to the reference product, with acceptable f2 values.

Based on the development data, the biopharmaceutical performance of the test product is considered similar if not exceeding that of the reference product. Yet, the proposed limit for dissolution testing is not considered appropriate as it is located in the plateau and furthermore it does not allow for discrimination between batches. As a consequence an MO was raised initially; the applicant is required to tighten the *in-vitro* dissolution specification in 3.2.P.5.1 according to the results obtained for the biobatches as per the Reflection Paper EMA/CHMP/CVMP/QWP/336031/2017 e.g. to NMT 75 % (Q) in 45 min. In the context of a CMA this can be addressed as a specific obligation post-approval by June 2022 **(SO4)**.

In summary, the finished product has been shown to be comparable to the reference product if not superior, based on key parameters *in vitro* dissolution and related substances profile/levels. However, several aspects of pharmaceutical development, including discussion of the proposed control strategy for the manufacturing process including manufacture of the polymorph form, need to be addressed, and compliance with current ICH Q8 (R2) should be established as discussed above.

In the context of the CMA, the quality documentation provided for ritonavir film-coated tablets is considered acceptable from a risk-based perspective, as the product is currently registered in several European countries with the currently proposed specifications.

The choice of container closure system for the co-packaged medicinal product is based on PF-07321332 tablets and is justified and was confirmed by results of accelerated stability studies. As for the bulk tablets, the suitability of the primary container (HDPE, with polypropylene closure) was confirmed by results of accelerated stability studies for 3 months. No significant changes were observed for water content, assay, related compounds, and dissolution.

No risk of nitrosamine formation is identified originating from the packaging components. No overages are used during manufacture of ritonavir film-coated tablets. Microbiological attributes and compatibility are not applicable for the proposed finished product.

Detailed information on the container closure system (LDPE bag placed in triple laminated aluminium bag) for ritonavir bulk tablets was provided including specifications, analytical procedures and certificates of analysis issued by both the suppliers and the product manufacturer.

2.4.6.1. Manufacture of the product process controls and characterisation

All manufacturing sites and their operations were defined. The manufacturing process uses three stages for preparation of the premix: Stage-I (RPM-I: preparation of premix), Stage-II (RPM-II:

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pulverisation), Stage-III (RPM-III: blending, sifting, packaging). Afterwards, the material is sifted/mixed and prepared for hot melt extrusion, milled/sifted, (pre)lubricated, before compression and coating take place. The process is considered as non-standard procedure due to the hot melt extrusion included. Process descriptions were provided along with flow charts. Batch formulae for production batch sizes were presented. Routine in-process controls were presented. For the intermediate a detailed specification including a description of analytical methods and certificates of analysis, packaging material and hold times were presented. However, stability data of the intermediate product are required and, the specifications for the packaging material for the intermediate product is awaited **(REC14)**. Overall, the process is well-described and controlled by in-process tests. Nevertheless, the applicant is expected to provide further details and justification for the control strategy employed based on development data **(REC14)**.
Process validation data were provided for commercial batches at both minimum and maximum batch size. Key parameter during dry mixing and lubrication was blend uniformity, monitored in individual samples taken at several locations to make sure that the active substance is evenly distributed throughout the blend. During compression and coating, it has been confirmed that the physical tablet parameters (mass variation, uniformity of dosage units, friability, hardness) comply with pre-defined requirements. The process has been shown to be reliable, robust and reproducible in order to obtain tablets that comply with the specifications and quality characteristics defined on the respective validation protocol.

Also, validation results of the manufacturing process of three batches of ritonavir premix were provided. The critical steps of the process were monitored. The critical steps of the process were monitored in order to ensure that the process is suitable and reproducible. The following critical steps were validated through additional or more frequent than routine in-process control testing: pulverising, sifting and packing. The results obtained demonstrate that the manufacture of ritonavir premix is acceptable and reproducible in order to obtain an intermediate complying with the specifications and quality characteristics defined in the respective validation protocol. Nevertheless, some additional validation data for the hot melt extrusion process should be provided, to justify time/temperature regimes in the context of chemical instability of the AS to ensure satisfactory quality specifications whilst the least temperature stress is applied. Furthermore, the process optimisation study results should be disclosed **(REC14)**.

2.4.6.2. Product specification analytical procedures, batch analysis, reference standards

The finished product release specifications include appropriate tests for this kind of dosage form including description, identification (HPLC and UV), average weight (mass), water content (KF), dissolution (Ph. Eur. - HPLC), uniformity of dosage units (content uniformity Ph. Eur.), related substances (HPLC), assay (HPLC) and microbial purity (Ph. Eur.).

During stability studies, tests for appearance, assay, degradation products, dissolution and microbial purity are performed. Different specifications limits are applied for shelf life concerning water content and degradation products. During shelf life, the following parameters are tested: Description, assay, related substances, water content, dissolution, microbial purity.

Sufficient information on specifications has been provided. The specifications for ritonavir 100 mg film-coated tablets are generally in line with the requirements of the relevant Ph. Eur. monographs, ICH guidelines and batch analysis data.

If not otherwise justified, the limit for dissolution testing should be revised as per the Reflection Paper EMA/CHMP/CVMP/QWP/336031/2017 (e.g. to NMT 75% (Q) in 45 min) (as discussed previously in Pharmaceutical Development (SO4)).

There are no impurities in the product that are different from those present in the active substance. If not otherwise justified, the limit for water content, which has been set to the shelf life specification with NMT 6.5% should be tightened according to the data obtained as the maximum amount found is 4 % **(REC15)**. In summary, satisfactory information or justification of specifications has been provided in the context of this CMA. Revision of specification limits for dissolution and water content is expected as discussed.

A risk assessment for elemental impurities as per ICH Q3D has been provided, which sufficiently justify absence of test for elemental impurities in the finished product. The component approach has been used. However, data of three consecutive batches or six pilot batches are awaited and the respective analytical methods validation data, should be provided **(REC15).**

A risk assessment for the presence of nitrosamines as per the requirements of EMA guidance on Information on nitrosamine for marketing authorisation holders (EMA/189634/2019 & CMDh/404/2019) and (EMA/428592/2019 & CMDh/405/2019) has been provided. For ritonavir premix and ritonavir 100 mg film-coated tablets no risk for presence of nitrosamine impurities was identified. However, for completeness of the assessment further information is awaited. Specifically, the analytical method validation data for the methods of analysis of nitrosamines impurities, should also be provided **(REC15).**

The analytical methods which are mentioned in the specifications have been sufficiently described. Validation design and appropriate validation data has been provided for almost all methods described under analytical procedures including the method used for the determination of blend assay, blend content uniformity. Validation data have been presented for the method used for determination of assay and dissolution testing as well as for identification by UV and microbial purity.

Information on reference standards used including certificates of analysis has been provided. Some information is still expected concerning the purpose of the reference standards used **(REC16)**.

Batch analysis data have been presented for four batches. All data were within the specifications. Certificates of analyses have been presented. However, clarifications concerning discrepancies of some of the specification parameters reported in the CoAs is awaited **(REC15)**.

Adventitious agents

There are no excipients of human or animal origin used in the manufacture ritonavir 100 mg Film-coated tablets.

2.4.7. Co-packed Paxlovid

2.4.7.1. Container closure system for the co-packaged finished product

The co-packed finished medicinal product Paxlovid consists of separately manufactured film-coated tablets (2 x PF-07321332 150 mg and 1 x ritonavir 100 mg), which are co-packaged into a blister.

The container closure system for PF-07321332 150 mg film-coated tablets and externally sourced ritonavir 100 mg film-coated tablets consists of a foil/foil blister system made from a composite Oriented PolyAmide/Aluminium Foil/Polyvinylchloride (OPA/Al/PVC) foil blister with aluminium foil lidding where each tablet is placed into an individual blister cavity. Illustrative drawings and representative IR spectra of the packaging components were provided. Some information concerning

declarations confirming regulatory compliance of material in contact with food should be provided **(REC10)**.

2.4.7.2. Stability for the co-packaged finished product

PF-07321332 150 mg film-coated tablets

Due to the accelerated pharmaceutical development, limited primary stability data is currently available for the PF-07321332 150 mg film-coated tablet.

In accordance with ICH guideline Q1A(R2), a primary stability study consisting of PF-07321332 150 mg film-coated tablets packaged in proposed commercial foil/foil blister packaging has been initiated. The primary stability batches were manufactured at 10% of the proposed commercial scale at Pfizer's Freiburg (Germany) site and packaged at the same facility.

Preliminary stability data for three primary batches of the 150 mg tablets were reported for three months at the long-term storage conditions of 30°C/ 75% RH and 25°C/60% RH and at the accelerated storage conditions of 40°C/ 75% RH. During stability, solely the stability indicating tests, appearance, assay, degradation products, water activity and dissolution were performed. Results met the specifications. However, the batch size of the primary stability batches should be detailed and the method used for determination of water activity should be described and validation data should be presented **(REC11).** In addition, photostability (in accordance with ICH guideline Q1B) of one batch was evaluated and data was provided. From the results it was concluded that PF-07321332 150 mg film-coated tablets are stable to light and no precautionary packaging or labelling is required.

Various supportive data of early development tablet formulations packaged in PCTFE/foil blisters, foil/foil blisters and (less protective) HDPE bottles were evaluated under different conditions. 3-month data at the long-term storage condition of 30°C/75% RH and at the accelerated storage condition of 40°C/75% RH for one batch of each formulation were reported. Additional supportive stability data from two developmental batches of the commercial formulation through 6 weeks storage at the long-term storage condition of 30°C/75% RH and at the accelerated storage condition of 40°C/75% RH were also presented.

Forced degradation studies on PF-07321332 150 mg film-coated tablets were performed, including thermal, thermal humidity and photolysis conditions, to establish the extent and nature of potential degradation pathways and to confirm the suitability of the assay and purity method. However, the stability indicating power for the method, which is used alternatively for the determination of assay, should be demonstrated **(REC9).**

Stress studies on film-coated tablets were performed. Total degradation products remained within specifications.

Based on the overall stability data from the primary stability studies, supportive studies, stress stability studies and forced degradation stability studies, the proposed shelf life and storage conditions are considered acceptable provided that the stability data will be monitored monthly **(REC11)**. In addition, the storage conditions will be reviewed and updated as necessary according to the stability data **(REC11)**.

Ritonavir film-coated tablets

Stability data for ritonavir 100 mg film coated tablets in the proposed co-packaged blister system is currently not available. Stability studies were carried out on three full batches of ritonavir 100 mg film-coated tablets packed in Alu-Alu blister and stored up to 36 months at 25ºC/60% RH and 6 months at

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40°C/75% RH. No significant changes were observed in description, water content, resistance to crushing of tablets, dissolution, related compounds, assay, XRD and microbiological examination of ritonavir 100 mg Film-coated tablets and the results were found to be well-within the specification valid at that time. XRD test should be included in the regular tests of the post-approval stability protocol and stability commitment, while it should further be confirmed that microbiological tests will be performed annually **(REC17).**

A forced degradation study was carried out as a part of the analytical method validation in order to prove the specificity of the HPLC method for assay and related compounds of ritonavir premix and ritonavir 100 mg film-coated tablets.

Supporting stability data for batches of commercially available ritonavir 100 mg film-coated tablets packed in Alu-Alu blister are presented, for which a shelf life of 24 months has been approved. According to the data up to 36 months at 25ºC/60% RH and 6 months at 40ºC/75% RH, no significant changes were observed in description, water content, hardness, dissolution, related compounds, assay, XRD and microbiological quality. The results were found to be well within the shelf life specification.

Stability results of ritonavir bulk tablets were also presented. The studies were conducted with three commercial batches, stored up to 12 months at ICH long term conditions (25°C/60% RH). All test parameters remain within specifications.

For the bulk tablets, a shelf life of 12 months is confirmed when stored up to 25°C with excursions up to 14 days at 5 ± 3°C, -20 ± 5°C, 50 ± 2°C, but the proposed storage condition for the bulk tablets ("Do not store below 25°C") should be justified **(REC17)**. A statement is provided to confirm that the requirements of CPMP/QWP/072/96 are taken into account for setting the shelf life of ritonavir film-coated tablets.

In addition, the ritonavir bulk tablets component is considered as intermediate product for Paxlovid finished product, which is being introduced in the last steps of manufacture of Paxlovid. Therefore, the contents of Module 3.2.P ritonavir bulk tablets should be integrated as sub-chapter in Module 3.2.P.3 of Paxlovid in order to avoid confusion and repeating of documents **(REC18)**.

In conclusion, the presented stability data for ritonavir 100 mg film-coated tablets show that tablets are stable for 24 months without any special storage conditions. The commercially available Hetero Ritonavir 100 mg tablet in foil/foil blister container closure system has an approved shelf life of 24 months, which is considered appropriate for the Pfizer co-packaged presentation as well.

Co-packaged finished product

Stability data have been provided for the PF-07321332 tablet and ritonavir tablets packaged separately in the proposed packaging material (as discussed above). However, stability data for the co-packed Paxlovid finished product have not been provided and information concerning the final co-packed Paxlovid finished product to be marketed is reflected poorly in the dossier. The respective sections of 3.2.P PF-07321332 tablets should be updated to include the missing information for the co-packed Paxlovid finished product to be marketed **(REC18)**.

The applicant stated that stability studies for the co-packaged Paxlovid finished product are currently scheduled to start in January/February 2022, depending on packaging schedules.

The final shelf-life and storage condition for the co-packaged finished product Paxlovid is based on the more stringent shelf-life and storage condition for either of the two products, which is PF-07321332 150 mg film-coated tablets. Therefore, based on the overall available stability data presented for both components of the co-packaged product, the proposed shelf-life of 1 year with storage conditions "Do

not store above 25°C. Do not refrigerate or freeze", as stated in the SmPC (sections 6.3 and 6.4) is acceptable.

The twelve months stability for the Paxlovid finished product is acceptable provided the applicant will monitor the stability data monthly and will immediately inform the authorities in the case of out of specification (OOS) results. Storage conditions "Do not store above 25°C", "Do not refrigerate or freeze" is accepted provided that these storage conditions will be updated as required when further stability data are available.

2.4.8. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The applicant has applied for conditional marketing authorisation (CMA). In the context of the current public health emergency situation due to COVID-19 pandemic and the pharmaceutical development of the proposed medicinal products, the submitted quality documentation is considered sufficient for CMA approval.

Paxlovid finished product comprises two separately manufactured dosage forms both presented as film-coated tablets. These two components of the finished product are film-coated tablets containing 150 mg PF-07321332 as active substance and film-coated tablets containing 100 mg ritonavir as active substance. For ease of daily co-administration, both components (PF-07321332 150 mg film-coated tablets and ritonavir film-coated tablets) are co-packaged in the same blister.

Active substance PF-07321332

The submitted information on development, manufacture, control and stability of the active substance indicate that currently manufactured batches are of appropriate quality and that is comparable to that of clinical development batches. Some issues, initially raised as MOs, in relation to the active substance should be addressed post-approval as Specific Obligations (SOs) in the context of the CMA. Two of these issues relate to the control strategy of the manufacturing process and the impurities in the active substance. A third issue that should be followed-up post approval as SO concerns the completion of the validation study of the method for assay and impurity testing, and of the method for the residual solvent.

Active substance ritonavir

Ritonavir is an established active substance described in the Ph. Eur. The supplier of ritonavir used in the manufacture of Paxlovid is Hetero Drugs Limited. Ritonavir from Hetero is already approved for use in other medicinal products in the EU, using the AMSF procedure; the ASMF is acceptable.

Finished product

PF-07321332 150 mg film-coated tablets are designed as an immediate release dosage form and are manufacture by a standard manufacturing process. Although relatively limited stability data were presented, they were adequate to establish an acceptable shelf life provided that the applicant will monitor the stability data monthly and will inform the authorities immediately in the case of out of specification results.

Ritonavir 100 mg film-coated tablets co-packaged in Paxlovid, are externally sourced and have been approved in EU countries since 2015 as a generic product of the reference product Norvir. Therefore, the quality of ritonavir film-coated tablets is considered acceptable in the context of the CMA. However, an issue concerning the acceptance criteria of the dissolution of ritonavir tablets, initially raised as MO should be addressed post-approval as a Specific Obligations (SO) in the context of the CMA.

Overall, the information on development, manufacture and control of the two components of the finished product (i.e. PF-07321332 150 mg film-coated tablets and ritonavir 100 mg film-coated tablets) has been presented in a satisfactory manner. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

At the time of the CHMP opinion, there were a number of minor quality issues having no impact on the benefit/risk ratio of the product, which pertain to supplementing various parts of the dossier module 3 with updated and new information relating to the PF-07321332 active substance attributes, manufacture, control strategy and stability of the finished product and to update the information relating to ritonavir tablet component in line with technical and scientific progress in compliance with Article 23 of Directive 2001/83/EC. These points are put forward as recommendations (RECs) for future quality development and were agreed by the applicant to be addressed within an acceptable timeframe.

The data presented to support consistent quality of the medicinal product Paxlovid is considered to be sufficient in the context of a conditional marketing authorisation in the current (COVID-19) pandemic emergency situation. To complete the quality documentation in the framework of the conditional marketing authorisation, the applicant should fulfil the mentioned specific obligations (SOBs) post-approval within an acceptable timeframe.

2.4.9. Conclusions on chemical, pharmaceutical and biological aspects

The quality of this medicinal product, submitted in the context of the current (COVID-19) pandemic, is considered to be consistent and acceptable in the context of a CMA in an emergency situation.

Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in an acceptable way. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that from a quality perspective the product should have a satisfactory and uniform clinical performance.

The submitted information indicate that currently manufactured product batches are of appropriate quality that is comparable to that of clinical development batches. However, in order to confirm that the quality of future batches will also remain appropriate and comparable to that of clinical development batches over the life cycle of the medicinal product a number of issues are expected to be addressed though fulfilment of specific obligations (SOs) within the defined timeframe. The identified issues discussed in this report and listed in List 1 are compatible with the granting of a CMA.

The CHMP has identified the following specific obligations (SOs) to address the identified quality developments issues that may have a potential impact on the safe and effective use of the medicinal product, and which therefore are needed to achieve comprehensive pharmaceutical quality data and controls for the active substances and the finished product. In the List 2 of this report the specific points that need to be addressed in order to fulfil the imposed specific obligations are detailed.

List 1. The issues identified in quality documentation that require specific obligations (SOs).

Description	Due date
1. In order to improve the control strategy description and to confirm a consistent impurity profile, additional details should be included in the manufacturing process proposed for the active substance PF-07321332 for commercial supply.	June 2022
2. In order to ensure comprehensive control of impurities throughout the lifecycle	June 2022

Description	Due date
of the product, the control strategy for the active substance PF-07321332 for the impurities including chiral impurities and the active substance should be fully established.	
3. In order to ensure comprehensive control of impurities throughout the lifecycle of the product, full validation data for the HPLC method for assay and impurity testing, and for the residual solvent method used for the control of the active substance PF-07321332 should be provided.	June 2022
4. In order to improve the control strategy for the ritonavir film coated tablets, the limit for dissolution specification of ritonavir film coated tablets should be tightened according to the results obtained for the biobatches, e.g. to NMT 75 % (Q) in 45 min.	June 2022

List 2. Detailed List of Specific Obligations (SOs)

Post-authorisation measure(s)	Motivation
1. In order to improve the control strategy description and to confirm a consistent impurity profile, additional details should be included in the manufacturing process proposed for the active substance PF-07321332 for The manufacturing process proposed for the active substance PF-07321332 for commercial supply and its control strategy should be clearly described and a) Therefore, amounts or ratios for all compounds, reagents, catalysts, and solvents should be documented. Process conditions and parameters like temperature, reaction time, pH, etc. should be established and described. It should be clearly defined in which of the b) If reprocessing is proposed the conditions should be described and the effect on the impurity profile should be	A clear description and definition of manufacturing process of the active substance and its control strategy is required as different process conditions may lead to a different impurity profile. The description of the process should be such that a consistent impurity profile is
Proposed post-authorisation measure 2 with proposed classification category 2:	Motivation/Background information on measure, including due date:
2. In order to ensure comprehensive control of impurities throughout the lifecycle of the product, the control strategy for the active substance PF-07321332 for the	Due to safety reasons the active substance control strategy for the impurities of the active substance needs to be fully established as this

Post-authorisation measure(s)	Motivation
impurities including chiral impurities and the active substance should be fully established. The control strategy for the new active substance PF-07321332 for the impurities including chiral impurities and the API should be fully established: a) The carry-over of impurities arising from the synthesis of the starting materials and the proposed manufacturing process of the API for commercial supply should be investigated on three pilot-or production batches unless already specified in the API specification. b) More information about the potential formation of other chiral impurities and their control strategy should be provided. c) Appropriate acceptance criteria for unidentified and identified impurities including chiral impurities and total impurities should be included in the starting material and intermediate specifications taking into account batch analysis data for starting materials and intermediates and considering the purging capacity of the manufacturing process. The methods for control of these impurities should be described. d) As committed by the applicant the description of in-house methods for the intermediate specifications and the need for control of additional intermediate material attributes will be presented in the next variation. e) If necessary, toxicological qualified acceptance criteria for additional impurities including chiral impurities should be included in the API specification.	have an influence on the safety of the AS Due date: June 2022 (a), b), c), e)) Due date: February 2022 (d)
Proposed post-authorisation measure 3 with proposed classification category 2:	Motivation/Background information on measure, including due date:
3. In order to ensure comprehensive control of impurities throughout the lifecycle of the product, full validation data for the HPLC method for assay and impurity testing, and for the residual solvent method used for the control of the active substance PF-07321332 should be provided. Full validation data for the control of active substance PF-07321332 for the HPLC method for assay and impurity testing and for the residual solvent method should be provided.	to demonstrate the suitability of the substance. Due date: June 2022

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Post-authorisation measure(s)	Motivation
	Motivation/Background information :
4. In order to improve the control strategy for the ritonavir film coated tablets, the limit for dissolution specification of ritonavir film coated tablets should be tightened ritonavir dissolution specification: The current limit for dissolution testing is not meaningful as it is located in the plateau. Further it does not allow for discrimination between batches. As a consequence, the applicant is required to tighten the in-vitro dissolution specification in 3.2.P.5.1 according to the results obtained for the	Compliance with EMA/CHMP/CVMP/QWP/336031/2017 Due date: June 2022

2.4.10. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Quality recommendations are covered in the list of recommendations in Annex I.

2.5. Non-clinical aspects

2.5.1. Introduction

Paxlovid contains two active substances: PF-07321332 and ritonavir. PF-07321332 is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (Mpro). Ritonavir inhibits the CYP3A-mediated metabolism of PF-07321332, thereby providing increased plasma concentrations of PF-07321332.

The non-clinical development programme was designed in accordance with ICH guideline M3. Ritonavir was originally developed as an antiretroviral agent used in HIV infection (at 600 mg BID dose); nowadays, it is exclusively used as a PK enhancer (mostly at 100 mg BID) for protease inhibitors in HIV and HCV infection; in the context of such PK enhancement use, ritonavir is often referred to as a 'booster'. As part of such boosted regimens ritonavir is of long-term use due to HIV being a chronic disease. Its non-clinical and clinical safety profile is well known and given that Paxlovid is intended for a 5 days treatment duration, no additional animal studies with ritonavir have been performed, which is acceptable. The following discussion on non-clinical aspects will therefore concentrate on PF-07321332.

2.5.2. Pharmacology

PF-07321332 is a potent and selective inhibitor of the SARS-CoV-2 3CLpro that exhibits a broad-spectrum activity across the Coronaviridae family of 3CL proteases demonstrating its potential for a "pancoronavirus" activity but of uncertain efficacy against notably MERS-CoV until adequate clinical efficacy demonstration. The critical amino acid residues involved in enzyme-inhibitor binding interactions are particularly well conserved within this family of viruses.

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2.5.2.1. Primary pharmacodynamic studies

In vitro primary pharmacodynamic studies

In vitro primary pharmacodynamic data are included in the clinical pharmacology section of this assessment report.

In vivo pharmacodynamic studies

A total of two *in vivo* studies were presented evaluating the antiviral activity of PF-07321332. PF-07321332 showed antiviral activity in mouse models with mouse-adapted (MA) SARS-CoV-2 infection in BALB/c and 129 mouse strains (studies 105036 and 022652). Oral administration of PF-07321332 at 300 mg/kg or 1000 mg/kg twice daily initiated 4 hours post-inoculation or 1000 mg/kg twice daily initiated 12 hours post inoculation with SARS-CoV-2 MA10 (mouse-adapted virus) resulted in reduction of lung viral titres and ameliorated indicators of disease (weight loss and lung pathology) compared to placebo-treated animals.

The applicant has used a mouse-adapted virus which was modified from the original virus with several nucleotide changes. The relevance of its nucleotide changes is not clear to the intended extrapolation to the clinical setting. The applicant has discussed the choice of the mouse-adapted virus as *in vivo* model rather than a modified mice model such as K18-hACE2 mice which could have been used with the SARS-CoV-2 and its variant. SARS-CoV-2 MA exhibited more clinically relevant phenotypes than those seen in Hfh4-ACE2 transgenic mice, which expresses human ACE2, and thus SARS-CoV-2 MA is used by numerous investigators in the SARS-CoV-2 field.

No animal studies have been performed to evaluate the reduction of viral load in the upper respiratory tract and the impact of PF-07321332 treatment on viral transmission. The applicant rightly pointed out that analysis of SARS-CoV-2 transmission in hamsters by Abdelnabi *et al* (preprint) shows that the treatment of hamsters by PF-07321332 prevents transmission of SARS-CoV-2.

While ritonavir at booster dose does not exhibit an *in vitro* antiviral activity on SARS-CoV-2, there is an ongoing *in vivo* study with PF-07321332 in combination with ritonavir using a mouse-adapted model of SARS-CoV-2 infection (MA-SARS-CoV-2) in BALB/c mice. At the present stage, the lack of this study for the combination PF-07321332/ritonavir is acceptable given that ritonavir is used as a PK enhancer and the lack of antiviral effect by ritonavir. However, ritonavir affects both 07321332 metabolism and transport. This study, which should be provided post-approval, is considered essential for a better understanding of PF-07321332 distribution and efficacy following co-administration of PF-07321332 and ritonavir.

2.5.2.2. Secondary pharmacodynamic studies

In vitro studies were undertaken against a wide panel of receptors, transporters, ion channels and enzyme assays, and the results indicated no significant inhibition of functional or enzyme activity at human relevant concentrations (study 100054569). No off-target was identified up to 100 µM (39x the predicted human unbound Cmax at the intended clinical regimen).

PF-07321332 was also tested for inhibitory activity against 11 PDE subtypes (1 to 11) and the IC_{50} values were determined to be >200 µM (study 20LJ074), which represented 78x the predicted human unbound PF-07321332 Cmax at the intended clinical regimen.

2.5.2.3. Safety pharmacology programme

PF-07321332 was assessed in a series of safety pharmacology studies to assess potential pharmacodynamic effects on vital organ systems (central nervous, cardiovascular, and respiratory).

For the *in vivo* safety pharmacology studies, two studies covering the respiratory and central nervous system in Wistar Han rats, different groups (study 8455743) and the cardiovascular system in cynomolgus monkeys (study 20GR275) were assessed.

Relating to the effects on pulmonary system, administration of 1000 mg/kg of PF-07321332 (Cmax 51.5 µg/ml from rat 2-wk study) single dose resulted in test article related higher respiratory rate (up to +44%) and minute volume (up to +38%) compared with vehicle controls from 40 to 160 minutes post-dose. Relating to the effects on CNS, in the quantitative locomotor assessment, administration of 1000 mg/kg of PF-07321332 single dose resulted in test article-related lower number of mean vertical movement counts (-36%) during the first 5 minutes of the assessment period and higher number of mean horizontal (+298%) and vertical (+838%) movement counts during the last 30 minutes of the assessment period compared with vehicle controls. These effects were observed at exposures 12-fold higher than the anticipated clinical Cmax. A no observed effect level (NOEL) of 60 mg/kg is reported (Cmax 13.3 µg/ml from rat 2-wk study), associated with PF-07321332 exposures 3.2-fold higher than the anticipated clinical Cmax.

Relating to the cardiovascular safety pharmacology study, it was conducted in conscious telemetered male monkeys in a cross-over design. PF-07321332 administered at 150 (75 BID) mg/kg/day (Cmax = 14.7 µg/ml) produced HR decreases of down to -14 bpm from 0.75–16.00 HPD and increased systolic, diastolic and mean blood pressure (up to +5 mmHg) from 0.75–5.5 HPD (diastolic only) and 7.25-9.00 HPD. The RR-interval was increased by up to +52 msec 0.75–16.00 HPD, consistent with the decrease in HR during this same time. Increases in both the PR interval (+3 msec) and QT-interval (up to +13 msec) were observed during the 0.75-9.00 HPD period, which were considered secondary to the decrease in HR. When the QT interval was corrected for HR (QTc), there was a test article-related decrease (down to -7 msec) during the 7.25-16.00 HPD period. It was also noted a decrease in LV +dP/dt max (down to -364 mmHg/sec) during the 0.75-9.00 HPD period. All measures returned to vehicle control levels within 24 HPD. These cardiovascular effects were observed at exposures 3.5-fold higher than the anticipated clinical Cmax. A no observed effect level (NOEL) of 40 (20 BID) mg/kg is reported, associated with PF-07321332 exposures 0.33-fold higher than the anticipated clinical Cmax. From *in vitro* and ex vivo data (studies 200804.QHJ, 20LJ076 and 20J075), there was no clinically meaningful effect of PF-07321332 on hERG, isolated guinea pig heart or isolated rat aorta assays. The IC_{50} values for PF-07321332 inhibition of the Nav1.5 (peak) sodium and the Cav1.2 calcium channel currents were both determined to be >300 µM, (study 20LJ073), which represented 117x the predicted human unbound PF-07321332 Cmax at the intended clinical regimen.

In these studies, no toxicokinetic parameters were included (except one measure of plasma concentration at 150 mg/kg/day in cardiovascular monkey study 20GR275). PF-07321332 Cmax values were extrapolated from 2-week studies in rats. Exposure from 4-week toxicity study are available; since Cmax observed in rats after 4-week administration were lower than those observed after 2-week administration, exposure margins extrapolated from the 2-week study in rat is acceptable. Exposure margins are expressed based on predicted human total PF-07321332 where a BID dose of 300/100 mg PF-07321332/ritonavir resulted in a Cmax of 4.14 µg/ml.

No safety pharmacology studies have been conducted with the combination of PF-07321332 with ritonavir. Given that that ritonavir is used as a PK enhancer and safety pharmacology studies were conducted at concentrations (*in vitro*) and doses (*in vivo*) that yielded exposures significantly higher

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than the predicted PK values of 300 mg/100 mg PF-07321332/ritonavir, the lack of safety pharmacology studies with the combination is acceptable.

2.5.2.4. Pharmacodynamic drug interactions

In vivo pharmacodynamic drug interaction studies with PF-07321332 have not been conducted. *In vitro* antiviral activity of PF-07321332 is discussed in the clinical pharmacology section.

2.5.3. Pharmacokinetics

The LC-MS/MS methods implemented were validated for the quantitation of PF-07321332 in plasma. No analytical methods were developed for quantitation of circulatory metabolites of PF-07321332 or quantitation of PF-07321332 in tissues in GLP toxicity studies given that no quantifiable metabolites of PF-07321332 in human plasma were observed when PF-07321332 is co-administered with ritonavir.

The absorption was evaluated in two single dose administration studies in rat and monkey to study the PK profile of PF-07321332 (studies 103131 and 111728). PF-07321332 was rapidly absorbed and exhibited a moderate CL, with a moderate to low Vss, resulting in t½ values of 5 hours in rats and <1 hour in monkeys. Following oral dosing, the overall bioavailability was moderate to high (29 to >100%) in rats but low (<10%) in monkeys. Repeat dose pharmacokinetics of PF-07321332 were evaluated following 14- or 15-day administration in the toxicity studies in rats and monkeys (studies 20GR276 and 20GR289) and in embryo-foetal development (EFD) studies in rats and rabbits (21GR132 and 21GR126). In rats, systemic exposures increased with dose and decreased with treatment duration. In monkeys, while systemic exposures also increased with dose, there was no decrease in exposure with treatment duration. On the contrary, in the 4-week study, at the two highest tested doses, exposures were higher at the end of treatment compared to Day 1. There were no consistent sex-related differences in systemic exposure. Systemic exposure increased with increasing doses in pregnant rats and rabbits.

The distribution study results showed that PF-07321332 was moderately bound to plasma proteins in rat, monkey and human and similar across these species (study 010657). Concentration-dependent protein binding was observed in rabbit plasma (YDP/067/394). PF-07321332 preferentially distributed into plasma relative to blood cells in rat, monkey and human (study 100444).

An *in vivo* distribution study (quantitative whole-body autoradiography, QWBA) is on-going. The results from that study should be provided as it will provide an understanding of the distribution of 14C-labelled drug-related material in tissues.

The metabolism of PF-07321332 was evaluated *in vitro* in liver microsomes, hepatocytes and *in vivo* in rats and monkeys (studies 084546, 072016, 082057, 021055, 090141). A total of six metabolites were detected arising from hydroxylation, dehydrogenation, and hydrolysis reactions. The major metabolite was M4 (PF-07329268). In plasma of rats and monkeys, unchanged parent drug was the most prevalent drug-related entity, with M4 as a major metabolite in monkeys. All oxidative metabolites were formed by CYP3A4/5, with other CYP enzymes contributing very minor amounts. Unchanged parent drug was also the most prevalent drug-related entity in rat urine and bile. In human plasma unchanged PF-07321332 was the main circulated compound, M4 and M5 were found at trace levels.

The urinary and/or biliary excretion was assessed in single-dose PK studies after IV or oral dosing of PF-07321332 to rats (study 103131) and monkeys (study 111728). The percentage of PF-07321332 dose excreted unchanged was 17% in the urine, 9% in the bile, and up to 11% in the faeces in rats, and 7% in the urine and 4% in the faeces in monkeys. The low percentage of PF-07321332 dose

excreted unchanged in urine, bile, and faeces along with the relatively low CLr suggests minor urinary and biliary contributions to the overall elimination of PF-07321332.

Mass balance excretory pathways and metabolic profile of unlabelled PF-07321332 was also assessed (studies 014401 and 021626). The primary excretion routes of orally administered PF-07321332 with ritonavir were urinary excretion of unchanged drug. In urine and faeces, unchanged PF-07321332 accounted for 82.5% of the drug material (55% in urine and 27.5% in faeces). M5 was present at 12.1% in faeces and urine, M8 (PF-07331782) at 4.2%, m/z 519 at 0.8% and M7 (acyl glucuronide of M5) at 0.3%of the dose. In rabbit and in monkey, M3, M4, M5 and m/z 498 were detected in plasma. All of these metabolites are below 10% the threshold specified in ICH M3 requested for toxicity assessment and no quantifiable metabolites of PF-07321332 in human plasma were observed when PF-07321332 is co-administered with ritonavir.

Animal data suggested minor urinary and biliary contributions to the overall elimination of PF-07321332 whereas clinical results suggested that the primary excretion routes of orally administered PF-07321332 with ritonavir were urinary excretion of unchanged drug.

2.5.4. Toxicology

The toxicology programme for PF-07321332 has been designed in line with the requirements of ICH M3 (R2) and taking into consideration the proposed treatment duration of 5-days.

2.5.4.1. Single dose toxicity

No single dose toxicity study was performed.

2.5.4.2. Repeat dose toxicity

The species used for the GLP compliant pivotal studies included rats and monkeys based on similar PK profile seen in these species compared to human. Furthermore, the pharmacological target of PF-07321332 is an exogenous entity (virus-specific protein) and therefore there are no pharmacologically relevant species. The oral route of administration was selected as it is the route of clinical administration.

The toxicity of PF-07321332 was evaluated in 4 GLP repeat-dose toxicity studies up to 1 month in duration in rats (studies 20GR276 and 21GR122) and cynomolgus monkeys (20GR289 and 20GR125). Two preliminary 4-days studies in rats (20GR250) and monkeys (20GR271) were also evaluated.

Rats were administered once daily and monkeys twice daily as in human. This administration twice daily in monkeys was not supported by $T_{1/2}$ which is <1h, however this regimen scheme was performed to mimic clinical regimen. Final reports have been submitted for the studies except for the 1-month study in rats and in monkeys (unaudited draft).

There were no adverse findings in any of the studies. The NOAELs were the highest doses administered 1000 mg/kg in rat and 600 mg/kg (300 BID) in monkeys and represented 11x/8.0x and 21x/14x for rats and monkeys (Cmax/AUC24), respectively, over the predicted human total PF-07321332 Cmax and AUC24 at a dose of 300/100 mg PF-07321332/ritonavir BID. Margins of exposure were calculated based on toxicokinetic data from the 2-week rat repeated dose toxicity study (20GR276) and predicted human total PF-07321332 Cmax of 4.14 µg/mL and AUC24 of 68.6 µg h/mL at a BID dose of 300/100 mg PF-07321332/ritonavir, therefore the margins of exposure are only indicative at this stage as the PopPK model is only based on PK data collected from healthy volunteers. All non-adverse test article related clinical findings observed in rats (salivation and soft faeces, increases in aPPT, prothrombin,

platelet count) or in monkeys (sporadic occurrence of emesis, increases in ALT, AST, fibrinogen) are monitorable in human. Test article related effects associated with the oral administration of PF-07321332 to rats up to 1000 mg/kg/day for 1-month were limited to non-adverse findings in the liver, thyroid and pituitary gland. The pattern of linked findings in the liver, thyroid and pituitary glands are consistent with a rat specific response to hepatic enzyme induction resulting in increased thyroxine catabolism, raised serum thyroid stimulating hormone and thyroid follicular cell hypertrophy and anterior pituitary vacuolation (Childs et al, 1982; Greaves, 2012; Rosol et al, 2013). This mechanism is usually considered to have little to no relevance to humans mostly because of the marked differences in plasma half-life of thyroid hormones and in binding to transport proteins between rodents and humans (Rosol et al, 2013). No such findings were observed in monkeys.

2.5.4.3. Genotoxicity

PF-07321332 was assessed in a series of genetic toxicity studies consisting of the microbial bacterial reverse mutation, *in vitro* cytogenetic (micronucleus in human lymphoblastoid TK6 cells), and *in vivo* rat micronucleus assay up to 1000 mg/kg/day (studies 20GR288, 20GR286 and 20GR276a). All *in vitro* tests were conducted with and without exogenous metabolic activation using concentrations up to applicable guideline limits or those limited by cytotoxicity or insolubility. PF-07321332 was not genotoxic in either *in vitro* or *in vivo* assays.

2.5.4.4. Carcinogenicity

No carcinogenicity studies have been performed. Considering that the duration of treatment is limited to 5 days, the absence of carcinogenicity studies is in-line with the recommendations of ICH S1A. There are no microscopic findings indicative of pre-neoplastic changes from the limited duration repeat dose toxicity studies.

2.5.4.5. Reproductive and developmental toxicity

Fertility and embryo-foetal development studies were evaluated in rats and rabbits with PF-07321332 (studies 21GR146, 21GR132 and 21GR126). Pre- and postnatal development was evaluated in rats (21GR149) based on the interim results.

In the fertility study, there was no adverse effect of PF-07321332 on parental endpoints and on the reproductive performance of male and female rats treated at doses up to 1000 mg/kg/day from 14 days premating. C-section data did not highlight any treatment-related adverse effect on early embryonic development in the treated vs. concurrent control group. At the NOAEL of 1000 mg/kg/day for parental toxicity and fertility, the AUC-based exposure ratio reached 4.3.

In the rat embryo-foetal development study, PF-07321332 was not shown to induce maternotoxicity, foetotoxicity or teratogenicity at doses up to 1000 mg/kg/day administered during the whole period of organogenesis. Foetal examination showed increased litter and foetal incidences of 27th presacral vertebrae (skeletal variation) at the high dose level compared to concurrent controls (litter: 6%, 0%, 5%, 21%; foetal: 0.93%, 0.00%, 0.56%, 4.29%) and outside historical control range (litter: 0-10.5%; foetal: 0-2.4%). Since there were no associated skeletal malformations or variations in associated structures, or any other adverse effect on embryo-foetal development, this finding could be considered as non-adverse. Overall, the maternal and developmental NOAEL was 1000 mg/kg/day in rats. At this dose level, the AUC-based exposure ratio was 7.8.

In the rabbit embryo-foetal development study, slight effects on maternal body weight gain and food consumption were noted during the treatment period at the high dose level of 1000 mg/kg/day, but

were not considered as adverse based on low magnitude of difference from control and lack of impact on absolute body weights. PF-07321332-related, adverse, lower foetal weight (0.91x control) was observed at 1000 mg/kg/day. At foetal examination, the foetal and/or litter incidences of a skeletal malformation (fused sternebrae) and visceral/skeletal variations (small gallbladder, misaligned sternebrae, bent hyoid arch) were increased compared to those in both concurrent and historical controls. As regards the increased incidence of small gallbladder, a paternally-mediated effect (see e.g. Stomp et al 2012) could not be excluded based on further analysis of sire records. Overall, the developmental NOAEL in rabbits was 300 mg/kg/day and corresponds to an AUC-based exposure ratio of 2.8.

In the ongoing pre- and postnatal development toxicity study conducted in rats, a significant decrease in preweaning pup body weight gain from PND 10-17 at 1000 mg/kg/day was observed and translated into a decrease in pup body weight on PND 17 and 21. This effect seems transient since there is no significant impact on F1 offspring body weight or body weight gain from PND 21-56. In comparison to the interim results, with the final results additional data on any potential treatment-related effects on F1 oestrous cycles, reproductive performance (incl. intrauterine survival of F2 embryos), neurobehavior (auditory startle response, motor activity, learning and memory), and macroscopic examination at necropsy will be reported.

As regards ritonavir, developmental toxicity was identified in rats and rabbits mainly at maternally toxic dose levels, whereas there was no effect on fertility in rats.

PF-07321332 does not present a phototoxicity potential. No combination studies with administration of PF-07321332 with ritonavir have been conducted. Ritonavir is an already marketed drug as a PK enhancer with well characterised nonclinical and clinical safety profiles. No PD activity of ritonavir at 100 mg (BID) dose is expected and no overlapping or additive toxicities between PF-07321332 and ritonavir are expected since no target organs have been identified after PF-07321332 administration in rats and monkeys up to 1-month duration. A combination toxicity study, therefore, will not provide any additional information beyond the known individual toxicity profiles of PF-07321332 and ritonavir.

2.5.4.6. Local tolerance

Local tolerance studies with PF-07321332 have not been conducted.

2.5.5. Ecotoxicity/environmental risk assessment

An ERA for Paxlovid was performed according to the current guideline, the phase II assessment is still ongoing. Results of OECD107 study indicated LogDow < 4.5 for PF-07321332, therefore there is no need to screen PBT potential of PF-07321332. The PECsw value for PF-07321332 with 5 days of treatment (0.041 µg/L) is still higher than the 0.01 µg/L action limit. For ritonavir, reference is made to literature for LogDow value (< 4.5). No study report or detailed description of the conditions of the performed test was provided. The Log Dow for ritonavir needs to be determined experimentally according to the current guideline and sufficient details of the test performance need to be provided to determine the acceptability of the study. The PECsw value for ritonavir with 5 days of treatment (0.014 µg/L) is also higher than the 0.01 µg/L action limit.

2.5.6. Discussion on non-clinical aspects

The non-clinical studies are submitted in accordance with legal requirements; available guidelines and scientific advice has been followed.

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Pharmacology

In vitro primary pharmacodynamic data is discussed under the clinical pharmacology section of this assessment report.

The *in vivo* proof of concept studies consistently support the antiviral activity of PF-07321332, as demonstrated by reduced infectious lung titres and ameliorated indicators of disease (weight loss and lung pathology) compared to placebo-treated animals in mouse models with mouse-adapted SARS-CoV-2 infection in BALB/c and 129 mouse strains. While ritonavir at booster dose does not exhibit an *in vitro* antiviral activity on SARS-CoV-2, the applicant confirmed there is an ongoing *in vivo* study with PF-07321332 in combination with ritonavir using a mouse-adapted (MA) model of SARS-CoV-2 infection (MA-SARS-CoV-2) in BALB/c mice. The final study report should be provided (**REC**). At the present stage, the lack of this study for the combination PF-07321332/ritonavir is acceptable given that ritonavir is used as a PK enhancer and the lack of antiviral effect by ritonavir. However, ritonavir affects both 07321332 metabolism and transport. This study is considered essential for a better understanding of PF-07321332 distribution and efficacy following co-administration of PF-07321332 and ritonavir.

No off-target was identified in secondary PD studies up to 100 µM (39x the predicted human unbound Cmax at the intended clinical regimen).

All pivotal safety pharmacology study reports contain GLP compliance statements, indicating they have been conducted in accordance with the principles of GLP, in an OECD MAD adherent country. Both *in vitro* and *in vivo* studies were conducted to address the safety pharmacology core battery, in line with ICH S7A. A higher respiratory rate (up to +44%), a higher minute volume (up to +38%), a lower number of mean vertical movement counts during the first 5 minutes of the assessment period (up to 36%) and a higher number of mean horizontal (+298%) and vertical (+838%) movement counts during the last 30 minutes were observed in rats after a single administration of 1000 mg/kg of PF-07321332 (12-fold higher than the anticipated clinical Cmax). In telemetered male monkeys the highest tested dose (150 (75 BID) mg/kg/day, 3.5-fold higher than the anticipated clinical Cmax) produced HR decreases of down to -14 bpm from 0.75–16.00 HPD and increased systolic, diastolic and mean blood pressure (up to +5 mmHg) from 0.75–5.5 HPD (diastolic only) and 7.25-9.00 HPD. The RR-interval was increased by up to +52 msec 0.75–16.00 HPD, consistent with the decrease in HR during this same time. Increases in both the PR interval (+3 msec) and QT-interval (up to +13 msec) were observed during the 0.75-9.00 HPD period, which were considered secondary to the decrease in HR. When the QT interval was corrected for HR (QTc), there was a test article-related decrease (down to -7 msec) during the 7.25-16.00 HPD period. PF-07321332 at 150 (75 BID) mg/kg/day also produced decreases in LV +dP/dt max (down to -364 mmHg/sec) during the 0.75-9.00 HPD period. These effects on safety pharmacology parameters were monitored in clinical trials and no safety concerns were identified and will be followed with the PSUR.

Pharmacokinetics

A nonclinical pharmacokinetic programme was carried out to evaluate the ADME properties of PF-07321332. All studies are available except the ongoing *in vivo* QWBA study performed with PF-07321332 (alone) which study report is requested by 31/03/2022 together with the applicant's assessment (**LEG**).

Toxicology

The non-clinical toxicology package for PF-07321332 has been designed in line with the requirements of ICH M3 (R2) and taking into consideration the proposed treatment period of 5-days in duration. All pivotal safety pharmacology study reports contain GLP compliance statements, indicating they have been conducted in accordance with the principles of GLP, in an OECD MAD adherent country.

Repeated dose toxicity study final reports have been submitted except for 1-month in rats and in monkeys. These final study reports 21GR122 and 21GR125 are requested by 31/01/2022 (**LEG**). In relation to reproductive and developmental toxicity, a rat fertility study and two EFD studies in rats and rabbits are completed and submitted. The pre- and postnatal development study was ongoing; the interim report has been provided. The final study report for the PPND (21GR149) is requested by 30/04/2022 (**LEG**). The applicant's submission of new non-clinical data should be accompanied with an updated non-clinical overview and related updated tabulated and written summaries.

The toxicity of PF-07321332 was evaluated in 4 pivotal GLP repeat-dose toxicity studies up to 1 month in duration in rats and cynomolgus monkeys. There were no adverse findings in any of the studies. The NOAELs were the highest doses administered (1000 mg/kg in rat and 600 mg/kg (300 BID) in monkeys and represented 11x/8.0x and 21x/14x for rats and monkeys(Cmax/AUC24), respectively, over the predicted human total PF-07321332 Cmax and AUC24 at a dose of 300/100 mg PF-07321332/ritonavir BID. The margins of exposure are only indicative at this stage. All non-adverse test article related clinical findings observed in rats (salivation and soft faeces, increases in aPPT, PT, PLT count) or in monkeys (sporadic occurrence of emesis, increases in ALT, AST, fibrinogen) are monitorable in human.

The margins of exposure are therefore only indicative at this stage and it is expected to be further substantiated with the awaited provision of a relevant PopPK model including PK data collected from the patients enrolled in the EPIC-HR study with relevant covariables to be studied (notably age, weight, formulation). The PopPK model should be updated and provided once available (refer to clinical pharmacology LEG).

The standard genotoxicity battery was performed, and negative results are acceptable by CHMP.

No adverse effect of PF-07321332 on fertility parameters were observed up to 1000 mg/kg/day (AUC-based exposure ratio reached 4.3). No effect of PF-07321332 on embryo-foetal development were observed in rats up to 1000 mg/kg/day (AUC-based exposure ratio was 7.8). In the rabbit embryo-foetal development study, slight effects on maternal body weight gain and food consumption were noted during the treatment period at the high dose level of 1000 mg/kg/day, but were not considered as adverse based on low magnitude of difference from control and lack of impact on absolute body weights. PF-07321332-related, adverse, lower foetal weight (0.91x control) was observed at 1000 mg/kg/day. The developmental NOAEL in rabbits was 300 mg/kg/day and corresponds to an AUC-based exposure ratio of 2.8. This is adequately reflected in section 5.3 of the SmPC. In the ongoing pre- and postnatal development toxicity study conducted in rats, a significant decrease in preweaning pup body weight gain from PND 10-17 at 1000 mg/kg/day was observed and translated into a decrease in pup body weight on PND 17 and 21. This effect seems transient since there is no significant impact on F1 offspring body weight or body weight gain from PND 21-56.

PF-07321332 does not present a phototoxicity potential. No combination studies with administration of PF-07321332 with ritonavir have been conducted.

An ERA for Paxlovid was performed according to the current guideline, the phase II assessment is still ongoing. The PECsw value for PF-07321332 with 5 days of treatment (0.041 µg/L) is higher than the 0.01 µg/L action limit. Based on literature, for ritonavir there is a Log Dow value (< 4.5). The Log Dow for ritonavir needs to be determined experimentally according to the current guideline and sufficient details of the test performance need to be provided to determine the acceptability of the study. The applicant needs to clarify this point in the further ERA update. The PECsw value for ritonavir with 5 days of treatment (0.014 µg/L) is also higher than the 0.01 µg/L action limit. The ERA part II should be provided (**REC**).

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2.5.7. Conclusion on the non-clinical aspects

The applicant sufficiently addressed concerns raised for the purpose of granting a CMA in an emergency situation.

The CHMP is of the view that non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

The CHMP considers the following measures necessary to address the non-clinical issues:

a) The ongoing whole body autoradiographic study in rats with PF-07321332 (alone) should be provided by 30 April 2022.

b) The final reports of the two on-going repeat-dose toxicity studies (21GR122 and 21GR125) should be provided by 31 January 2022.

c) The final report of the on-going pre- and post-natal development study (21GR149) should be provided by 30 April 2022.

Nonclinical recommendations and legally binding measures are covered in Annex I.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

No routine GCP inspection was conducted for this application and no issues and/or concerns that would warrant the need for a GCP inspection were identified during the assessment of the clinical data submitted in support of the application. This is in addition to the listing of any GCP inspections conducted, with the respective reports, the standard statement that the applicant claimed GCP compliance of all trials included in the application and the statement of compliance with Directive 2001/20/EC for trials conducted outside the EU.

Table 1. Tabular overview of clinical studies

Study ID	Study Title	Study Details/Primary Endpoints	Total Sample Size
Study 1001 (Completed)	A Phase 1, randomised, double-blind, sponsor-open, placebo controlled, single-	FIH study of PF-07321332 in healthy adult participants. Study 1001 is a 5-part study.	

Study ID	Study Title	Study Details/Primary Endpoints		Total Sample Size
	and multiple-dose escalation study to evaluate the safety, tolerability, and pharmacokinetics of PF-07321332 in healthy adult participants	PART-1 (SAD) PART-2 (MAD) PART-5 (supratherapeutic exposures for QTc assessment)	Frequency, severity, and causal relationship of TEAEs and withdrawals due to TEAEs. Frequency and magnitude of abnormal laboratory findings. Changes from baseline in vital sign measurements and 12-lead ECG parameters	PART-1: 13 participants PART-2: 29 participants PART-5: 10 participants
		PART-3 (relative bioavailability):	Ratio of AUC_{last}, AUC_{inf} and C_{max} of tablet formulation and suspension	PART-3: 12 participants
		PART-4 (metabolism and excretion):	Percent recovery and cumulative recovery of drug-related material in urine and feces	PART-4: 6 participants
Study 1010 (Ongoing)	A Phase 1, non-randomised, open-label study to assess the pharmacokinetics, safety and tolerability of PF-07321332 boosted with ritonavir in adult participants with moderate hepatic impairment and healthy participants with normal hepatic function	Plasma PF-07321332 PK parameters: C_{max}, AUC_{last}, AUC_{inf} (if data permit)		8 participants without hepatic impairment and 8 participants with moderate hepatic impairment
Study 1011 (Completed)	A Phase 1, non-randomised, open-label study to assess the pharmacokinetics, safety and tolerability of PF-07321332 boosted with ritonavir in adult participants with renal impairment and in healthy participants with normal renal function	Plasma PF-07321332 PK parameters: Cmax, AUC_{inf} (or AUC_{last} if AUC_{inf} cannot be reliably estimated) Urine PF-07321332 PK parameters: A_e, CL_r, if applicable and as data permit		34 participants (8 each in mild, moderate, severe renal impairment, and 10 healthy participants)
Study 1012 (Ongoing)	A Phase 1, open-label, 3-treatment, 6-sequence, 3-period cross-over study to estimate the effect of PF-07321332/ritonavir and ritonavir on the pharmacokinetics of dabigatran in healthy participants	AUC_{inf} and C_{max} of dabigatran with PF-07321332/ritonavir (test) versus dabigatran alone (reference)		~ 24 healthy participants

Study ID	Study Title	Study Details/Primary Endpoints	Total Sample Size
Study 1013 (Ongoing)	A Phase 1, open-label, 3-treatment, 6-sequence, 3-period crossover study to estimate the effect of PF-07321332/ritonavir and ritonavir on the pharmacokinetics of midazolam in healthy participants	AUC_{inf} and C_{max} of midazolam with PF-07321332/ritonavir (test) versus midazolam alone (reference)	~12 healthy participants
Study 1014 (Completed)	A Phase 1, open-label, fixed sequence, 2-period crossover study to estimate the effect of carbamazepine on the pharmacokinetics of PF-07321332 boosted with ritonavir in healthy participants	PF-07321332 C_{max} and AUC_{inf} with carbamazepine (test) versus without carbamazepine (reference)	12 healthy participants
Study 1015 (Completed)	A Phase 1, open-label, fixed sequence, 2-period crossover study to estimate the effect of itraconazole on the pharmacokinetics of PF-07321332/ritonavir in healthy participants	PF-07321332 C_{max} and AUC_{tau} with itraconazole (test) versus without itraconazole (reference)	12 healthy participants
Study 1005 (Completed)	An interventional efficacy and safety, Phase 2/3, double-blind, 2-arm study to investigate orally administered PF-07321332/Ritonavir compared with placebo in non-hospitalised symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illness	Primary objective: • To compare the efficacy of PF-07321332/ritonavir to placebo for the treatment of COVID-19 in non-hospitalised symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease. Primary endpoint: • Proportion of participants with COVID-19 related hospitalisation or death from any cause through Day 28.	Total ~3100

Study 1005 (EPIC-HR, C4671005) is the single pivotal study supporting this conditional marketing authorisation application. This Phase 2/3, randomised, double-blind, placebo-controlled study in non-hospitalised, symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illness will determine the efficacy, safety, and tolerability of PF-07321332/ritonavir compared with placebo in a 1:1 ratio.

Additionally, there are on-going studies 1002 and 1006 for the treatment of COVID-19 in patients who are at low risk of progressing to severe disease and in the preventing of symptomatic SARS CoV-2 infection in adult household contacts of individuals with symptomatic COVID-19, respectively.

2.6.2. Clinical pharmacology

Paxlovid (PF-07321332/ritonavir) is a combination therapy of PF-07321332, a new chemical entity, which is a potent and selective peptidomimetic inhibitor of the SARS-CoV-2 3CL, a viral encoded enzyme that is critical to SARS-CoV-2 replication cycle, and ritonavir.

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In the current submission, the applicant is seeking an initial approval for Paxlovid for the treatment of adult and adolescent patients (12 years of age and older weighing at least 40 kg) with symptomatic, confirmed COVID-19 who are at high risk for progressing to severe disease, including hospitalisation and/or death.

The proposed recommended oral dose of PF-07321332/ritonavir is 300 mg/100 mg twice daily (BID). The drug product for registration is a tablet containing PF-07321332 at one strength 150 mg and a tablet containing ritonavir at one strength 100 mg.

The clinical pharmacology programme as presented in Table 1 consisted of 7 Phase 1 studies performed completed or ongoing in healthy volunteers. The following Phase 1 studies have been conducted:

- 1 SAD and MAD study in Caucasian and Japanese healthy subjects (Study 1001)
- Relative bioavailability, QTc analysis, food effect and mass balance study (Study 1001)
- 6 PK studies investigating intrinsic (Studies 1010 and 1011 for respectively hepatic and renal impairment) and extrinsic factors (Studies 1012, 1013, 1014, 1015).

Phase 1 studies 1012, 1013 and Phase 2/3 studies 1002 and 1006 are ongoing. PK data from these studies will be submitted as soon as they become available.

A population PK analysis was performed and comprised PK data from healthy volunteers only. In addition, a simulation exercise was performed (separated report) to evaluate the predictive performance of the developed Pop-PK model on the observed PK data in patients from Study 1005.

2.6.2.1. Pharmacokinetics

Methods

Analytical methods

Throughout the clinical development, two bioanalytical methods were developed to quantify, simultaneously, PF-07321332 and ritonavir, in human K2EDTA plasma (Report c4679002), and only PF-07321332 in urine (Report c4679003). Both methods were developed and validated by York Bioanalytical Solution (York, YO26 6QR, UK).

Generally, the used bioanalytical methods appear to be adequate and comply with acceptance criteria of the bioanalytical method validation EMA Guideline. Description and validation reports were provided with satisfactory results regarding specificity, sensitivity, precision, accuracy, dilution factor linearity, matrix effect. Short and long-term stability of the analytes in biological matrix were tested and shown to be satisfactory. ISR were provided for each study with satisfactory results (100%).

Pharmacokinetic data analysis

Standard non-compartmental (model-independent) PK methods were used to calculate PK parameters (C_{max}, C_{min}, T_{max}, AUCs, CL/F and Vz/) using the NCA approach.

The Population PK analysis (Report PMAR-EQDD-C467a-POC-1246) was performed using a nonlinear mixed effects modelling methodology as implemented in the nonlinear mixed effects modelling (NONMEM) software system, version 7.5.0, using first-order conditional estimation method with interaction (FOCEI) as the estimation method.

Perl-speaks-NONMEM (PsN) version 5.2.6 was used for prediction corrected visual predictive check (pcVPC), and sampling importance resampling (SIR) for generating the model parameter uncertainty.

R (version 4.0.3) and/or R libraries was/were used for data manipulations, exploratory graphical and numerical analyses, model diagnostics, post-processing of NONMEM output, creation of simulation data sets, as well as data summary.

Overall, the standard NCA and the population methodology are acceptable for PK data analyses.

Statistical analysis

Generally, standard summary statistics (e.g. mean, median, standard deviation [SD], and coefficient of variation [CV]) have been generated. For comparison, in most cases the 90 % confidence intervals (CI) were calculated in case of equivalence testing. In addition, in case significance levels were used, the significance level in most trials was 5%. This was considered acceptable.

Absorption

Following oral single administration, at the recommended dose of PF-07321332/ritonavir 300 mg/100 mg, median Tmax was 3 hours and ranged between 1 to 6 hours, indicating that absorption is rapid. For note, the observed geometric mean PF-07321332 (CV%) Cmax and AUCinf were 2.21 µg/mL (33) and 23.01 µg*hr/mL (23), respectively.

Absolute Bioavailability

The absolute bioavailability of PF-07321332 was not investigated.

Relative bioavailability / Bioequivalence

Several oral formulations of PF-07321332 were developed and evaluated during the development programme:

- An extemporaneously prepared oral suspension used in Studies **1001** and **1015**
- An uncoated 250 mg immediate release (IR) tablet used for Study **1001** (Part 3)
- A 100 mg IR film-coated tablet used for Study **1011** and in a few patients in the Phase 2/3 Study **1005**
- A 150 mg IR film-coated tablet used for Study **1005** and other Phase 2/3 studies (Studies **1002** and **1006**) as well as in a Phase 1 study **1014.**
-

The clinical study supplies for the 150 mg tablets used for the pivotal phase 3 study **1005** were manufactured at both the Pfizer Groton (Connecticut, USA) and Freiburg (Germany) using identical formulation and manufacturing process.

The proposed commercial formulation dosage form for PF-07321332 is two 150 mg IR film-coated tablets and one 100 mg tablet of ritonavir.

Comparison of uncoated tablet 250 mg versus suspension 250 mg

The relative bioavailability of PF-07321332 formulated as the 250 mg tablet vs 250 mg oral suspension was evaluated in Study **1001** (Part 3) in 12 healthy volunteers without ritonavir combination, as part of an open label, randomised, 3 period, 3 sequence cross-over design (food effect also investigated, please refer to the next section) with a wash-out period of 2 days.

The estimated ratio of geometric means for Cmax was 56.38% (90% CI of the ratio 43.42%-73.19%) and for AUClast was 81.21% (90% CI of the ratio 69.21%–95.28%). Cmax and AUClast of uncoated tablet was reduced by 44% and 19%, respectively compared to the suspension formulation.

Dissolution profiles of the tablet 100 mg vs 150 mg

The comparability of PF-07321332 film coated tablets from representative batches of 100 mg and 150 mg was investigated through dissolution profiles comparison at a clinical dose of 300 mg (3X 100 mg vs 2 x 150 mg) at three different pH. An f2 test was calculated to assess similarity of dissolution profiles between the two tablet formulations, and all values were ≥50 suggesting equivalence in dissolution performance of PF-07321332 3x100 mg versus 2x150 mg tablets.

Dissolution profiles of tablet 150 mg by site Manufacturing

The dissolution performance of representative batches of PF-07321332 150 mg film-coated tablets manufactured at Groton, CT, US and Freiburg; Germany sites was assessed in dissolution media over the physiological pH range. Similarly, to the preceding the estimated f2 were ≥50 suggests that *in vitro* dissolution performances are equivalent.

Influence of food

The effect of a high fat meal was investigated at two levels, following the administration of 250 mg PF-07321332 alone (Study **1001** –**Part 3**) or in combination with ritonavir (Study **1001 Part 1**) in a cross-over design.

Results, indicated that relative to fasted conditions and in combination with ritonavir, administration with high-fat meal causes only a slight increase on Cmax (geometric mean ratio of 1.15) and no evident effect on exposure AUCs (geometric mean ratios of 1.01 and 1.01, for AUC0-t, AUC0-inf respectively). Tmax was delayed by 1.25 h and half-life slightly increased by 1h in the fed state compared to fasted state (6.9 vs 6 h).

Overall, the applicant preconise that commercial tablet formulation could be administered without regards to food. The proposed dosing recommendation could be supported.

Table 2. Statistical summary of plasma PF-07321332 PK parameters when administered with ritonavir- Food effect (Part 1 SAD, Study 1001)

	Adjusted Geometric Means			
Parameter (Unit)	PF-07321332 250 mg Suspension/ ritonavir 100 mg, Fed (Test)	PF-07321332 250 mg Suspension/ ritonavir 100 mg, Fasted (Reference)	Ratio (%) (Test/Reference) of Adjusted Geometric Means[a]	90% CI (%) for Ratio[a]
AUC_{inf} (ng.hr/mL)	28640	28220	101.52	(89.57, 115.07)
AUC_{last} (ng.hr/mL)	28020	27600	101.53	(90.18, 114.31)
C_{max} (ng/mL)	3323	2882	115.30	(99.36, 133.79)

Influence of gastric modifier

The influence of gastric modifier was not investigated.

Distribution

PF-07321332 was found to be weakly bound to plasma protein (69%). B/P ratio was approximately 0.6 indicating a limited penetration of PF-07321332 into red blood cells.

Following administration of PF-07321332/ritonavir supplied as tablet formulation at 300 mg/100 mg, the mean apparent volume of distribution (Vz/F) in healthy volunteers was 109.4 L. For note, results from the PopPK analysis (based on 20 healthy volunteers using the oral suspension) indicated a total apparent distribution volume of 111 L for a 300 mg/100 mg (theoretical dose).

Elimination

The excretion and biotransformation of a 300mg/100 mg PF-07321332/ritonavir oral dose as suspension was investigated in 6 healthy subjects using ^{19}F-NMR and HPLC-MS/MS methods.

By quantitative ^{19}F-NMR, mean ± SD (range) mass recovery was 84.9% ± 8.9% (70.7-95.5%) which consisted of PF-07321332 at 80.7± 8% and M8 metabolite at 4.2%± 1.3% (silent due to loss of trifluoroacetyl group). The excretion into urine and faeces was 48.6% and 35.3%, respectively, mainly as unchanged PF-07321332. Most material excreted in urine emerged in the first 24 h while in faeces in 5 days.

PF-07321332 was found to be predominantly metabolised by CYP3A enzymes. Metabolite profiling was performed in the three matrices (plasma, urine and faeces). In plasma unchanged PF-07321332 was the main circulated compound, M4 and M5 were found at trace levels. In urine and faeces after normalisation of the data to complete mass balance, unchanged PF-07321332 accounted for 82.5% of the drug material (55% in urine and 27.5% in faeces). M5 was present at 12.1% in faeces, M8 at 4.2% in plasma. The proposed metabolic scheme is presented in the following figure.

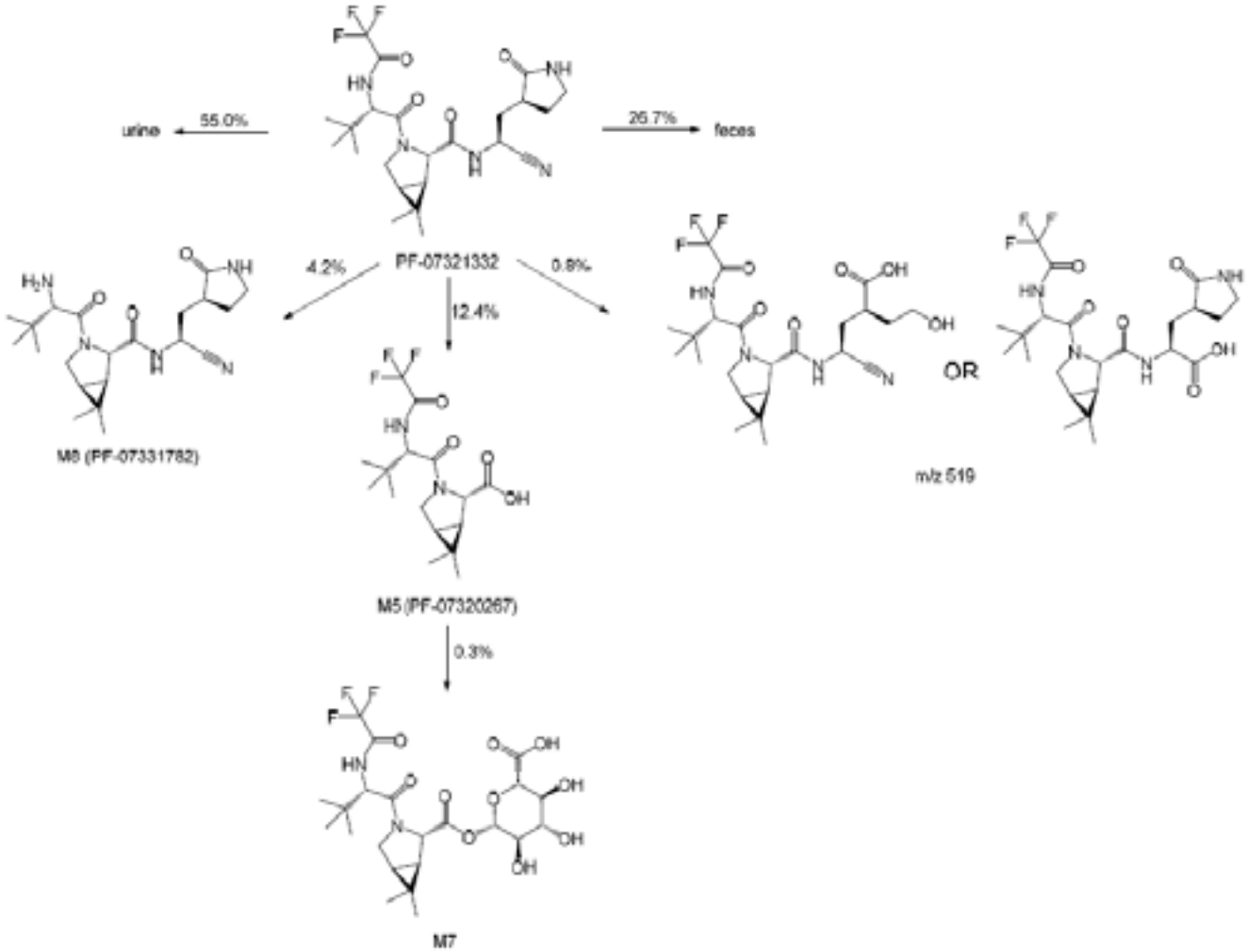

Figure 4 : Summary profile of PF-07321332 metabolism and disposition in healthy participant

Across clinical studies in healthy volunteers after single or multiple oral doses of PF-07321332/ritonavir as oral suspension half-life ranged from 6.8 to 9.5 h. After single oral dose PF-07321332/ritonavir as tablet formulation half-life ranged from 6.05 to 7.72 h. At the recommended 300/100 mg PF-07321332/ ritonavir dose in the fasted state, the arithmetic mean (+SD) terminal elimination half-life of PF-07321332, following single dose was 6.1 (1.8) hours.

Dose proportionality and time dependency

Dose proportionality

Dose proportionality of PF-07321332 (with or without ritonavir) was investigated following single and multiple escalating oral dose in healthy volunteers during Study 1001.

Part 1 (SAD) of Study 1001

The interval of investigated doses ranged from 150 to 1500 mg for PF-07321332 (without ritonavir) and PF-07321332/ritonavir at two dose levels 250 and 750 mg. PK parameters following SAD of PF-07321332 (with or without ritonavir) as oral suspension are presented in Table 3 and associated median PK profiles in Figure 5.

Table 3. Descriptive summary of plasma PF-07321332 PK parameters (Part 1 –SAD, Study 1001)

Parameter (Unit)[a,b]	PF-07321332 150 mg (Suspension), Fasted (N=4)	PF-07321332 500 mg (Suspension), Fasted (N=4)	PF-07321332 1500 mg (Suspension), Fasted (N=4)	PF-07321332 250 mg (Suspension)/ ritonavir 100 mg, Fasted (N=4)	PF-07321332 250 mg (Suspension)/ ritonavir 100 mg, Fed (N=4)	PF-07321332 750 mg (Suspension)/ ritonavir 100 mg, Fasted (N=4)
N1, N2	4, 3	4, 2	4, 0	4, 4	4, 4	4, 4
AUC_{inf} (ng.hr/mL)	2247 (42)	5480, 5450	NR	28220 (14)	28640 (17)	66760 (45)
AUC_{inf}(dn) (ng.hr/mL/mg)	14.97 (42)	11, 10.9	NR	112.8 (14)	114.2 (17)	89.14 (45)
AUC_{last} (ng.hr/mL)	2125 (34)	3753 (29)	10870 (47)	27600 (13)	28020 (16)	64230 (39)
AUC_{last}(dn) (ng.hr/mL/mg)	14.15 (34)	7.507 (29)	7.247 (47)	110.4 (13)	112.0 (16)	85.77 (40)
CL/F (L/hr)	66.83 (43)	91.2, 91.8	NR	8.865 (14)	8.735 (17)	11.22 (45)
C_{max} (ng/mL)	667.7 (28)	674.4 (38)	1538 (32)	2882 (25)	3323 (13)	5086 (25)
C_{max}(dn) (ng/mL/mg)	4.450 (28)	1.349 (38)	1.025 (32)	11.53 (25)	13.32 (13)	6.782 (25)
$t_{1/2}$ (hr)	2.023 ± 0.54556	18.5, 25.6	NR	6.935 ± 1.0794	6.005 ± 1.6502	12.86 ± 8.4196
T_{max} (hr)	0.634 (0.550 - 1.50)	1.00 (0.517 - 1.00)	1.00 (0.533 - 2.00)	2.75 (1.50 - 4.00)	4.00 (4.00 - 4.00)	2.00 (1.50 - 4.00)
V_z/F (L)	190.6 (36)	2440, 3390	NR	87.98 (28)	73.48 (47)	181.9 (35)

Ritonavir dosed at -12h, 0h and 12h post-dose.
Source: Table 14.4.5.1.1 and 16.2.5.5.1.1
N = Total number of participants in the treatment group
N1 = Number of participants contributing to the summary statistics
N2 = Number of participants where $t_{1/2}$, AUC_{inf}, AUC_{inf}(dn), CL/F and V_z/F were determined
NR = Not Reported
a. Geometric Mean (Geometric %CV) for all except: Median (Range) for T_{max} and arithmetic mean ± SD for $t_{1/2}$
b. Individual values were listed when there were less than 3 evaluable measurements
Summary statistics were not presented if fewer than 3 participants had reportable parameter values.

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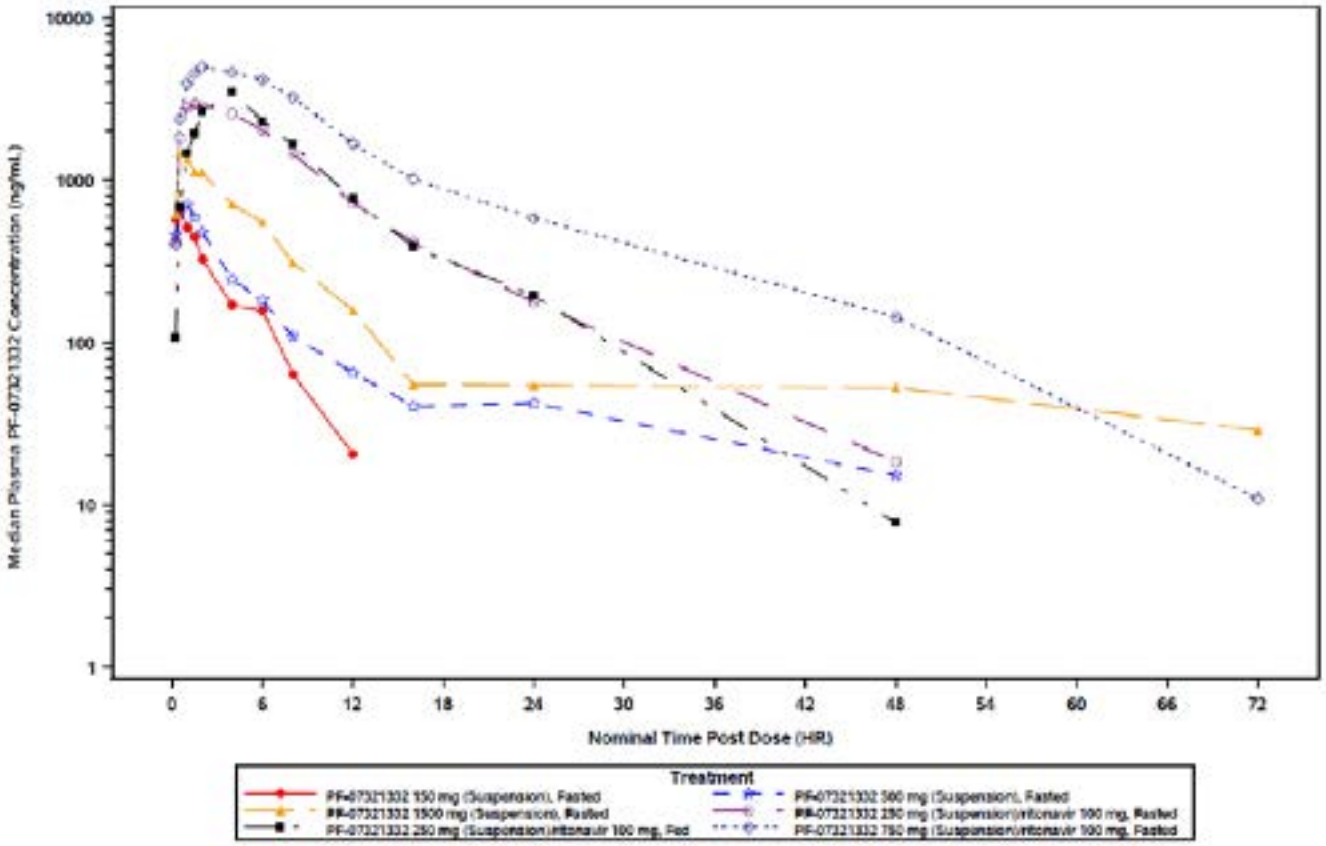
Figure 5: Median plasma PF-07321332 concentration time profiles following single oral doses of PF-07321332 with or without ritonavir (Part 1-SAD-Study 1001)



Part 2 (MAD) of Study 1001

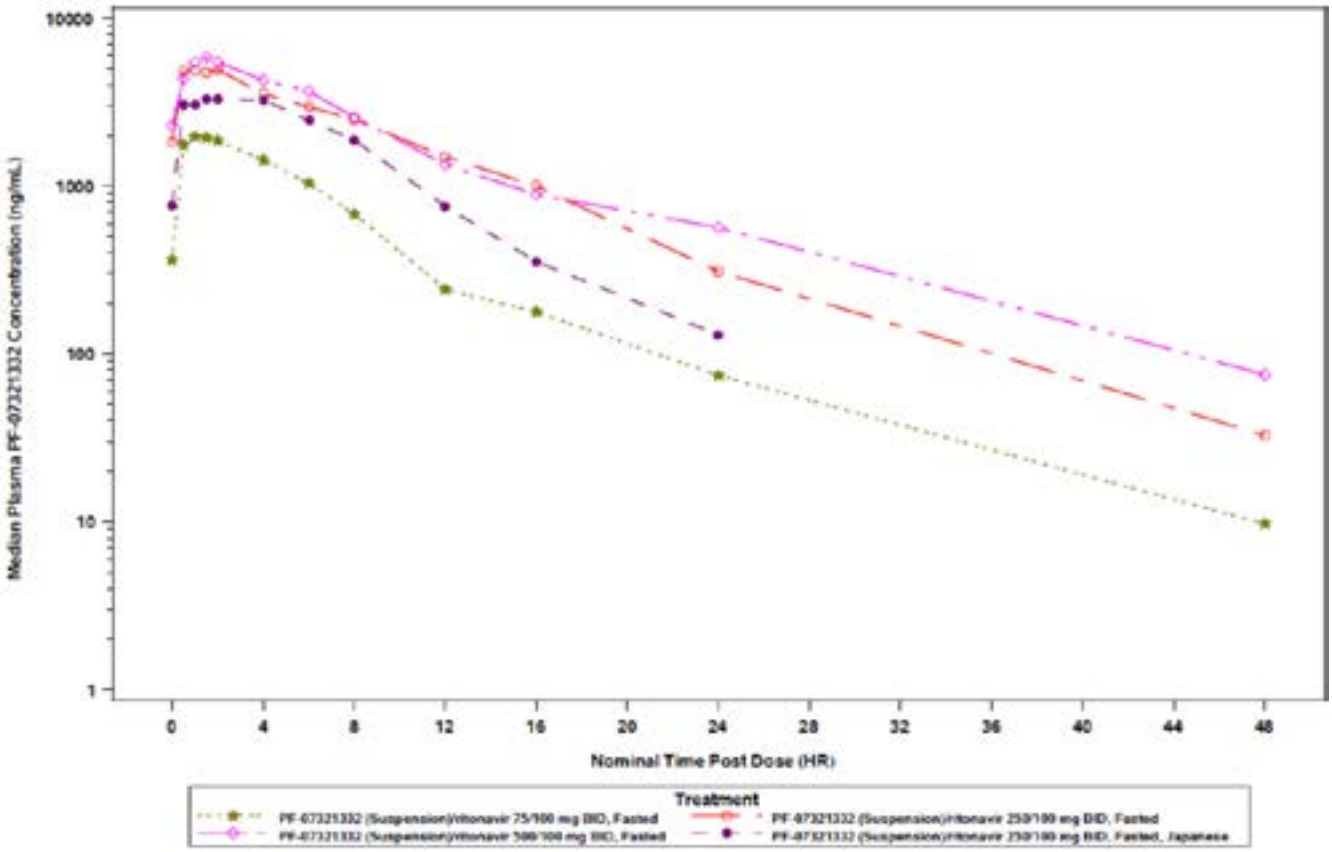
Part 2 (MAD) used PF-07321332/ritonavir from 75 mg/100 mg to 500 mg /100 mg. PK parameters following MAD of PF-07321332 enhanced by ritonavir as oral suspension are presented in **Table 4** and associated median PK profiles at Day 10 in Figure 6.

Table 4. Descriptive summary of plasma PF-07321332 PK parameters (Part 2 –MAD, Study 1001)

Parameter (Unit)[a]	PF-07321332 (Suspension)/ritonavir 75/100 mg BID, Fasted (N=4)	PF-07321332 (Suspension)/ritonavir 250/100 mg BID, Fasted (N=4)	PF-07321332 (Suspension)/ritonavir 500/100 mg BID, Fasted (N=7)	PF-07321332 (Suspension)/ritonavir 250/100 mg BID, Fasted, Japanese (N=4)
Day 1				
N1	4	4	7	4
AUC_{tau} (ng hr/mL)	6017 (33)	18700 (43)	22010 (37)	13130 (26)
AUC_{tau} (dn) (ng hr/mL/mg)	80.19 (33)	74.76 (43)	45.23 (37)	52.60 (26)
C_{max} (ng/mL)	1042 (28)	2435 (36)	3051 (32)	1925 (25)
C_{max}(dn) (ng/mL/mg)	13.89 (28)	9.755 (36)	6.103 (32)	7.698 (25)
T_{max} (hr)	1.75 (1.00 - 2.00)	1.50 (1.00 - 4.00)	2.00 (1.50 - 2.17)	2.75 (1.00 - 4.02)
Day 5				
N1	4	4	7	4
AUC_{tau} (ng hr/mL)	12570 (17)	35560 (26)	38150 (23)	25480 (26)
AUC_{tau} (dn) (ng hr/mL/mg)	167.7 (17)	141.9 (26)	76.32 (23)	102.0 (26)
C_{tau} (ng/mL)	1049 (17)	2963 (26)	3181 (23)	2124 (26)
CL/F (L/hr)	5.966 (17)	7.032 (26)	13.11 (23)	9.814 (26)
C_{max} (ng/mL)	2224 (27)	4774 (21)	5296 (21)	3674 (28)
C_{max}(dn) (ng/mL/mg)	29.66 (27)	19.10 (21)	10.59 (21)	14.70 (28)
C_{min} (ng/mL)	251.0 (11)	1315 (37)	1195 (29)	707.3 (35)
PTR	8.857 (27)	3.635 (21)	4.430 (14)	5.194 (19)
R_{ac}	2.091 (24)	1.901 (22)	1.685 (29)	1.937 (18)
$R_{ac,\ Cmax}$	2.133 (25)	1.959 (16)	1.733 (24)	1.909 (26)
T_{max} (hr)	1.00 (1.00 - 1.50)	0.750 (0.500 - 1.50)	1.50 (1.00 - 2.02)	1.26 (1.00 - 2.02)
Day 10				
N1,N2	4, 4	4, 4	7, 7	4, 4
AUC_{tau} (ng hr/mL)	12650 (16)	37780 (27)	39780 (20)	26930 (15)
AUC_{tau} (dn) (ng hr/mL/mg)	168.3 (16)	151.1 (26)	79.56 (20)	107.7 (15)
C_{tau} (ng/mL)	1053 (16)	3147 (27)	3314 (20)	2245 (14)
CL/F (L/hr)	5.933 (16)	6.617 (27)	12.57 (20)	9.278 (15)
C_{max} (ng/mL)	2055 (14)	5123 (24)	5607 (17)	3772 (21)
C_{max}(dn) (ng/mL/mg)	27.40 (14)	20.49 (25)	11.22 (17)	15.08 (21)
C_{min} (ng/mL)	245.3 (27)	1480 (27)	1279 (31)	12.50 (2.0814162E15)
PTR	8.383 (16)	3.462 (5)	4.385 (17)	6.270 (32)
R_{ac}	2.104 (30)	2.022 (16)	1.757 (26)	2.047 (16)
$R_{ac,\ Cmax}$	1.971 (34)	2.101 (16)	1.840 (29)	1.962 (14)
$t_{1/2}$ (hr)	7.955 ± 2.0401	6.795 ± 1.7072	8.047 ± 1.7871	5.163 ± 2.0915
T_{max} (hr)	1.00 (1.00 - 2.00)	1.00 (1.00 - 2.00)	1.50 (1.00 - 2.00)	1.50 (0.500 - 2.02)
V_z/F (L)	66.43 (24)	63.40 (13)	142.4 (37)	65.04 (31)
Ae_{tau} (mg)	47.83 (12)	129.9 (4)	116.5 (122)	135.4 (5)
Ae_{tau} %	63.79 (12)	51.81 (4)	23.35 (121)	54.20 (5)
CL_r (L/hr)	3.782 (20)	3.433 (23)	2.934 (128)	5.028 (11)

Source: Table 14.4.5.1.2.1 and 14.4.5.1.2.2
N = Total number of participants in the treatment group
N1 = Number of participants contributing to the summary statistics
N2 = Number of participants where $t_{1/2}$ and V_z/F were determined
a. Geometric Mean (Geometric %CV) for all except: Median (Range) for T_{max} and arithmetic mean ± SD for $t_{1/2}$
For the parameters analyzed on the log scale, zero values had been substituted with 0.0001 prior to log transformation.
Summary statistics were not presented if fewer than 3 participants had reportable parameter values.

Figure 6. Median plasma PF-07321332 concentration time profiles following multiple oral doses of PF-07321332/ritonavir (Part 2-mAD-Study 1001)



Overall, based on phase 1 dose-escalation data (Study **1001**) in healthy volunteers, the systemic exposures (Cmax, AUCs) of PF-07321332 boosted by 100 mg of ritonavir appeared to exhibit less than dose proportional increase over the dose range of 75 mg to 500 mg after single and multiple oral administration.

Time dependency

Median plasma PF-07321332 concentration time profiles including Ctrough concentrations are presented in **Figure 7** below and associated PK parameters in Table 4. Overall, after repeated administration, steady-state plasma concentrations appeared to have been achieved by Day 2 with minimal accumulation (~2) after BID dosing.

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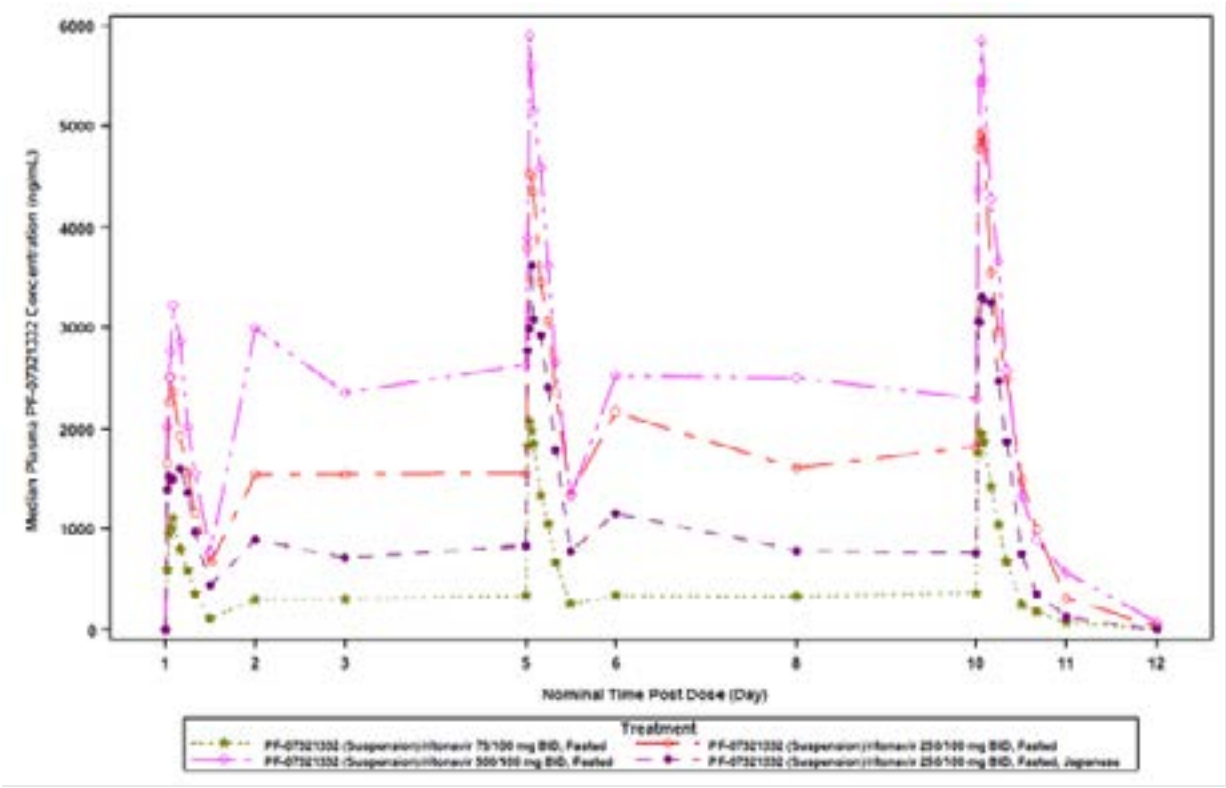
Figure 7. Median plasma PF-07321332 concentration -time profiles across all dosing days following MAD of PF-07321332/ritonavir (Part 2, MAD, Study 1001)



Population PK modelling

A preliminary population PK model of PF-07321332 was developed using plasma concentration data collected in healthy adult data from Study C4671001 (data cutoff date 30 June 2021). The analysis PK dataset included 536 evaluable plasma concentrations from 20 subjects who received 250 and 750 mg single dose and 75, 250 and 500 BID administration of PF-07321332 (suspension formulation) in combination with 100 mg ritonavir (RTV). Modelling used NONMEM, version 7.5. The first-order conditional estimation method with interaction was used during model development.

The final model was a linear 2-compartment model with first-order absorption, a dose-dependent absorption implemented by separate power functions for ka and relative bioavailability (F1) and a linear elimination. Standard allometric scaling of body weight with exponents fixed to 0.75 and 1 was applied on clearance (CL/F) and volumes of distribution, respectively. Residual random effects were described with a combined proportional and additive model in the log domain. IIV were included on all parameters, with a full variance and covariance of the Ω matrix. IOV was included to ka.

Parameter estimates for the final model are presented below.

Table 5. Parameter estimates for the final population PK model based on preliminary data from Study C4671001

	Final Run (CP1:ST-21050660)			1000 SIR[a] Run Statistics				
Parameter	Estimate	%RSE	Shrinkage (%)	Mean	%RSE	Median	Lower 2.5%	Upper 97.5%
CL (θ_1) [L/h]	1.02	18.9		1.02	10.7	1.02	0.800	1.24
V2 (θ_2) [L]	8.20	20.8		8.21	13.0	8.21	6.03	10.2
Q (θ_3) [L/h]	0.444	8.91		0.446	5.58	0.447	0.395	0.493
V3 (θ_4) [L]	5.65	20.2		5.84	17.5	5.90	3.68	7.64
$k_{a\,log}$ (θ_5) [1/h]	22.7	4.15		22.6	2.67	22.6	21.5	23.9
$k_{a\,power}$ (θ_6)	-0.533	6.25		-0.537	5.30	-0.536	-0.592	-0.481
$F1_{log}$ (θ_7)	1.06	30.5		1.05	23.1	1.05	0.591	1.56
$F1_{power}$ (θ_8)	-0.375	16.7		-0.376	10.4	-0.378	-0.455	-0.305
Proportional Error (θ_9) [%]	3.36	111		3.73	57.6	3.50	0.506	7.82
Additive Error (θ_{10}) [ng/mL]	399	11.5		405	30.2	375	250	671
$\omega^2_{1,1}$ IIV_{CL} [%CV]	26.4	29.2	1e-10	26.0	19.6	25.9	20.4	31.0
$\Omega_{2,1}$ COV_{CL-V2}	0.0684	36.0		0.0646	22.1	0.0637	0.0377	0.0962
$\omega^2_{2,2}$ IIV_{V2} [%CV]	30.7	41.9	5.73	31.6	29.3	31.4	22.1	39.7
$\Omega_{3,1}$ COV_{CL-k_a}	0.0582	73.2		0.0602	51.2	0.0599	0.00709	0.122
$\Omega_{3,2}$ COV_{V2-k_a}	0.138	41.4		0.133	33.5	0.129	0.0489	0.227
$\omega^2_{3,3}$ IIV_{k_a} [%CV]	54.3	33.6	15.5	55.3	32.7	54.2	39.3	72.8
$\Omega_{4,1}$ COV_{CL-V3}	0.125	58.6		0.104	43.8	0.0987	0.0157	0.229
$\Omega_{4,2}$ COV_{V2-V3}	0.0393	152		0.0279	116	0.0262	-0.0589	0.121
$\Omega_{4,3}$ COV_{k_a-V3}	-0.151	90.5		-0.148	62.5	-0.149	-0.347	0.0269
$\omega^2_{4,4}$ IIV_{V3} [%CV]	69.9	73.0	7.89	69.1	49.1	66.4	38.2	101
$\omega^2_{5,5}$ IOV_{k_a} [%CV]	60.7	15.6	38.1;51.6;5.23[b]	60.8	15.3	61.2	50.7	68.6
$\sigma^2_{1,1}$	1 Fixed		5.58	1 Fixed				

In general, structural parameters were precisely estimated (low %RSE <20%), except for F1 at 1 mg dose (%RSE = 30.5%). However, proportional error, variance and covariance of the Ω block were poorly estimated (%RSE >30%). This is specifically problematic for the proportional residual error estimated to be low 3.36% but with an RSE% of 111%. These high %RSE and the high condition number (>1000) suggested that the final model is over-parameterised, which is expected given the inclusion of a full variance-covariance block for IIV and the available limited data. Sampling importance resampling were performed and overall were in line the model parameters estimates. All η and ε shrinkage were <20% except for IOV in ka. No major deficiencies were noted GOF plots. The pcVPCs indicated that the final model described the data reasonably well; even clear under-prediction of the low 5th quantile at 250 mg dose with RTV fed and fasted regimens (Please refer to the respective figures) and tendency to over-predict the terminal elimination phase are noted.

The additive error was estimated at 339 ng/L (more than 33 times the LLOQ of 10 ng/mL and even larger than the target IC90% value of 292 ng/mL). Such finding, with the poor precision of the proportional error portion compromise the validity of the model. To handle this point during simulations, the large residual errors was excluded. This approach is not endorsed as it would imply estimation of PK parameters and associated variabilities necessary different from that in the final model and used for simulation. Therefore, model-based PK predictions should be considered with caution.

The parameter estimates after adjustment by F1 at a dose of 300 mg are CL 8.2 L/h, volume of distribution 111 L, and ka 1.1 h-1. This gives a population mean half-live T1/2 of 15 hours, which is not consistent with that obtained from NCA calculations (mean T1/2 =7 hours). No clear estimate of the bioavailability 300 mg dose is provided / could be found. Importantly, given the observed 44% lower Cmax in tablets compared to the suspension formulation (relative bioavailability part in study

1001), the adequacy of using the current model (based only on tablet formulation data) to simulate PK data for the tablet formulation is not deemed adequate.

The covariate (age, body weight, BMI, ethnicity, renal and hepatic impairment) effects could not be considered adequately explored given the very limited data and the demographic characteristics of subjects included in the dataset (ranges of age, BW and renal clearance were [21-56y], [58-99 kg] and [70 -141 ml/min], respectively and no information on BMI, ethnicity and hepatic impairment could be found). For note, a high-fat meal reduced ka by approximately 50%. However, considering its minimal impact on Cmin, and the inclusion of IIV and IOV on ka, the applicant did not retain the food effect in the final model for subsequent simulation.

Using the final Pop-PK model and doses from 100 to 500 mg/100mg RTV BID for 5 days, the predicted PK exposures (Table 6) showed that, for a typical 70 kg subject, a dose of PF-07321332/ritonavir 300/100 mg BID would result in median Day 1 and steady state Ctrough (=C12h) concentrations ~3-4 x IC90 and ~6 x IC90, respectively. With this dose, it is projected to have >90% of subjects would achieve Ctrough ≥IC90 even after the first dose and with IIV in CL inflated to 60%.

Table 6. Predicted C12h and Percentage of Simulated Subjects Achieving C12h above IC90 of 292 ng/mL (IIV in CL Inflated to 60%)

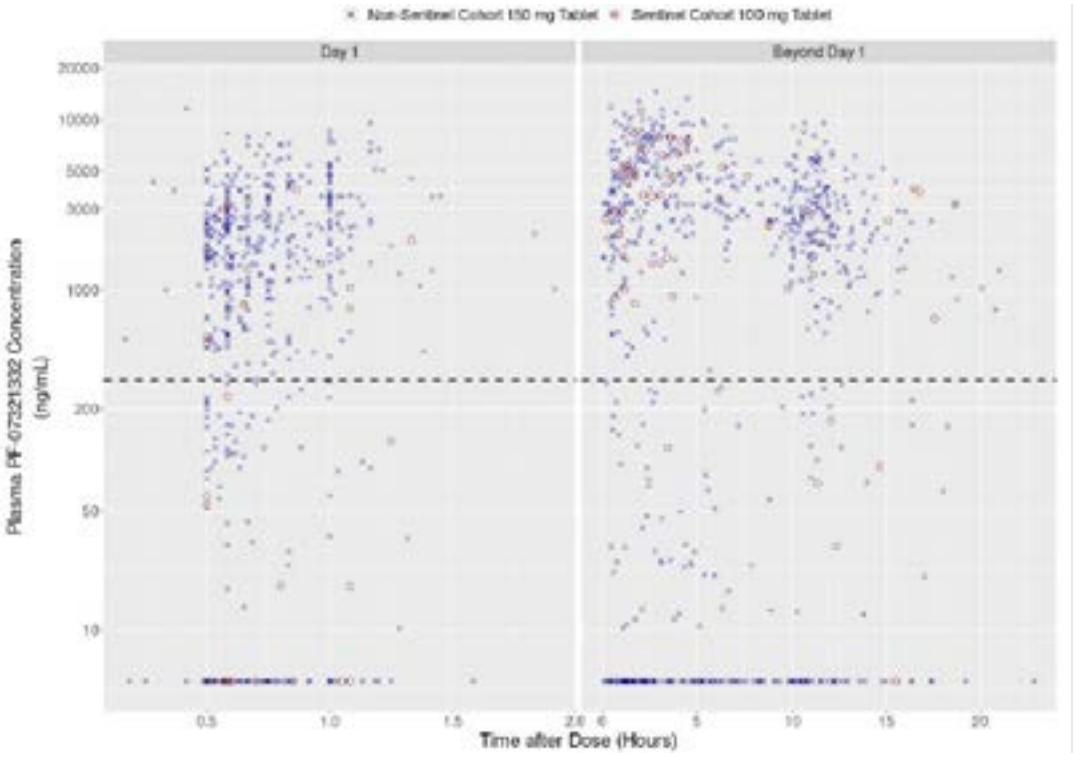
Dose (mg) + RTV*	Dose Number	C_{12h} (ng/mL) Median	10^{th} percentile	90^{th} percentile	% Subjects Achieved $C_{12h} \geq IC_{90}$
100	1st (Day 1)	458	141	1018	71.5
	2nd (Day 1)	631	175	1546	79.2
	9th (Day 5)	852	238	2276	85.3
200	1st (Day 1)	743	228	1608	85.0
	2nd (Day 1)	1012	281	2443	89.2
	9th (Day 5)	1361	383	3575	93.4
300	1st (Day 1)	987	307	2124	90.7
	2nd (Day 1)	1347	378	3202	93.6
	9th (Day 5)	1800	498	4670	95.7
400	1st (Day 1)	1209	378	2565	94.0
	2nd (Day 1)	1657	468	3879	95.3
	9th (Day 5)	2197	605	5679	97.4
500	1st (Day 1)	1417	449	2979	95.5
	2nd (Day 1)	1952	552	4516	96.5
	9th (Day 5)	2563	704	6640	97.8

Pharmacokinetics in target population

Preliminary PK data were collected from the ongoing pivotal efficacy and safety Phase 2/3 study (**C4671005**) in patients with confirmed diagnosis of SARS-CoV-2 infection who were at increased risk of progressing to severe illness. Patients received PF-07321332/ritonavir or placebo orally q12h for 5 days (10 doses total). Sparse PK sampling was collected on Day 1 (0.5 to 1.5 hr post dose), on Day 5 (up to 2 hours pre-dose) and optionally on Days 2, 3, or 4. At cutoff date (28 October 2021), a total of 1298 plasma PF-07321332 concentrations, including 1068 evaluable samples and 230 (17.7%) BLQ samples from 601 patients were available for analysis. There were 46 participants who did not have any evaluable samples (all observations were BLQs).

The observed plasma PF-07321332 concentrations in patients are shown in **Figure 8**.

Figure 8. Observed Plasma PF-07321332 Concentration versus Time after Dose for Participants with COVID-19 on PF-07321332/ritonavir 300 mg/100 mg q12h in Study C4671005 Stratified by Day



PK data at Day 5 (Table *7*) indicated that 140 out of 173 (>80%) patients achieved a Cmin≥ IC90. When excluding the BLQ samples during Day 5 visit, 140 out of 153 (>90%) patients achieved the target Cmin. Overall, the observed concentrations from patients appears to be consistent with those (dose-normalised to 300 mg) in the healthy participants. However, it is worth noting that a high number of BLQ (17.7% of the dataset) was observed after and beyond the first dose. Such finding requires further investigation. Of these BLQ, 95 samples (41.3%) were collected at Day 1, while no BLQ samples at or beyond 30 min post-dose was observed in healthy volunteers after of PF-07321332/ritonavir dosing.

Table 7. Summary of Cmin at the Planned Day 5 Visit and Percentage of Participants in Study C4671005 Achieving C_{min} ≥EC90

Scenario	Number of Participants	Observed C_{min}[a] (ng/mL) Median	10th percentile	90th percentile	BLQ[b] Samples Number	Percentage	Participants with $C_{min} \geq EC_{90}$ Number	Percentage
All Participants	173	2180	0	5600	20	11.6	140	80.9
Excluded Participants with only BLQ Samples	167	2290	57.2	5698	14	8.38	140	83.8
Excluded All Participants with BLQ Samples on Day 5	153	2440	701	5808	0	0	140	91.5

Repository artifact ID FI-26856380. Lines 1–2 substituted.
BLQ = below limit of quantification; C_{min} = minimum concentration; EC_{90} = concentration required for 90% of maximum effect.
[a]Samples collected between 10 and 14 hours post-dose at the planned Day 5 visit.
[b]BLQ defined as <10 ng/mL and was set to 0.

A predictive check (simulation) approach was performed to assess the adequacy of the preliminary Pop-PK model in describing the patient data from Study 1005 (PF-07321332/ritonavir 300 mg/100 mg BID).

Overall, a fair agreement was observed. The majority of the PF-07321332 concentrations in COVID-19 patients fall within the 90% prediction interval generated from simulation. The median observed data

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at Day 1 (Figure 9) and at steady state (**Figure 10**) appears to be consistent with the model predictions generated Pop-PK model. However, as noted above, a high number of unexpected BLQ concentrations after the first dose and at steady was observed.

Figure 9. Median and 90% Prediction Intervals (5th and 95th percentile) for PF-07321332 concentrations after first dose based on 1000 Simulations (PF-07321332/ritonavir 300 mg/100 mg q12h) overlaid with observed Data from Study C4671005

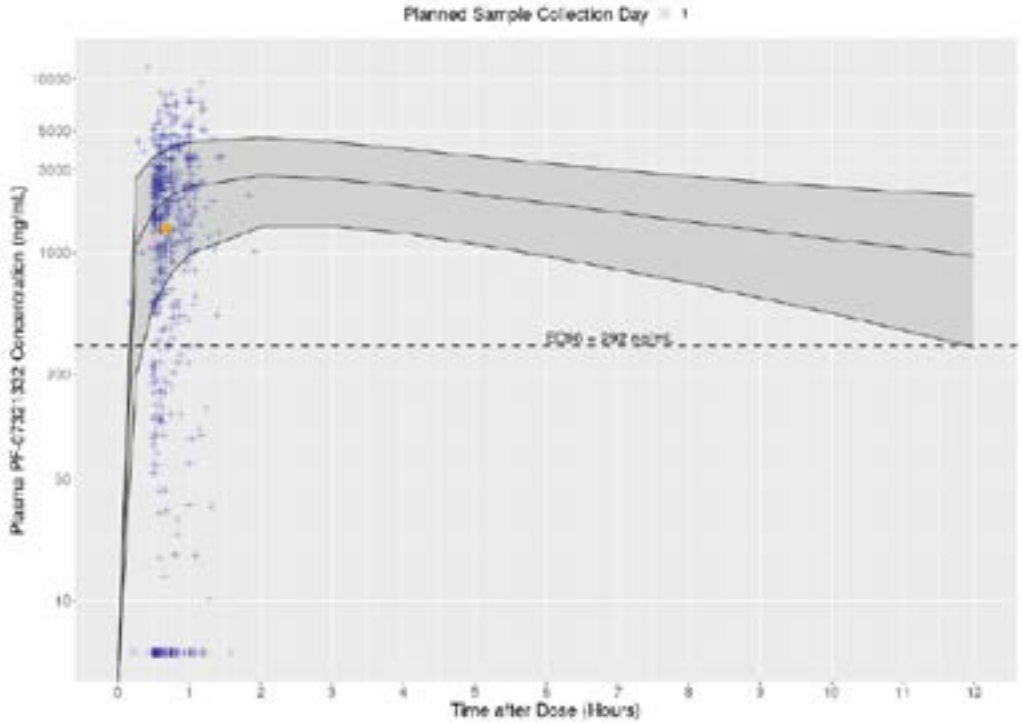
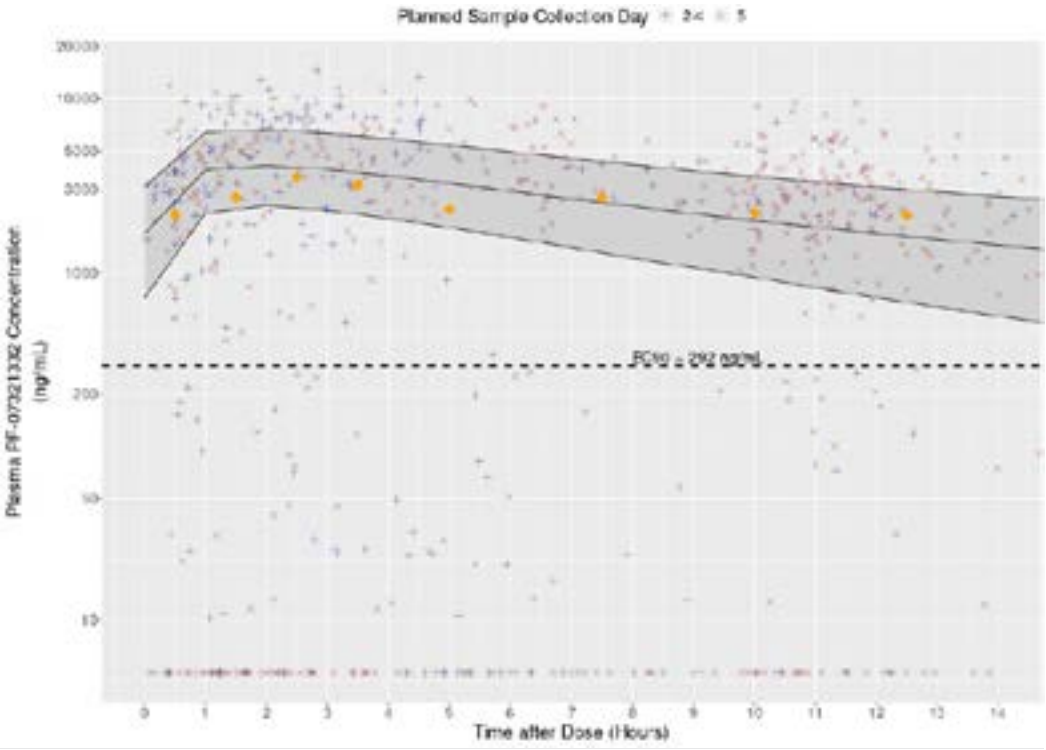


Figure 10. Median and 90% Prediction Intervals (5th and 95th percentile) for PF-07321332 concentrations at steady-state based on 1000 Simulations (PF-07321332/ritonavir 300 mg/100 mg q12h) overlaid with observed Data from Study C4671005



Special populations

Renal impairment

A formal study (**C4671011**) investigated the effect of mild, moderate and severe impairment on the PK of PF-07321332. Subjects were administered a single oral 100 mg dose of PF-07321332 in combination with the PK enhancer ritonavir administered as a 100 mg dose at -12, 0, 12, and 24 hours relative to PF-07321332 dosing. The number of subjects per category of renal impairment was n=8 versus 10 subjects for the normal healthy controls. The estimated eGFR calculated using CKD-EPI equation was used a measure of renal function.

PK data indicated that PF-07321332 systemic exposure increased with increasing severity of renal impairment, specifically in the moderate and severe impaired subjects Figure 11,

Table **8**). The geometric mean (90% CI) ratios for Cmax and AUCinf relative to subjects with normal renal function were:

- For the mild impaired group: 129.78% (101.93%, 165.25%) and 123.84 % (99.64%, 153.91%), respectively
- For the moderate impaired group: 138.12% (113.18%, 168.55%) and 187.40% (148.52%, 236.46%), respectively
- For the severe impaired group: 148.02% (111.40%, 196.68%) and 304.49 % (237.60%, 390.21%), respectively

Consistent with the increase on PF-07321332 systemic exposures, the apparent CL/F and CLr decreased with increased renal impairment severity. Mean CL/F in the moderate and severe group

decreased 47% and 67% and mean renal clearance decreased 47% and 80% respectively compared to the normal renal functional group.

Figure 11. Median Plasma PF-07321332 Concentration-Time Plot, Following a Single Oral Dose of PF-07321332/Ritonavir, Protocol C4671011

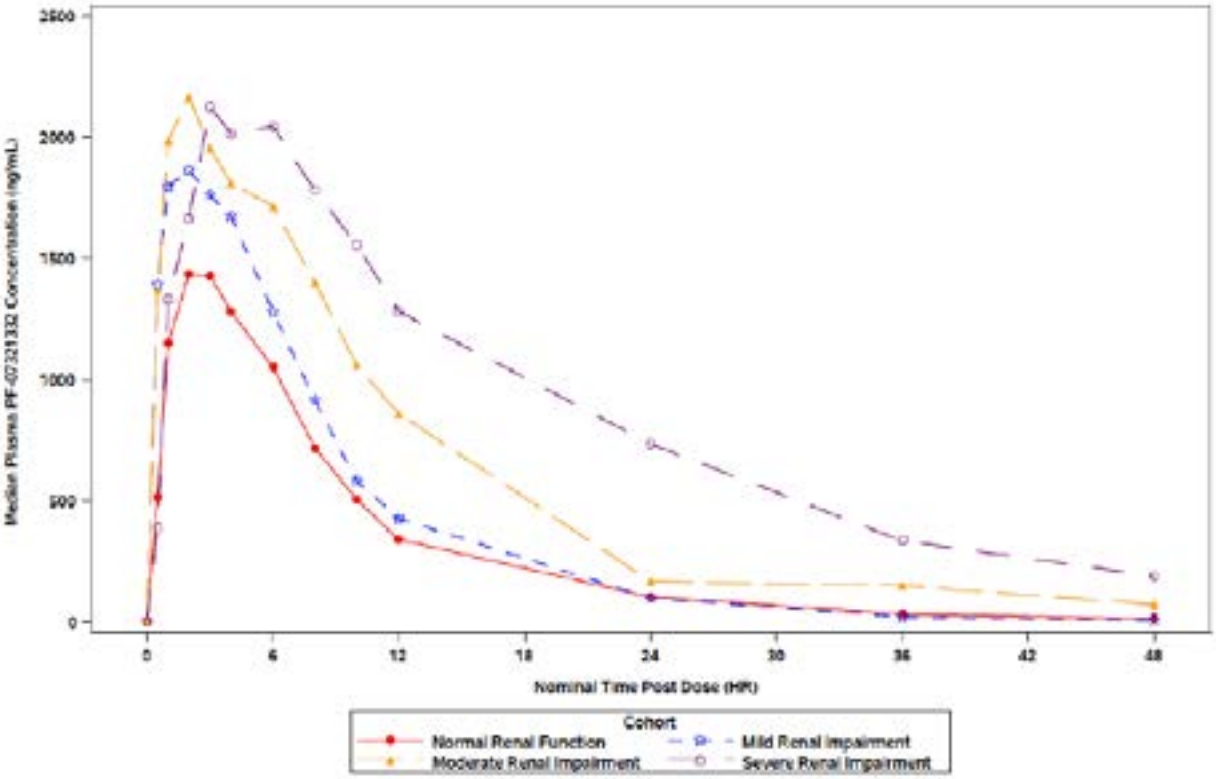


Table 8: Descriptive Summary of Plasma and Urine PF-07321332 PK Parameters. Protocol C4671011

Parameter (Unit)[a]	Normal Renal Function (N=10)	Mild Renal Impairment (N=8)	Moderate Renal Impairment (N=8)	Severe Renal Impairment (N=8)
N1, n	10, 10	8, 8	8, 6	8, 7
AUC_{inf} (ng.hr/mL)	14460 (20)	17910 (30)	27110 (27)	44040 (33)
AUC_{last} (ng.hr/mL)	14270 (20)	17770 (30)	26660 (21)	39420 (28)
C_{12} (ng/mL)	341.9 (35)	438.0 (30)	785.6 (33)	1213 (33)
C_{24} (ng/mL)	99.10 (35)	112.8 (55)	179.1 (108)	694.2 (42)
CL/F (L/hr)	6.913 (20)	5.581 (30)	3.689 (27)	2.270 (33)
C_{max} (ng/mL)	1600 (31)	2077 (29)	2210 (17)	2369 (38)
$t_{1/2}$ (hr)	7.725 ± 1.8234	6.606 ± 1.5344	9.948 ± 3.4171	13.37 ± 3.3225
T_{max} (hr)	2.000 (1.00 - 4.00)	2.000 (1.00 - 3.00)	2.500 (1.00 - 6.00)	3.000 (1.00 - 6.05)
V_z/F (L)	74.95 (35)	51.95 (32)	50.34 (27)	42.73 (26)
Ae (mg)	31.20 (45)	42.65 (23)	30.83 (56)	18.46 (50)
Ae %	31.20 (45)	42.65 (23)	30.83 (56)	18.46 (50)
CL_r (L/hr)	2.180 (50)	2.395 (33)	1.154 (71)	0.4398 (73)

Hepatic impairment

A formal study (**C4671010**) investigated the effect of moderate hepatic impairment on the PK of PF-07321332, in comparison to matched healthy subjects with normal hepatic function. Subjects were administered a single oral 100 mg dose of PF-07321332 in combination with the PK enhancer ritonavir administered as a 100 mg dose at -12, 0, 12, and 24 hours relative to PF-07321332 dosing. The number of subjects was n=8 in each cohort. Categorisation of participants into normal hepatic function or hepatic impairment group was based on Child-Pugh scores.

The study is still ongoing and only a preliminary PK report (22 November 2021) is provided.

Preliminary median PK profiles and PK data by hepatic function are shown in Figure 12 and summarised in Table 9. Overall, data suggest that PK exposure following single dose administration of PF-07321332 enhanced with ritonavir in subjects with moderate hepatic impairment (AUCinf = 15.07 µg*h/mL and Cmax 1.92 µg/mL) were comparable to those in participants with normal hepatic function AUCinf = 15.28 µg*h/mL and Cmax = 1.89 µg/mL).

Figure 12. Median Plasma PF-07321332 Concentration-Time Profiles Following a Single Oral Dose of PF-07321332 Enhanced with Ritonavir

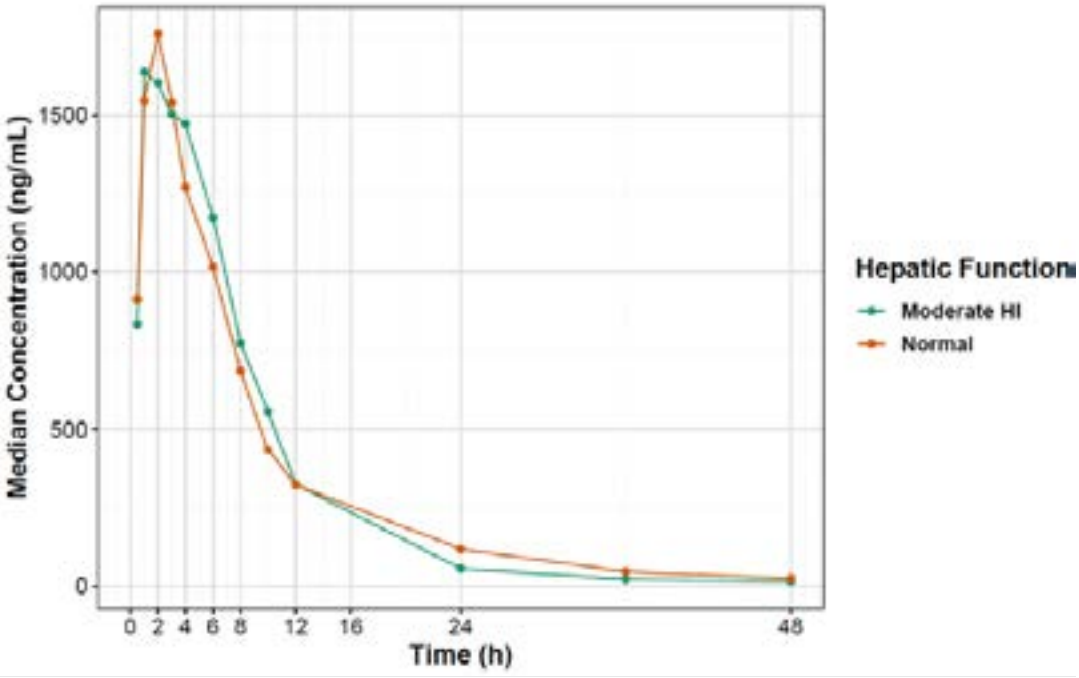


Table 9. Descriptive Summary of Preliminary (Unaudited) Plasma PK Parameters of PF-07321332 by Hepatic Function in Study C4671010

Hepatic Function	PK Parameters[a]				
	N,n[b]	T_{max} (hr)	C_{max} (µg/mL)	AUC_{inf} (µg.hr/mL)	$t_{½}$ (hr)
Normal Hepatic Function	8,8	2 (0.5-2)	1.89 (20)	15.28 (36)	7 (29)
Moderate Hepatic Impairment	8,8	1.5 (1-2)	1.92 (48)	15.07 (43)	5.5 (32)

Abbreviations: %CV = percent coefficient of variation; AUC_{inf}= Area under the concentration-time curve from time zero to last measurable concentration; C_{max}= Peak plasma concentration; T_{max}=Time to achieve C_{max}; $t_{½}$=Half-life

a. Geometric mean (geometric % CV) except $t_{½}$ and T_{max}. Arithmetic mean and %CV for $t_{½}$ and median (range) for T_{max}.
b. N is total number of subjects, n=number of subjects with estimates of half-life

Gender

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No formal dedicated PK study was performed to investigate the potential effect of gender on the PKs of PF-07321332.

Among the 20 subjects included in the dataset for PF-07321332, both sexes were represented with less female (n= 4; 20 %) than male (n = 16; 80 %). Sex was not identified as a significant covariate on the PK parameters of PF-07321332. However, such conclusion should be sought cautiously as the validity of the population-PK analysis is still to be proven.

Race / Ethnicity

No formal dedicated PK study was performed to investigate the potential effect of gender on the PKs of PF-07321332.

Race effect on PF-07321332/ritonavir PK has been explored as part of Study 1001 in only 4 Japanese healthy volunteers. AUCtau and Cmax values were approximately 30% and 21-26%, respectively, lower in Japanese participants compared to Caucasian subjects. Drug accumulation was similar in Japanese compared to Caucasian subjects (~2).

Body weight

No formal dedicated PK study was performed to investigate the potential effect of body weight on the PKs of PF-07321332.

The Population model included an allometric relationship of baseline body weight on apparent clearance (CL/F) and apparent volume of distribution (V/F) with exponents fixed to 0.75 and 1, respectively. However, the impact of this covariate on the systemic exposure of PF-07321332 was not clearly shown / explored (no results could be found).

Elderly

Preliminary PK data provided in patients (study C4671005) indicates an age between 18 and 86 years. However, the number of elderly patients included in the following subgroups of age: [65 to 74 years], [75 to 84 years] and >85 years is not detailed.

No subject older than 65 years was included in Population dataset.

Children and adolescents

No PK data are available. The safety and efficacy of PF-07321332/ritonavir in children and adolescents below the age of 18 years have not yet been established.

The applicant claimed an indication covering the adolescents aged 12 years of age and above and weighing > 40 kg with the same dosing regimen as adults, 300/100 mg PF-07321332/ritonavir BID. According to the applicant, the proposed dose is justified based on Population PK simulations.

The preliminary Population PK model was used to simulate exposures in adolescent patients >40 kg. These model-based simulations suggest that a PF-07321332/ritonavir 300 mg/100 mg BID dose in adolescents (i.e., ≥12 to < 18 years of age) provides reasonably comparable exposures in adults receiving the same dose and maintained PF-07321332 plasma concentration above EC90 over the entire dosing interval suggestive of pharmacodynamic activity of PF-07321332/ritonavir and thus the therapeutic response.

The distribution of simulated C_{min} on Day 5 by dose of either PF-07321332/ritonavir 150 mg/100 mg BID or 300 mg/100 mg BID regimen in adolescent subjects are depicted in ***Figure 13***. The distribution of simulated Cmin on Day 5 based on adults from the Study 1005 is provided for reference. Summary statistics for simulations results for all exposure parameters are presented in Table 10.

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Figure 13 : Distribution of Cmin on Day 5 by Treatment in Simulated Adolescent Subjects

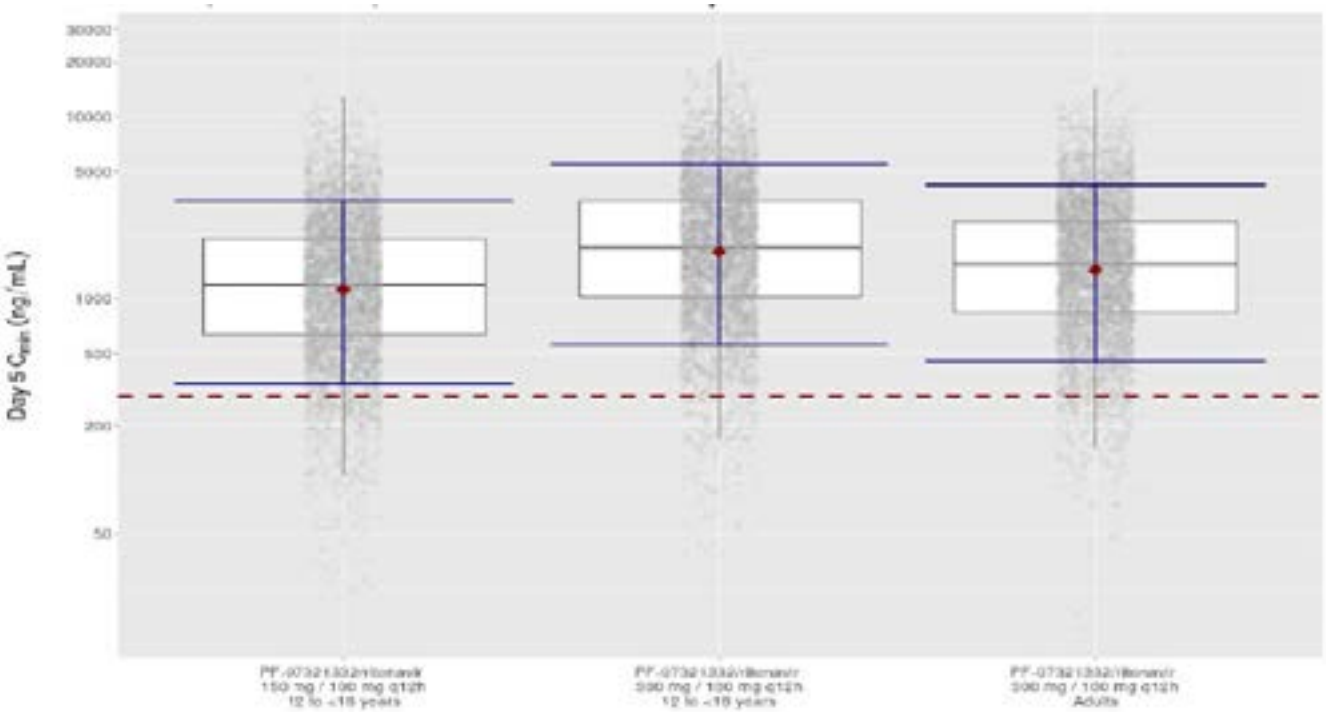

Table 10. Statistical Summary (Geometric Mean and Percentiles) of the Output of the Modelling and Simulation Evaluation

Age Group	Dose (mg) + Ritonavir 100 mg q12h (BID)	N	$AUC_{0\text{-}12h}$ (ng·h/mL)			C_{max} (ng/mL)			C_{min} (ng/mL)		
			Geo Mean	Percentile		Geo Mean	Percentile		Geo mean	Percentile	
				10^{th}	90^{th}		10^{th}	90^{th}		10^{th}	90^{th}
12 to <18 years	150	5000	27602	12302	61731	3825	2077	7114	1122	340	3435
	300	5000	42797	19099	95375	5592	2996	10501	1807	556	5476
Adults	300	5000	32239	14404	71154	4079	2160	7786	1440	453	4214

Based on these simulations, a considerable overlap in C_{min} values of PF-07321332 between the PF-07321332/ritonavir 150 mg/100 mg BID and PF-07321332/ritonavir 300 mg/100 mg BID administrations in adolescents as compared to reference C_{min} values in adults (300 mg/100 mg BID). As that could be expected, a dose of PF-07321332/ritonavir 300 mg/100 mg BID in adolescents achieved a larger distribution of subjects above the *in vitro* EC90 of 292 ng/mL as compared to those receiving the 150 mg/100 mg BID regimen, but detailed difference and statistical comparison was not provided.

Pharmacokinetic interaction studies

Paxlovid interaction profile, as a co-packed combination of PF-0713321332, and ritonavir, has been investigated mainly by assessing PF-0713321332 interaction potency in studies 102559 (CYP inducer via AhR, CAR and PXR), 103243 (UGT and CYP inhibitors), 113907 and 12202 (CYP inhibitions), 020944 (transporter inhibition), 124535 and 095737 (substrate of efflux transporters, P-gp and BCRP),

and studies -013448, -110227, -114514, -124557 and - 013448 (hepatobiliary/renal uptake transporters). Interaction studies was also studied as part of clinical trials in studies -1014 and 1015, to characterise the effects of carbamazepine on the single dose PK of PF-07321332 300 mg/ritonavir 100 mg in healthy participants and to estimate the effect of multiple doses of itraconazole on the PK of PF-07321332 following multiple doses of PF-07321332/ritonavir respectively.

Paxlovid as perpetrator

The Appraisal of PF-07321332 interaction profile was based on *in vitro* studies. Its induction potential, inhibition of UGTs, inhibition of CYPs isoforms, as well as inhibition of transporters were performed in line with EMA drug-drug interaction guideline (CPMP/EWP/560/95/Rev. 1).

PF-07321332 was found to be an inducer of CYP3A4, CYP2B6, CYP2C8 and CYP2C9. It was identified as time-dependent inhibitor of CYP3A4 with estimated KI of 15.5 µM and 13.9 µM, and estimated Kinact to 0.0142 min-1, and 0.0165 min-1, using respectively midazolam and testosterone as substrate. PF-07321332 was also an inhibitor of P-gp (IC50 70.6 µM), OATP1B1 (IC50 44.4 µM), and OCT1 (IC50 138.1 µM). Based on *in vitro* results, PF-07321332 may *in vivo* inhibit OCT1. For renal transporters, MATE1 Rr=0.023, slightly above the cut-off criteria (Rr≥0.002). However, since metformin is also substrate of OCT1, significant interactions with metformin could not be excluded. With respect to OATP1B1 inhibition potential, PF-07321332 shows an Rh of 0.110, which is above the EMA cut-off criteria of 0.04. Given the large drug-drug interaction spectrum of Paxlovid, clinical interaction study to assess the magnitude of interaction with these transporters or thorough justification of the lack of such investigation based on scientific evidence and rationale should continue.

Ritonavir (RTV) interaction profile was based on Norvir SmPC. RTV is an inducer of CYP1A2, CYP2C8, CYP2C9, and CYP2C19, as well as inducer of UGTs. Ritonavir has also shown to be a time-dependent inhibitor of CYP3A4, an inhibitor of CYP2D6, and a P-gp inhibitor.

Overall, based on *in vitro* studies, Paxlovid, as co-packed combination of PF-07321332 with ritonavir, is considered inhibitor of CYP2D6, P-gp, BCRP, OATP1B1, OATP1B3, and OCT1. It induces UGTs, CYP3A4, CY2B6, CYP2C8, CYP2C9, CYP1A2, and CYP2C19.

There is a possibility of additive effect in the induction of CYP enzymes. However, taking in consideration the low dose of ritonavir used for a short duration and its predicted induction of less than 30%, it can be agreed that this magnitude of induction unlikely to necessitate dose adjustments and that it is appropriate to give guidance within the Paxlovid label based on Norvir (ritonavir) label which already states the risk of induction that was observed for higher doses.

Paxlovid net effect on CYP3A4 and P-gp substrates *in vivo* is not yet established given Paxlovid is substrate, inhibitor, and inducer of CYP3A4, and also substrate and inhibitor of P-gp. This is currently being assessed in the following on-going studies, DDI study 1013 with midazolam, and DDI study 1012 with dabigatran. Preliminary PK data from the midazolam DDI study was provided. The study consists of 3 treatments: single oral dose of midazolam 2 mg (Treatment A); PF-07321332/ ritonavir 300/100 mg q12h (total 9 doses) + single oral dose of midazolam 2 mg on the Day 5 morning (Treatment B); ritonavir 100 mg q12h (total 9 doses) + single oral dose of midazolam 2 mg on the Day 5 morning (Treatment C). The test/reference ratios of the adjusted geometric means (90% CI) for midazolam AUCinf and Cmax were 1430.02 % (1204.54%, 1697.71%) and 368.33% (318.91%, 425.41%), respectively, when midazolam was co-administered with PF-07321332/ritonavir (Test) compared of midazolam administered alone (Reference). Midazolam CL/F was decreased by 93% and t½ was increased by 2-fold, when midazolam was co-administered with PF-07321332/ritonavir compared of midazolam administered alone. The test/reference ratios of the adjusted geometric means (90% CI) for midazolam AUCinf and Cmax were 1645.15 % (1385.75%, 1953.11%) and 387.20% (335.25%, 447.21%), respectively, when midazolam was co-administered with ritonavir (Test) compared of

midazolam administered alone (Reference). Midazolam CL/F was decreased by 94% and t½ was increased by 2.3-fold, when midazolam was co-administered with ritonavir compared of midazolam administered alone. Midazolam systemic exposure increased several-fold when co-administered with the strong CYP3A inhibitor ritonavir. However, coadministration of midazolam with PF-07321332/ritonavir did not result in any further increase in midazolam exposure compared to ritonavir alone. This information was included in the SmPC.

As a precautionary measure, other potential victim drugs were added in 4.3 and 4.5 sections of Paxlovid SmPC.

Concomitant therapy with ritonavir- or cobicistat-containing regimen, it is indicated that no dose adjustment is needed and that Patients diagnosed with human immunodeficiency virus (HIV) or hepatitis C virus (HCV) infection who are receiving ritonavir- or cobicistat-containing regimen should continue their treatment as indicated. Although it is acceptable to conclude that it may be essential to administer ritonavir together with PF-07321332 to get the PK enhancement of PF-07321332, doses of ritonavir higher than 100 mg twice-a-day may increase incidence of adverse reactions. The benefit of Paxlovid in HIV and HCV patients who are receiving a PK booster, and subsequently are also infected with SARS-CoV-2 and need Paxlovid, is considered outweighing the risk of adverse events associated with an additional booster dose of ritonavir or cobicistat. Staggering of dose or skipping the ritonavir administration if PF-07321332 administered at the same time as other ritonavir-regimen would be confusing to patients and prone to error because some HIV treatments are QD and other BID. Therefore, keeping the PK booster together with associated protease inhibitor as indicated is considered acceptable.

It is noteworthy that given the high-risk targeted population (including notably old patients, patients with cardiovascular disease), additional DDI studies with amiodarone and clozapine notably as victim drugs should have been performed by the applicant, since critical in this population. These studies could allow these patients, for whom treatment cessation could not be clinically easily handled, to benefit from Paxlovid treatments.

Paxlovid as victim

Administered with ritonavir, PF-07321332 is mainly excreted unchanged. Notably, 55.0% and 27.5% of the dose is excreted as parent compound in urine and faeces, respectively. Regarding the fraction of PF-07321332 metabolised, CYP3A4 was identified as the major contributor (fm = 0.99) of the oxidative metabolism, based on *in vitro* studies.

PF-07321332-transporter interaction profile was studied based on *in vitro* inhibition studies. PF-07321332 was found to be a substrate of the human MDR1 P-gp.

In vivo PF-07321332 interaction profile was assessed in clinical studies with a potent inhibitor and an inducer of CYP3A4 enzyme. After co-administration of PF-07321332/ritonavir (300/100 mg SD) and carbamazepine (dose escalation design: 100mg BID from day 1 to 3, 200mg BID from day 4 to 7, 300 mg BID from day 8 to 15), the AUC0-∞ and Cmax of PF-07321332 were decreased by 55% and 43%, respectively, as compared to administration of PF-07321332/ritonavir alone.

Based on *in vivo* results, the SmPC specified a contraindication for the coadministration of Paxlovid with potent CYP3A inducers regarding the significant clinical impacts on both PF-07321332 and ritonavir PK.

After co-administration of PF-07321332/ritonavir (5 oral doses 300/100 mg q12h) and itraconazole (200 mg orally q24h for 8 days), the AUCtau and Cmax of PF-07321332 were increased by 38% and 19%, respectively, as compared to administration of PF-07321332/ritonavir alone. PF-07321332 exposure increases observed in the itraconazole study are not expected to be clinically relevant.

Therefore, no dosing adjustment of PF-07321332/ritonavir is necessary when a CYP3A4 inhibitor is co-administrated with Paxlovid.

Overall, the applicant has proposed to integrate the long list of DDI related to ritonavir, including contraindications. The CHMP has considered that this conservative measure should indeed apply at this stage. However, the CHMP has judged necessary to explain the reasoning in a dedicated introductory statement to the physicians before the table of DDI in the SmPC *"**As a conservative measure,** the drug-drug interactions pertaining to ritonavir used in chronic HIV infection (600 mg BID when originally used as an antiretroviral agent and 100 mg BID as currently used as a pharmacokinetic enhancer with antiretroviral agents), should apply for Paxlovid. Future investigations may enable to adjust the recommendations related to drug-drug interactions to the 5 days treatment duration of Paxlovid"*

The CHMP is committed to revisit for adjustment the ritonavir driven DDI in relation to the use of Paxlovid as soon as the requested data in pharmacokinetics would be available (including PopPK), to better guide healthcare professionals especially in the outpatients setting less familiar with those ritonavir driven DDI than HIV specialists at hospital. The CHMP has alerted healthcare professionals organisations on the complexity of the interaction profile of this treatment.

The applicant is expected to particularly review the contraindication with drugs expected to be used in the targeted population at high risk of progression to severe COVID-19 including drugs for which treatment cessation cannot be foreseen even for a short period, such as amiodarone, clozapine.

2.6.2.2. Pharmacodynamics

Mechanism of action

PF-07321332 is a peptidomimetic inhibitor of the coronavirus type 3C protease (3CLpro), including the SARS-CoV-2, 3CL protease. Inhibition of the 3CL protease renders the protein incapable of processing polyprotein precursors, leading to inhibition of viral replication.

From the co-crystal structure of PF-07321332 bound to SARS-CoV-2 3CLpro, 6 contact residues (Cys145, Gly143, Glu166, His163, Phe140, His164) were identified in the active site of 3CLpro to form either covalent or hydrogen bonds between 3CLpro and PF-07321332. Examination of residues within 4 Å from PF-07321332 binding sites identified 7 additional potentially critical residues. The conservation of these contact residues was assessed by aligning SARS-CoV-2 genomes with complete and high coverage sequences (N = 3,163,857; GISAID; last accessed 11-08-2021). The 13 residues explored (presented in **Table 11**) were highly conserved, with frequency of mutation <0.024%.

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Table 11. Mutations at Key PF-07321332 Contact Residues on SARS-CoV-2 3CLpro

Residue Position	Reference AA	Mutation(s)	Number of Subjects	Interaction with PF-07321332
41	His (H)	H41Y, H41L	3	Catalytic site, hydrophobic contact
49	Met (M)	M49I, M49T, M49V, M49L, M49K	745	Side chain Hydrophobic contact
54	Tyr (Y)	Y54*	1	No direct contact
140	Phe (F)	None	0	Backbone Hydrogen bond
143	Gly (G)	G143S, G143C	5	Backbone Hydrogen bond
145	Cys (C)	C145I, C145F, C145Y	4	Catalytic site (covalent bond)
163	His (H)	None	0	Side chain Hydrogen bond
164	His (H)	H164N	2	Backbone Hydrogen Bond
165	Met (M)	M165I, M165K, M165V, M165L, M165T	42	Side Chain Hydrophobic contact
166	Glu (E)	E166G	3	Backbone and side chain contact
167	Leu (L)	L167*, L167I, L167S	38	Side Chain Hydrophobic contact
168	Pro (P)	P168S, P168R, P168A, P168T	122	Side Chain Hydrophobic contact
189	Gln (Q)	Q189K, Q189*, Q189H, Q189L	15	No direct contact

PF-07321332 has also demonstrated selectivity for coronavirus 3CLpro, showing little or no activity against a panel of human proteases, as well as HIV protease. IC50 against human chymotrypsin was >10 μM and against all other tested proteases was >100 μM.

Primary and Secondary pharmacology

Antiviral activity

PF-07321332 exhibited antiviral activity against SARS-CoV-2 infection of dNHBE cells, a primary human lung alveolar epithelial cell line (EC_{50} value of 61.8 nM and EC_{90} value of 181 nM) after 3 days of drug exposure (**Table 12**).

It is considered as a pancoronavirus antiviral against other alpha and betacoronaviruses (SARS-CoV-1, HCoV-229E, MERS-CoV, HCoV-OC43, HCoV-HKU1, and HCoV-NL63). But the clinical relevance uncertain since only based on *in vitro* data with no clinical data available except against SARS-Cov-2.

PF-07321332 activity is selective to the coronavirus family and PF-07321332 did not inhibit enterovirus 71 (EV71) or human rhinovirus 1B (HRV1B) viral-induced CPE, (EC50 >100 μM), nor did it demonstrate cytotoxicity in noninfected rhabdomyosarcoma cells or Hela cells (CC50 of >100 μM).

The *in vitro* antiviral activity was demonstrated in VeroE6 ACE-2 cells with an EC50 of 0.0745 μM in the presence of P-gp inhibitor to better represent physiological cells, A549-ACE2 cells with EC50/EC90 values of 0.0779 μM / 0.215 μM, and physiologically relevant dNHBE (differentiated normal human bronchial epithelial) cells with EC50 of 0.0618 μM and 0.0326 μM, at Day 3 and Day 5 post-infection respectively. The metabolite, PF-07329268 inhibited SARS-CoV-2 CPE in VeroE6 ACE-2 cells with an EC50 value of 0.690 μM, in the presence of P-gp inhibitor. The antiviral activity of PF-07321332 was specific and not due to cellular toxicity (no cytotoxicity was observed up to >100 μM in VeroE6 ACE-2 cells) resulting in a TI of >21.5 in the absence of P-gp inhibitor.

Table 12. EC50 for PF-07321332 and Remdesivir in dNHBE Cells at 3 and 5 Days Post Inoculum

Virus Collection Day	PF-07321332							
	[a]EC50 (μM)			GeoMean (95% CI)	[a]EC90 (μM)			GeoMean (95% CI)
	N=1	N=2	N=3		N=1	N=2	N=3	
3	0.0757	0.0678	0.0461	0.0618 (0.0324 to 0.118)	0.157	0.141	0.2676	0.181 (0.0769 to 0.425)
5	0.0555	0.0231	0.0271	0.0326 (0.0102 to 0.104)	0.0924	0.0436	0.0440	0.0561 (0.0192 to 0.164)
Virus Collection Day	Remdesivir							
	[a]EC50 (μM)			GeoMean (95% CI)	[a]EC90 (μM)			GeoMean (95% CI)
	N=1	N=2	N=3		N=1	N=2	N=3	
3	0.0019	0.0053	0.0026	0.00297 (0.000805 to 0.0109)	0.0043	0.0099	0.0322	0.0111 (0.000901 to 0.137)
5	0.0024	0.0069	0.0098	0.00545 (0.000885 to 0.0336)	0.008	0.0136	0.0349	0.0156 (0.0024 to 0.0993)

a. EC_{50} curves were fit to a Hill slope of 3 when >3 and defined by top dose only which was ≥50%.
b. Data generated at Utah State University: (2020). SARS-CoV-2 (USA_WA1/2020; Washington strain). Study Report PF-07321332_23Oct20_010204.

Systemic exposure of PF-07321332 in humans is likely limited by CYP3A4 mediated metabolism. As such, ritonavir, a strong CYP3A4 inhibitor is co-administered with PF-07321332 in clinical trials in order to boost exposure. Ritonavir exhibited no inhibition of SARS-CoV-2 viral replication in A549-ACE2 cells up to 3 μM. No host cell cytotoxicity was observed for PF-07321332 or ritonavir up to 3 μM in non-infected A549-ACE2 cells.

Efficacy in major SARS-CoV-2 Variants of Concern (VOC)

The antiviral activity of PF-07321332 against SARS-CoV-2 variants B.1.1.7 (Alpha), B.1351 (Beta), P.1 (Gamma) and B.1.1.1.37 (Lambda, λ) and B.1.621 (Mu, μ) was demonstrated using a cytopathic effect protection assay in Vero E6 P-gp Knockout cells, with reported EC50 values of 75.3 nM, 171 nM, 87.7 nM, 59.5nM and 65.1 nM respectively, compared with 96.3 nM for WA1 (USA-WA1/2020). Due to the inability of the SARS-CoV-2 delta variant to exhibit CPE in the Vero E6 P-gp knockout cell line, the variants were also evaluated in Vero E6 TMPRSS2 with P-gp inhibitor. Mean EC50 values were 92.8 nM, 170 nM, 217 nM, 204 nM, 93 nM, and 82.2 nM and 138 nM in the USA-WA1/2020 SARS-CoV-2 strain and alpha, beta, gamma, lamda, and delta and Mu variants, respectively (remdesivir assay control EC50 range: 79.8 – 169 nM). Vero E6-TMPRSS2 is a relevant model for SARS-CoV-2 and close to "physiological" conditions. SARS-CoV-2 target cells are respiratory epithelial cells expressing ACE2 and TMPRSS2 (with absence of PGP efflux system).

The impact of PF-07321332 on viral loads was also measured using a qPCR-based method, showing inhibition of the VeroE6 Pgp knockout cells with mean EC50 values of 32.2 nM, 41.0 nM, 127.2 nM, 24.9 nM, 21.2 nM, 15.9 nM and 25.7 nM in the USA-WA1/2020 SARS-CoV-2 strain and the alpha, beta, gamma, delta, lambda and Mu variants, respectively (remdesivir EC50 1.9 - 14.8 nM). The activity *in vitro* on beta variant was of lesser extent.

The Delta variant represented the most prevalent VOC circulating notably in Europe when the phase 2/3 clinical study C4671005 was performed. Therefore, the population has quasi exclusively consisted in patients infected by this VOC (98%, in vast majority 21J sublineage). Four isolates that are representative of the sub lineages of Delta (21A, 21I and 21) were tested and demonstrated susceptibility to PF-07321332 across the different clades. The Delta variants tested all had Mpro sequences that were identical to the reference strain. From a large genomic surveillance of ~2.2 million Delta isolates in GISAID, ~92% are identical to reference strain Mpro sequence. There are a small percentage of Delta subvariants that contain mutations at K88R, K90R, V73I and A260V (Table below). Three mutations (K88R, K90R, A260V) have been tested with no significant drop in potency by biochemical assay. The applicant plans to also test the V731I change and has been requested by the CHMP to shortly test activity of emerging VOC.

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Table 13. Mutation and Global Frequency Analysis for Delta Variant from GISAID (B.1.617.2 and AY.X; n=2,218,609)

Mutation	Frequency
K90R	1.13%
K88R	0.35%
A260V	0.31%
V73I	0.23%
~92% of Delta isolates share the same 3CLpro sequences with the reference sequence (Wuhan-1)	

All patients with treatment failure TF (7 events) from study C4671005, were infected by a 21J isolate compared to 37 events of TF in the placebo participants (27 infected with 21J-Delta). The applicant clarified that Mpro retrieved from consensus genome sequence for these 7 events are all identical to reference sequence. The allele frequency of minor variants found are less than 5.05%, with a median value of 2.04%. There is therefore a low probability that these breakthrough cases are due to a lack of effectiveness against Delta clades 21J. The applicant is planning on isolating the viruses from the breakthrough cases and testing them in an antiviral assay against PF-07321332 for confirmatory purposes. The applicant was requested to substantiate the resistance data through the analysis of treatment failure in all applicant's clinical studies, since at this stage the resistance pattern of Paxlovid remains to be determined. Even *in vitro*, only the model of MHV-3CL was used and not the relevant SARS-CoV-2.

Upon CHMP request to obtain data on the predominant circulating Omicron VOC, the applicant provided dedicated results**:** PF-07321332 showed antiviral activity against the Omicron variant with EC50 values of 70 nM and 23 nM in the HeLa-ACE2 and Vero-TMPRSS cells compared to the SARS-CoV-2 USA-WA1/2020 strain which had EC50 values of 207 nM and 38 nM in the same cell lines, respectively (**Table 14**). No PGP inhibitor was used in Vero-TMPRSS cells contrary to other variants tested in this cell line. Out of 166 omicron isolates retrieved from GISAID, two mutations have been found in the 3CLpro. The P132H mutation has been found in all omicron isolates thus far and A70S has been found in one omicron isolate, both are located greater than 18 angstroms from the inhibitor. In a biochemical assay with recombinant Mpro expressing P132H, the activity was not reduced compared to the USAWA1/2020 Mpro (ki=0.635 Ki fold change <1).

Table 14. PF-07321332 activity against SARS-CoV-2 variants in HeLa-ACE2 cells and Vero-TMPRSS Cells

SARS CoV 2	Drug	HeLa ACE2 Geomean IC_{50} (nM) N=2	Vero TMPRSS2 Geomean IC_{50} (nM) N=1
USA-WA1/2020	PF-07321552	207	38
	Remdesivir	1590	47
	EIDD-1931	NC	1117
(mouse-adapted) MA-SARS-CoV-2/WA1	PF-07321332	128	17
	Remdesivir	498	16
	EIDD-1931	NC	762
Alpha variant (B.1.1.7)	PF-07321552	118	22
	Remdesivir	612	38
	EIDD-1931	NC	597
Beta variant (B.1.351)	PF-07321332	225	121
	Remdesivir	504	25
	EIDD-1951	NC	2348
Delta variant (B.1.617.2)	PF 07321332	169	73
	Remdesivir	603	14
	EIDD-1931	NC	1810
Omicron variant (B.1.1.529)	PF 07321332	70	23
	Remdesivir	759	19
	EIDD-1031	NC	253

EIDD-1931 is the active metabolite of molnupiravir. NC= Mean not calculated as first experiment did not determine an IC_{50}.
1 Arithmetic means calculated for the HeLa-ACE2 only as Vero-TMPRSS is only N=1

Viral resistance

PF-07321332 was only evaluated in resistance selection assay against murine hepatitis virus (MHV) infected L929 cells (10 passages). This led to the emergence of P55L and S144A mutations in 3CLpro as well as two lower frequency mutations (Thr129Met, Thr50Lys) in 3CLpro gene (frequency <4.6%).The presence of the substitutions P55L and S144A, was associated with a decrease in PF-07321332 susceptibility with 4.4 to 5-fold increase in mean EC50 values (ranging from 2.65-2.93 µM compared to 0.6 µM for parent MHV in murine L929 cells), **Table 15**. These preliminary results indicate a possible likelihood of resistance development to PF-07321332, however the clinical relevance of these results remains unclear. S144A reduced PF-07321332 susceptibility by 90-fold (based on Ki value) in a biochemical assay.

The applicant confirmed that *In vitro* selection of PF-07321332 resistant SARS-CoV-2 is being evaluated to further substantiate the genetic barrier, which appears limited at this stage. Mutants that can replicate at each passage should be monitored for reduction viral fitness or decrease in susceptibility to the treatment.

Table 15. Antiviral Activity of PF-07321332 against Mutant MHV

MHV Virus and mutant:	Mutations	Titer at 48h post-infection (PFU/mL)	Log reduction at 48h post-infection (PFU/mL)	EC_{50} Geomean µM (Range)	EC_{50} Fold-change
Parent Virus	N/A	1.5e+06	N/A	0.60 (0.4-1.0)	1
30XEC50-13	Pro55Leu, Ser144 Ala Thr129Met, Thr50Lys	12500	2 logs	2.93 (2.0-4.5)	4.9
40XEC50-11	Pro55Leu, Ser144 Ala Pro15Ala	25000	2 logs	2.80 (1.6-4.4)	4.7
30XEC50-1	Pro55Leu, Ser144 Ala	125000	1 log	2.63 (1.4-3.9)	4.4
40XEC50-1	Pro55Leu, Ser144 Ala	72500	2 logs	2.65 (1.6-3.8)	4.4

N/A = not applicable

Potency against mutated SARS-COV-2 3CL protease enzymes

The potency of PF-07321332 to inhibits the proteolytic activity of mutant SARS-CoV-2 3CL protease was evaluated using a biochemical assay.

The tested mutants were:

a) The low frequency mutations at key contact residues on SARS-CoV- 2 3CL-Protease. Those with drop in potency are six: E166A (33-fold change), F140A (39-fold change), H164N (6.4-fold change), H172Y (233-fold change), Q189K (65.4- fold change), and Y54A (23.6-fold change).

b) Emerging naturally occurring mutations found in the population; those with drop in potency were A234V, D248E, P108S, T135I, T45I, G15S and the Ki change is less than 5-fold.

c) Mutations emerging from the resistance experiment using MHV surrogate for SARS-CoV-2. Those with drop in potency are S144A and the double mutation S144A and E55L.

The table below summarises results for the 14 mutants that showed a statistically significant drop in potency, with GeoMean Ki values of 1.84 - 217 nM and with a fold change to wild type potency SARS-CoV-2 3CLpro ranging from 2.0 to 233-fold change.

Table 16. Potency of PF-073211332 Against 3CL-Protease Mutations with Significance (P-Value) Compared to Wild Type

Mutant	Potency Shift	Fold Shift in Potency	Ki (nM) GeoMean	Ki (nM) lower 95% CI	Ki (nM) upper 95%	n	p-value[b] to wild type Ki
A70T	More	2.75	<0.339	0.241	0.476	5	0.00721
A234V	Less	2.52	2.35	0.821	6.73	5	0.0286
D248E	Less	3.66	3.41	0.896	13.0	4	0.0158
E166A	Less	33.4	31.2	15.1	64.3	6	2.71E-07
F140A	Less	39.0	36.4	22.4	59.2	6	1.72E-08
G15S	Less	4.36	4.07	2.62	6.32	4	0.000179
H164N	Less	6.41	<5.98	1.95	18.3	8	0.00183
H172Y	Less	233	217	78.0	604	3	1.51E-07
P108S	Less	2.77	2.59	1.76	3.81	4	0.00193
Q189K	Less	65.4	61.0	50.1	74.4	6	2.12E-08
S144A	Less	91.9	85.7	36.9	199	3	6.80E-08
S144A & E55L	Less	101	94.2	23.5	377	3	2.49E-05
T135I	Less	3.46	3.23	0.350	29.7	3	0.0482
T45I	Less	1.97	1.84	1.09	3.10	4	0.0176
Y54A	Less	23.6	22.0	14.2	34.3	4	1.70E-07
Wild Type	N/A	N/A	0.933	0.471	1.85	5[a]	N/A

a. The n values represent the number of Ki values used to determine the geomean and CI which is lower than the experiment count due to censoring, ie experimental values that are < or > are excluded from GeoMean calculation.
b. p-value calculated as a t-test statistic for log Ki values compared to wild type

To evaluate the impact of the above-mentioned mutations i.e G15S, S144A, H164N, E166A, H172Y, Q189K on virus replication fitness as well as on PF-07321332 activity, each mutation was engineered into recombinant SARS-CoV-2. L89F and K90R, were introduced into recombinant viruses as controls, as they had no significant impact on 3CLpro inhibition of PF-07321332 in the enzymatic assay. Generation of recombinant viruses containing Y54A or F140A was not successful, consistent with the possible lethality of these mutations to virus replication.

Of the recombinant mutant viruses tested, Q189K showed reduced virus RNA replication (4-fold than those of the wildtype at 72 hours post-infection), while K90R had increased levels (4-fold than those of the wildtype at 48 and 96 hours post-infection). Recombinants containing L89F, S144A or E166A had similar replicated virus RNA levels to those of the wildtype virus (**Table 17**). Testing is ongoing to evaluate replication fitness of other mutant viruses.

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Table 17. Comparison of Virus RNA Levels vs Wild Type at Different Time Points

Time	Mutant Virus	RNA Ratio [a]	95% Lower CI	95% Upper CI	Dunnett p-value [b]
24	L89F	1.09	0.55	2.18	0.9945
	K90R	1.27	0.64	2.54	0.7639
	S144A	0.6	0.3	1.21	0.1877
	E166A	1.24	0.62	2.47	0.8338
	Q189K	1.37	0.69	2.73	0.5664
48	L89F	2.19	0.73	6.55	0.1989
	K90R	4.04	1.35	12.1	0.0121
	S144A	1.16	0.39	3.45	0.9937
	E166A	1.23	0.41	3.66	0.9726
	Q189K	0.55	0.18	1.65	0.4155
72	L89F	1.6	0.45	5.67	0.7314
	K90R	1.23	0.35	4.38	0.9837
	S144A	0.33	0.09	1.17	0.0921
	E166A	0.3	0.08	1.06	0.0622
	Q189 K	0.25	0.07	0.89	0.0314
96	L89F	3.04	0.97	9.53	0.0577
	K90R	4.3	1.37	13.5	0.0121
	S144A	1.32	0.42	4.14	0.9255
	E166A	1.01	0.32	3.18	1
	Q189 K	0.71	0.23	2.22	0.8474

[a] Ratio of Virus RNA over USA-WA1 RNA
[b] Testing of Virus RNA vs Wild-type SARS-CoV-2 (USA-WA1) RNA

Virological data from study C4671005

Viral titres measured via RT-PCR in nasal swabs over time

Participants with samples collected using unvalidated (local) swabs or collected at non-NP sites were excluded from this POC assessment, as were participants with no virus detected at baseline (0 copies/mL). Viral load below the detection limit of 100 copies/mL was imputed as approximately 50 copies/mL, ie, using 1.69 Log10 (copies/mL) for Log10 (viral load) values below 2 Log10 (copies/mL).

Results in the mITT analysis set were also examined by serology status and baseline viral load (**Table 18**). As expected, the additional viral load reduction from PF-07321332/ritonavir treatment relative to placebo were more apparent in participants who were seronegative than participants who were seropositive (-1.230 versus -0.473 log10 copies/mL, p=0.0022), and more apparent in participants with higher versus lower ((≥4 log10 copies/mL versus < 4 log10 copies/mL) viral load at baseline -1.020 versus -0.475 log10 copies/mL, p=0.0109). Compared to results in the overall mITT population, similar findings were observed when viral load over time was analysed by serology status and by baseline viral load. Viral load results at Day 1 and Day 5 (and over time) for the mITT1 and mITT2 analysis set were consistent with the mITT analyses (**Table 19**).

Results should be interpreted with particular caution in terms of magnitude given the descriptive analysis.

Viral load results over time for the mITT2 analysis set were consistent with the mITT analyses.

Table 18. Statistical Analysis of Observed and Change From Baseline in Log10 Transformed Viral Load (copies/mL) Data Over Time - mITT Analysis Set (Protocol C4671005)

		Observed			Change from baseline						Versus Placebo		
Visit	Treatment	n	Mean (SD)	Median (range)	n	Mean (SD)	Median (range)	n1	LS Mean (SE)	95% CI	LS Mean Diff (SE)	95% CI of Diff	p-value
Baseline	PF-07321332 300 mg + Ritonavir 100 mg (N=697)	552	5.984 (2.075)	6.395 (1.700, 9.160)									
	Placebo (N=682)	553	5.868 (2.102)	6.310 (1.700, 9.150)									
Day 3	PF-07321332 300 mg + Ritonavir 100 mg (N=697)	529	4.164 (2.245)	4.490 (0.000, 8.570)	529	-1.821 (1.832)	-1.710 (-7.990, 4.130)	526	-1.880 (0.098)	(-2.072, -1.688)	-0.553 (0.114)	(-0.776, -0.330)	<.0001
	Placebo (N=682)	525	4.668 (2.410)	5.120 (0.000, 9.540)	525	-1.201 (1.755)	-1.230 (-7.920, 5.590)	517	-1.327 (0.100)	(-1.523, -1.132)			
Day 5	PF-07321332 300 mg + Ritonavir 100 mg (N=697)	508	2.804 (1.900)	2.775 (0.000, 7.820)	508	-3.202 (1.752)	-3.115 (-8.420, 3.450)	505	-3.271 (0.096)	(-3.458, -3.083)	-0.868 (0.105)	(-1.074, -0.661)	<.0001
	Placebo (N=682)	507	3.602 (2.330)	3.770 (0.000, 8.700)	507	-2.252 (1.809)	-2.170 (-8.190, 5.100)	499	-2.403 (0.096)	(-2.592, -2.213)			
Day 10	PF-07321332 300 mg + Ritonavir 100 mg (N=697)	502	1.499 (1.638)	1.700 (0.000, 7.340)	502	-4.535 (2.102)	-4.920 (-8.660, 1.360)	499	-4.575 (0.086)	(-4.744, -4.407)	-0.439 (0.099)	(-0.633, -0.245)	<.0001
	Placebo (N=682)	475	1.867 (1.810)	1.700 (0.000, 7.630)	475	-3.978 (2.108)	-4.090 (-8.680, 4.830)	467	-4.136 (0.089)	(-4.310, -3.962)			
Day 14	PF-07321332 300 mg + Ritonavir 100 mg (N=697)	507	0.914 (1.299)	0.000 (0.000, 8.090)	507	-5.098 (2.129)	-5.460 (-8.980, 3.990)	504	-5.141 (0.080)	(-5.298, -4.984)	-0.162 (0.084)	(-0.326, 0.003)	0.0541
	Placebo (N=682)	500	0.990 (1.318)	0.000 (0.000, 6.540)	500	-4.833 (2.106)	-5.135 (-8.730, 3.970)	492	-4.980 (0.081)	(-5.138, -4.821)			

N = number of participants in the analysis set.
n = Number of participants with non-missing data in the analysis set.
n1 = Number of participants with non-missing data in the analysis set and the covariates in the statistical model.
Participants are excluded from the analysis for reasons of Not Detected or Missing baseline viral load result. Results from local swab use are also excluded.
Results are obtained from a Mixed Effects Repeated Measures (MMRM) Analysis of Covariance Model: Treatment, Visit, Visit by Treatment interaction as fixed effects, geographic region, baseline SARS-CoV-2 serology status, baseline viral load score and nasopharyngeal sample site (Y/N) as covariates along with participant as a random effect.

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Table 19. Statistical Analysis of Observed and Change From Baseline in Log10 Transformed Viral Load (copies/mL) Data Over Time - mITT1 Analysis Set (Protocol C4671005)

		Observed			Change from baseline						Versus Placebo		
Visit	Treatment	n	Mean (SD)	Median (range)	n	Mean (SD)	Median (range)	n1	LS Mean (SE)	95% CI	LS Mean Diff (SE)	95% CI of Diff	p-value
Baseline	PF-07321332 300 mg + Ritonavir 100 mg (N=1039)	814	5.673 (2.103)	5.980 (1.700, 9.160)									
	Placebo (N=1046)	831	5.529 (2.157)	5.910 (1.700, 9.150)									
Day 3	PF-07321332 300 mg + Ritonavir 100 mg (N=1039)	767	3.910 (2.179)	4.040 (0.000, 8.570)	767	-1.756 (1.743)	-1.700 (-7.990, 4.130)	760	-1.782 (0.077)	(-1.934, -1.631)	-0.468 (0.091)	(-0.647, -0.290)	<.0001
	Placebo (N=1046)	779	4.324 (2.392)	4.670 (0.000, 9.540)	779	-1.193 (1.734)	-1.190 (-8.030, 5.590)	769	-1.314 (0.077)	(-1.466, -1.162)			
Day 5	PF-07321332 300 mg + Ritonavir 100 mg (N=1039)	736	2.703 (1.834)	2.705 (0.000, 7.820)	736	-2.977 (1.778)	-2.935 (-8.420, 3.560)	729	-3.012 (0.076)	(-3.161, -2.863)	-0.695 (0.085)	(-0.861, -0.530)	<.0001
	Placebo (N=1046)	741	3.340 (2.271)	3.160 (0.000, 8.700)	741	-2.166 (1.785)	-2.130 (-8.190, 5.100)	731	-2.317 (0.076)	(-2.465, -2.168)			
Day 10	PF-07321332 300 mg + Ritonavir 100 mg (N=1039)	730	1.436 (1.585)	1.700 (0.000, 7.340)	730	-4.275 (2.104)	-4.440 (-8.660, 1.980)	722	-4.281 (0.067)	(-4.414, -4.149)	-0.351 (0.078)	(-0.503, -0.198)	<.0001
	Placebo (N=1046)	709	1.714 (1.763)	1.700 (0.000, 7.630)	709	-3.768 (2.046)	-3.750 (-8.680, 4.830)	699	-3.931 (0.068)	(-4.064, -3.797)			
Day 14	PF-07321332 300 mg + Ritonavir 100 mg (N=1039)	740	0.871 (1.251)	0.000 (0.000, 8.090)	740	-4.813 (2.144)	-5.130 (-8.980, 3.990)	732	-4.829 (0.063)	(-4.952, -4.706)	-0.168 (0.067)	(-0.299, -0.037)	0.0122
	Placebo (N=1046)	744	0.963 (1.306)	0.000 (0.000, 6.540)	744	-4.515 (2.130)	-4.680 (-9.150, 3.970)	735	-4.661 (0.063)	(-4.784, -4.538)			

N = number of participants in the analysis set.
n = Number of participants with non-missing data in the analysis set.
n1 = Number of participants with non-missing data in the analysis set and the covariates in the statistical model.
Participants are excluded from the analysis for reasons of Not Detected or Missing baseline viral load result. Results from local swab use are also excluded.
Results are obtained from a Mixed Effects Repeated Measures (MMRM) Analysis of Covariance Model: Treatment, Visit, Visit by Treatment interaction as fixed effects, geographic region, symptom onset duration (<=3, >3), baseline SARS-CoV-2 serology status, baseline viral load score and nasopharyngeal sample site (Y/N) as covariates along with participant as a random effect.

Resistance analysis

The applicant submitted viral NGS analysis data from 878 subjects treated in study 005, of whom 371 participants had a matched D1 and D5 sample analysed for TEMs (***Table 20***).

Table 20. Distribution of VOC by Treatment and Treatment Failure

CLADE	PF-07321332 300 mg + Ritonavir 100 mg		Placebo		ALL
	No Treatment Failure	Treatment Failure	No Treatment Failure	Treatment Failure	
20A	0(0%)	0(0%)	0(0%)	1 (0.11%)	1 (0.11%)
20C	1 (0.11%)	0(0%)	2 (0.23%)	0(0%)	3 (0.34%)
20G	1 (0.11%)	0(0%)	0(0%)	0(0%)	1 (0.11%)
20I (Alpha, V1)	1 (0.11%)	0(0%)	0(0%)	0(0%)	1 (0.11%)
20J (Gamma, V3)	2 (0.23%)	0(0%)	1 (0.11%)	0(0%)	3 (0.34%)
21A (Delta)	45 (5.13%)	0(0%)	29 (3.3%)	0(0%)	74 (8.43%)
21G (Lambda)	2 (0.23%)	0(0%)	0(0%)	0(0%)	2 (0.23%)
21H (Mu)	2 (0.23%)	0(0%)	0(0%)	0(0%)	2 (0.23%)
21I (Delta)	70 (7.97%)	0(0%)	61 (6.95%)	9 (1.03%)	140 (15.95%)
21J (Delta)	301 (34.28%)	7 (0.8%)	316 (35.99%)	27 (3.08%)	651 (74.15%)

Note:
880 subjects has Day 1 and/or Day 5 sequencing data available, out of those subjects, only 878 received either placebo or PF-07321332/Ritonavir. Percentages in parentheses were calculated using a total of 878 subjects. For each subject, CLADE is determined from Day 1 Sample, if Day 1 sample is not available, Day 5 Sample will be used.

Table 21 examines the association between baseline Mpro/3CLpro gene mutations versus those without Mpro/3CLpro mutations.

Table 21. Summary of Association Between Baseline (Day 1) 3CLpro Mutations and Treatment Failure

	PF-07321332 300 mg + Ritonavir 100 mg (N=384)	Placebo (N=385)
3CL^{pro} mutation at baseline, N1 (%)	43 (11.2%)	44 (11.4%)
Participants with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28	0 (0.0%)	2 (4.5%)
No 3CL^{pro} mutation at baseline, N2 (%)	333 (86.7%)	326 (84.7%)
Participants with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28	5 (1.5%)	33 (10.1%)
Comparing Mutation versus No Mutation		
Odds Ratio (95% CI)	NE	0.45 (0.10, 1.96)
p-value	NE	0.2868

N is participants with sequencing data and baseline viral load ≥4 log10 copies/mL.
Odds ratio, 95% CI and p-value are produced by a logistic regression. These actions occur at the various event levels: Events < 10, logistic regression not performed; 10 ≤ events < 30, performed with no covariates; 30 ≤ events < 40, also adj. by baseline viral load and by serology status; 40 ≤ events < 50, also adj. by age; 50 ≤ events < 60, also adj. by gender; 60 ≤ events < 70, also adj. by symptom onset (≤ 3 days, > 3 days); 70 ≤ events < 110, also adj. by received/expected to receive mAbs; Events ≥ 110, also adj. by geographic regions.
Baseline visit is set up according to study days of Day -2 to Day 1. For day 1 records, only results that are within 1 hour post start of dosing will be treated as baseline data.
3CL^{pro} mutations are within the defined regions of 3CL ^{pro} gene, 3CL cleavage or PF-07321332 contact sites.
Mutations identified with a frequency ≥5%.
NE = Not evaluable due to a logistic regression not performed if the number of events < 10 or if there are 0 observations in any outcome category.

Individual mutations within the Mpro/3CLpro gene region and in Mpro/3CLpro target cleavage regions were also monitored. Table 22 shows Mpro/3CLpro gene or cleavage mutations that occurred in more than 2 Paxlovid treated participants by treatment and TF in the 371 participants with Day 1 and Day 5 matched samples.

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Table 22. Mpro/3CLpro Contact and Cleavage Treatment Emergent Mutations by Treatment and Treatment Failure in >2 Participants.

Genome Region	NSPPOS	AAREF	AASUB	3CLpro TYPE	PF-07321332 + Ritonavir Treatment Failure (n=3)	Placebo Treatment Failure (n=14)	PF-07321332 + Ritonavir (n=168)	Placebo (n=203)
Mpro/3Clpro	46	S	F		0	0	1	0
			P		0	0	1	0
	107	Q	X		0	0	2	0
	153	D	Y		0	0	2	0
	189	Q	H	Contact	0	0	1	0
			K		1	0	6	7
	190	T	I	Contact	0	0	2	0
			A		0	0	0	1
	222	R	X		0	0	2	0
	260	A	T		0	0	1	0
			V		0	0	3	0
	269	K	I		0	0	1	0
			N		0	0	1	0
			X		0	0	1	0
	270	F	D		0	0	1	0
			V		0	0	1	0
			X		0	0	1	0

Protein	AAPOS	AAREF	AASUB	3CLpro TYPE	PF-07321332 + Ritonavir Treatment Failure (n=3)	Placebo Treatment Failure (n=14)	PF-07321332 + Ritonavir (n=168)	Placebo (n=203)
helicase	5328	A	S	Cleavage	0	0	2	0
3'-to-5'_exonuclease	6449	T	I	Cleavage	0	0	2	0
			P		0	0	1	0
	6451	L	F	Cleavage	0	0	1	0
			H		0	0	1	0
			I		0	0	1	0

Baseline visit is set up according to study days of Day -2 to Day 1. For day 1 records, only results that are within 1 hour post-start of dosing will be treated as baseline data. TEM in this table is defined as a mutation identified at Day 5 among participants with both Baseline and D5 valid sequencing data (samples with viral load ≥2.7 Log10 copies/mL were submitted for sequencing). Mutations identified with a frequency ≥5%.

Associations between TEMs in Mpro/3CLpro gene regions and treatment were also examined statistically (***Table 23***).

The prevalence of TEMs were higher in placebo compared to PF-07321332 /ritonavir-treated participants and additional analysis is ongoing.

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Table 23. Summary of Association between Treatment Emergent Mutations with Log10 Viral Load ≥4 and Treatment

	PF-07321332 300 mg + Ritonavir 100 mg (N=168)	Placebo (N=215)
Participants with Any Treatment Emergent Mutation	89 (53.0%)	145 (67.4%)
Odds ratio (95% CI) vs Placebo	0.51 (0.33, 0.79)	
p-value vs Placebo	0.0029	
3CL^{pro} (Nsp5) whole gene region, n (%)	8 (4.8%)	13 (6.0%)
Odds ratio (95% CI) vs Placebo	0.78 (0.31, 1.92)	
p-value vs Placebo	0.5846	
PF-07321332 contact sites within 3CL ^{pro} gene, n (%)	3 (1.8%)	2 (0.9%)
Odds ratio (95% CI) vs Placebo	NE	
p-value vs Placebo	NE	
3CL^{pro} protein cleavage sites within genes that express SARS-CoV-2 proteins, n (%)	4 (2.4%)	4 (1.9%)
Odds ratio (95% CI) vs Placebo	NE	
p-value vs Placebo	NE	
Other regions in the SARS-CoV-2 genome, n (%)	89 (53.0%)	145 (67.4%)
Odds ratio (95% CI) vs Placebo	0.51 (0.33, 0.79)	
p-value vs Placebo	0.0029	

N is participants with sequencing data and baseline viral load ≥4 log10 copies/mL and a valid viral load measurement at Day 5.
Treatment Emergent Mutation in this table is defined as mutation identified at Day 5 among participants with VL ≥4 log10 copies/mL.
Odds ratio, 95% CI and p-value are produced by a logistic regression. These actions occur at the various event levels: Events < 10, logistic regression not performed; 10 ≤ events < 30, performed with no covariates; 30 ≤ events < 40, also adj. by baseline viral load and by serology status; 40 ≤ events < 50, also adj. by age; 50 ≤ events < 60, also adj. by gender; 60 ≤ events < 70, also adj. by symptom onset (≤ 3 days, > 3 days); 70 ≤ events < 110, also adj. by received/expected to receive mAbs; Events ≥ 110, also adj. by geographic regions.
Baseline visit is set up according to study days of Day -2 to Day 1. For day 1 records, only results that are within 1 hour post start of dosing will be treated as baseline data.
3CL^{pro} mutations are within the defined regions of 3CL ^{pro} gene, 3CL cleavage or PF-07321332 contact sites.
Mutations identified with a frequency ≥5%.
NE = Not evaluable due to a logistic regression not performed if the number of events < 10 or if there are 0 observations in any outcome category.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Several oral formulations of PF-07321332 were developed and evaluated during the development programme (oral suspension, uncoated tablet at 250 mg, film coated tablet of 100 mg and 150 mg). Presently only one relative bioavailability study was performed comparing performance of the oral suspension to the uncoated tablet at 250 mg and based on the results from Study 1001 Part 3, the biocomparison between these two formulations clearly indicated that they were different with a 44% decrease on Cmax and 19% decrease on AUClast. However, such results should be interpreted with caution since ritonavir boosted formulations were not compared (for example 250mg/100 mg oral suspension vs 250 mg/100 mg uncoated tablet).

Between uncoated tablet dosed at 250 mg and film coated tablet dosed at 100 (or 150 mg), minor changes are observed in terms of drug loading and presence/absence of coated ingredients. Only dissolution tests were performed 1) between the film-coated tablets dosed at 100 mg and 150 mg, and 2) between site manufacturing of the 150 mg film-coated tablet with for both satisfactory results based on f2. Therefore, at least, an *in vitro* dissolution test comparing the 250 mg uncoated tablet with the film coated tablets should be performed (**REC**).

The applicant proposed to test the formulation effect as a covariate in the future PopPK model development, this is acceptable provided the PK dataset will include all the formulations used during the clinical development programme (oral suspension, 250 mg uncoated tablet, 100 mg and 150 mg film-coated tablets and 150 mg film-coated tablet by manufacturing process). This analysis should be provided as part of the updated PK Pop model.

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Following administration of PF-07321332/ritonavir supplied as tablet formulation at 300 mg/100 mg, the mean apparent volume of distribution (Vz/F) in healthy volunteers was 109.4 L. However, in patients the Vz/F was not explored / provided.

Overall, in healthy participants in the fasted state, the arithmetic mean (+SD) terminal elimination half-life ($t_{1/2}$) of PF-07321332, following single dose of 300/100 mg PF-07321332/ ritonavir, was 6.1 (1.8) hours. However, no information regarding $t_{1/2}$ of PF-07321332 in patients could be found. This should be further investigated / confirmed in patients.

Population PK modelling

A preliminary population PK modelling report (PMAR-EQDD-C467a-Proof of Concept-1246) based only on n= 20 healthy adult and the suspension formulation data (study C4671001, cutoff date 30 June 2021) was provided.

In summary, the preliminary Population PK model and model-based simulations (PMAR-EQDD-C467a-Proof of Concept-1246) was not considered valid / reliable. Several issues are raised:

a) The residual error model appears to be mis-specified. In one hand, the additive term, estimated to 339 ng/L, is considered too high (30-fold) compared to lower limit of quantification (10 ng/mL). In the other hand, the proportional error (even low =3.36%) was estimated with very poor precision (RSE% =111%). This questions the validity of the model.

b) To minimise the large additive error (higher than the target IC90% value of 292 ng/mL), the residual errors was excluded in the simulations. This approach is not endorsed as it would imply estimation of PK parameters and associated variabilities necessary different from that in the final model. Therefore, model-based PK predictions should be considered with caution (as issued from a model whose adequacy to the observed data has not been demonstrated).

c) Large discrepancy (more than 2-fold) for the estimation of the terminal half-live T1/2 between the population approach (15h) and the NCA calculations (7h) was observed. This should be justified and its impact on model-based predictions should be further discussed.

d) The model-based PK predictions projected with the tablet formulation are not deemed reliable. In one hand, the Pop-PK model was developed using only the suspension formulation and on the other hand, Cmax of the tablet formulation appears 44% lower than that of the suspension formulation (Please refer to the relative bioavailability part in study 1001).

Only very limited data in healthy volunteers (n=20) are part of the analysed dataset. The lack of PopPK model with all completed data from healthy volunteers and especially more full data from patients in pivotal phase 2/3 studies (very sparse data essentially steady state Ctrough are actually available) was consider critical caveat by the CHMP; it is deemed to better inform the model. Therefore, the applicant should update the model by inclusion of these data. The covariate effects (age, body weight, BMI, ethnicity, renal and hepatic impairment, pharmaceutical formulation, disease) should be explored as part of the work required to update the model. This is important to formally demonstrate the similarity of the PK features of PF-07321332 in patients compared to healthy volunteers and to address clear dosing recommendations for the specific subgroups that currently are not clearly informed (renal impairment, hepatic impairment, elderly, obese and underweighted patients). The update Population PK model should be submitted by 31 March 2022 (**LEG**).

Pharmacokinetics in target population

Preliminary PK data were collected from the ongoing pivotal efficacy and safety Phase 2/3 study (C4671005) in patients with confirmed diagnosis of SARS-CoV-2 infection. Patients received PF-07321332/ritonavir or placebo orally q12h for 5 days (10 doses total). Sparse PK sampling was

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performed: A total of 1298 plasma PF-07321332 concentrations, including 1068 evaluable samples and 230 (17.7%) BLQ samples from 601 patients were available for analysis.

The available PK data at day 5 indicated that 140 out of 173 (>80%) patients achieved a Cmin≥ IC90. When excluding the BLQ samples, 140 out of 153 (>90%) patients achieved the target Cmin. Even the observed concentrations from patients appears to be consistent with those in healthy participants (dose-normalised to 300 mg), more rich data in patients are required to allow reliable estimation of the PK parameters of PF-07321332 in the target population. In addition, it is worth noting that a high number of BLQ (17.7% of the dataset) was observed after and beyond the first dose. Such findings are expected to be revisited in the elaboration of the updated popPK model with inclusion of the PK data.

Special populations

Renal and hepatic impairment:

A formal dedicated PK study (C4671011) was performed to investigate the effect renal impairment on the PK of PF-07321332. Participants were graded using the recommended metric creatinine clearance CLCR (absolute GFR expressed as mL/min). Overall, the applicant propose that no dose adjustment is needed in mild renal impairment. Besides, the dose of PF-07321332 should be reduced by one-half: PF-07321332/ritonavir 150 mg/100 mg BID. These dosing recommendations in these two subgroups are agreed.

In severe renal impaired subjects, an increase of AUC by 204% was observed compared to the normal renal group. In addition, no appropriate dosing recommendations in this subgroup are currently proposed. Thus, based on the significant 3-fold increase on the systemic exposure of PF-07321332 in patients with severe renal impairment (eGFR <30 mL/min), including ERSD (end-stage renal disease) haemodialysis patients, it is recommended, from a PK perspective, to not use the drug product in this subgroup of patients. This is reflected accordingly in the SmPC, as an explicit warning, to discourage the use at this stage, pending further investigations notably based on update of popPK model.

A formal study (1010) investigating the effect of moderate hepatic impairment on the PK of PF-07321332, in comparison to matched healthy subjects with normal hepatic function, was performed.

The study is still ongoing and only a preliminary PK report is provided.

No dose adjustment for patients with mild or moderate hepatic impairment is proposed by the applicant. Provided that PK data/conclusion is confirmed in, the proposed dosing recommendations in patients with mild and moderate hepatic impairment could be agreed. The final clinical study report for C4671010 should be provided (**REC**).

At this time, no clinical / PK data are available for patients with severe hepatic impairment. Pending availability of clinical (efficacy/safety) data and an appropriate dosing recommendation with PF-07321332 in this subgroup of patients, it is recommended, from a PK perspective, to not use the drug product in patients with severe hepatic impairment. This is reflected accordingly in the SmPC, as an explicit warning, to discourage the use at this stage, pending further investigations notably based on the update of PopPK model.

It is noteworthy that during the Art 5.3 (December 2021), the CHMP recommended as a very conservative measure a contraindication for the severe hepatic impairment and for the severe renal impairment. However, given that a larger safety database from the final analysis of the unique C4671005 clinical study (around 1000 patients treated) with no major safety concern identified (which is in line with the lack of the target organs identified from the non-clinical data) and given that rather than evidence of harm, there is a lack of data to inform on a posology in patients with severe renal impairment and severe hepatic impairment, the CHMP concluded to remove the contraindication while including warnings. The CHMP has elaborated explicit warnings to alert healthcare professionals that no

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dose recommendation could be established and that further investigations were ongoing (having in mind the forthcoming update of PKPD).

Gender:

The provided investigations regarding a potential gender effect on the PKs of PF-07321332 are not considered conclusive or informative as the validity of the Population model is not proven. The effect will be investigated as part of the update PopPK model.

Race / Ethnicity:

Race effect on PF-07321332/ritonavir PK has been investigated as part of Study 1001 in only 4 Japanese healthy volunteers. AUCtau and Cmax values were approximately 30% and 21-26%, respectively, lower in Japanese participants compared to Caucasian subjects. Drug accumulation was similar in Japanese compared to Caucasian subjects (~2).

PTR (Peak to through ratio) was 6.27 therefore with an observed geometric mean Cmax of 3772 ng/mL which consequently leads to a geometric mean Cmin of 601 ng/mL (only twice the EC90 target). Importantly, cautions should be taken with this result since only 4 subjects were included in the analysis. These preliminary results will be confirmed by using the awaited update PopPK analysis.

Body weight:

Overall, the provided investigations regarding a potential body weight effect on the PKs of PF-07321332 are not considered conclusive or informative. Therefore, the PKs of PF-07321332 in the obese and underweighted patients is not considered as clearly elucidated and the updated popPK model is expected to this purpose.

Elderly:

Overall, the PKs of PF-07321332 in elderly patients could not be considered elucidated yet and additional analyses are requested to allow a better understanding of the age effect in this subgroup. Again, the update PopPK model is expected to this purpose.

Children and adolescents

The safety and efficacy of PF-07321332 in children and adolescents below the age of 18 years have not yet been established.

No PK data are available. Thus, the PKs of PF-07321332 in adolescent patients <18 years is not considered elucidated yet.

For the current CMA under assessment, the applicant claimed that adolescent patients > 40 kg could be treated with Paxlovid with the same dose as adults, 300/100 mg PF-07321332/ritonavir BID.

According to the applicant, this dose is justified based on Population PK simulations; however, this extrapolation is based on PK data in healthy volunteers, which the CHMP considered as not adequate. As per the simulated data, it is expected that a PF-07321332/ritonavir 300 mg/100 mg BID dose in adolescents (i.e., ≥12 to < 18 years of age) will provide comparable exposures in adults receiving the same dose and maintained PF-07321332 plasma concentration above EC90 over the entire dosing interval suggestive of a therapeutic response. However, such conclusion is not endorsed from a PK perspective. The preliminary Population PK model used to simulate exposures in adolescent patients is not considered valid/ reliable; and therefore, no valid conclusion could be drawn the model-based simulations. Together with the lack of PK data (PK of PF-07321332 not characterised in adolescents) and clinical data (efficacy and safety) in the target adolescent population, this issue regarding dose selection is considered of a major concern. Consequently, the applicant withdrew the adolescent patient population from the indication.

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Interactions

Based on *in vitro* studies, and given the calculated R values being below or just above the 2012 EMA guidance cut-off criteria for MATE1 respectively, the potential for PF-07321332 to cause clinically significant DDI based on inhibition of MATE1 only would be low, but interactions with OCT1, and OATP1B1 *in vivo* could not be excluded. The applicant has committed to perform a PBPK model exercise with commercial software (SimCYP) utilising compound files for metformin and rosuvastatin. The PBPK modelling robustness should be demonstrated and high level of qualification of the model should be provided (multiple substrates, multiple perpetrators, based on *in vivo* results), to waive the need for a clinical DDI study. Otherwise clinical studies to document the magnitude of interactions of these widely prescribed drugs are needed, especially for metformin. If possible, careful attention to patient co-medicated with metformin should be brought in the on-going studies. (**REC**).

Due to both inhibition, and induction effect of Paxlovid, as co-packed combination of PF-07321332 and ritonavir, on CYP3A4 and P-gp, the net effect of Paxlovid on CYP3A4 and P-gp drug substrates needs to be assessed *in vivo*.

Given the high-risk targeted population (including notably old patients, patients with cardiovascular disease), additional DDI studies with amiodarone and clozapine notably as victim drugs and critical in this population, should have been performed. These studies could allow these patients, for whom treatment cessation could not be clinically easily handled, to benefit from Paxlovid treatments. The applicant should improve the characterisation of the DDI profile post-authorisation.

Drug-drug interactions are being assessed in studies 1013 with midazolam, and study 1012 with dabigatran. According to preliminary study results of the DDI study conducted with midazolam, midazolam exposure (AUCinf) was increased by 14.3-fold and Cmax increased by 3.86 fold in co-administration with PF-07321332/ ritonavir 300/100 mg. The full CSR for 1013 and the clinical DDI study with dabigatran should be provided (**REC**).

Taking the relatively short duration of treatment with Paxlovid into account (5 days), it is acknowledged that the current proposal for section 4.5 of the SmPC based on the interactions derived from ritonavir use in HIV treatment may be too restrictive. Nevertheless, in the absence of dedicated studies, more refined and therefore relevant recommendations can currently not be provided. The applicant should improve the characterisation of the DDI profile post-authorisation with the objective of enlarging patient population eligible to Paxlovid. Having in mind this issue, the CHMP has addressed a letter to several Healthcare Professionals organisation to raise awareness about the DDI with Paxlovid.

Pharmacodynamics

PF-PF-07321332 is an orally bioavailable 3CLpro (3C-like protease) peptidomimetic inhibitor shown to be active against SARS-CoV-2 3CLpro (EC50=61.8 nM, in dNHBE cells). The *in vitro* data supports the selectivity of PF-07321332 for SARS-CoV-2 3CLpro with low or no measurable cytotoxicity in mammalian cells.

PF-07321332 demonstrated antiviral activity against the alpha, beta, lambda, gamma, delta, mu and omicron variants with EC50 values ranging between 59.5-171 nM in a cell-based assay similar to EC50 values of the control agent remdesivir with however a moderate decrease in PF-07321332 susceptibility against the beta variant (4-fold increase in EC50 $p<0.05$). PF-07321332 showed *in vitro* antiviral activity against the Omicron variant with EC50 values of 70 nM and 23 nM in the HeLa-ACE2 and Vero-TMPRSS cells, compared to the SARS-CoV-2 USA-WA1/2020 strain which had EC50 values of 207 nM and 38 nM in the same cell lines, respectively.

PF-07321332 was only evaluated in resistance selection assay against MHV infected L929 cells (10 passages). *In vitro* selection of PF-07321332 resistant SARS-CoV-2 should be provided. It is

recommended as well to conduct the assay against variants currently circulating (mainly Omicron and Delta) (**REC**).

In phenotypic assessments for naturally occurring (based on public data) Mpro/3CLpro mutations, reduced PF-07321332 activity (≥3-fold higher Ki values) was identified for the following substitutions: G15S (4.4-fold), T135I (3.5-fold), S144A (91.9-fold), H164N (6.4-fold), H172Y (233-fold), Q189K (65.4-fold), and D248E (3.7-fold). The clinical impact of these polymorphisms is unknown. Additional biochemical analysis in non-naturally occurring mutations showed higher Ki values for the following: Y54A (23.6-fold), F140A (39.0-fold), and E166A (33.4-fold). Cell based PF-07321332 antiviral activity against all the mutant viruses should be performed (**REC**).

It is agreed that there is a low probability that events of TF in the Paxlovid arm of study C46710053CL which all occurred in patients infected with the Delta (21J) subvariant are due to a lack of effectiveness against this clade. The applicant clarified that Mpro retrieved from consensus genome sequence for these 7 events are all identical to reference sequence and the allele frequency of minor variants found on Mpro are less than 5.05%. Phenotypic analysis to determine the impact of these specific mutations on potency and cell based antiviral activity are to be performed (**REC**).

Individual mutations within the Mpro/3CLpro gene region and target cleavage regions were also monitored among participants who had a matched D1 and D5 sample analysed for TEMs in study C4671005. A260T substitution emerged in one Paxlovid subject and the A260V substitution emerged in 3 other subjects; neither emerged in any placebo subjects. A260T/V could be a possible Paxlovid TEM. Nevertheless, the potential impact of either substitution on resistance is unclear as no TF occurred in any of these patients. In a biochemical assay with recombinant Mpro expressing A260V, no reduction in PF-07321332 susceptibility was observed. This is also the case for the Mpro D153Y, Q107X and cleavage site T6449I substitutions that emerged in 2 Paxlovid treated subjects each and TF occurred in any of these patients. Mutations should continue to be monitored for possible clinical evidence of treatment resistance and the full planned genotyping and phenotyping analyses at baseline and in treatment failure from the pivotal study 1005 should be provided (**REC**).

The Mpro Q189K substitution emerged in 5 Paxlovid and 7 placebo treated subjects. It is thus unclear if Q189K could be considered a TEM. In addition, genomic position 189 is located in an AT rich region and probability of sequencing artefacts are high; nevertheless, this position should also continue to be monitored closely for possible clinical evidence of Paxlovid resistance. One case of TF was observed in Paxlovid treated subjects and the mutation has shown a drop in potency by biochemical assay (65-fold change).

2.6.4. Conclusions on clinical pharmacology

The pharmacokinetics and pharmacodynamics of Paxlovid have been described in support of the use in the target population in the context of a conditional marketing authorisation to be used under emergency situations and a particular medical need. The CHMP considers the following measures necessary to address the clinical pharmacology issues:

a) The PopPK model results including PK data collected from the patients enrolled in the EPIC-HR study with relevant covariables and relevant update to the exposure margins should be provided by 31 March 2022

Clinical pharmacology recommendations and legally binding measures are covered in the list of post-authorisation measures in Annex I.

2.6.5. Clinical efficacy

The clinical development is based on the single pivotal Phase 2/3 C4671005 study conducted in non-hospitalised, symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illnesses.

Of note, two other Phase 2/3 clinical studies are conducted, but are not part of this procedure: (i) in non-hospitalised symptomatic adult participants with COVID 19 who are at standard risk of progressing to severe illness (Study C4671002), and (ii) the second as a post-exposure prophylaxis regimen (i.e., close contacts of patients with positive COVID-19) (Study C4671006).

Table 24. Overview of key efficacy data submitted

Study id and design / reference	Key objectives / endpoints	Population	Inclusion/ exclusion criteria	Treatment	Main efficacy results
Therapeutic indication					
Study 1005	Primary objective: • To compare the efficacy of PF-07321332/ritonavir to placebo for the treatment of COVID-19 in non-hospitalised symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease. Primary endpoint: • Proportion of participants with COVID-19 related hospitalisation or death from any cause through Day 28.	Non-hospitalised, symptomatic adult participants with COVID-19, who were at increased risk of progressing to severe illness (including n = 1361)	Main inclusion criteria: • Confirmed SARS-CoV-2 infection as determined by RT-PCR (other molecular or antigen tests) within 5 days prior randomisation • Initial onset of signs/symptoms attributable to COVID-19 within 5 days prior randomisation • Has at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19 : diabetes, overweight (BMI > 25), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease,	• 300/100 mg PF-07321332/ritonavir administered orally q12h for 5 days • placebo administered orally q12h for 5 days	• mITT: A 6.32% (95% CI: -9.041% to -3.593%; p<0.0001) absolute reduction, reducing the primary endpoint event rate from 7.093% to 0.776%, with PF-07321332/ritonavir in comparison with placebo treatment. • mITT-1: A 5.765% (95% CI: -7.917% to -3.613%; p<0.0001) absolute reduction, reducing the primary endpoint event rate from 6.764% to 0.999%, with PF-07321332/ritonavir in comparison with placebo treatment.

			hypertension, sickle cell disease, neurodevelopmental disorders, active cancer, medically related technological dependence, or were 60 years of age and older regardless of comorbidities Main exclusion criteria: • History of hospitalisation for the medical treatment of COVID-19 • Current need for hospitalisation or anticipated need for hospitalisation within 48 hours after randomisation • Prior to current disease episode, any confirmed SARS-CoV-2 infection • Has received or is expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit. • Oxygen saturation of <92%		

2.6.5.1. Dose response study

No dose response study was conducted. The dose selection for the pivotal study was based on relevant available preclinical and clinical data, including repeat-dose toxicology studies, clinical safety, and PK data from the Phase 1 study (C4671001), and *in vitro* pharmacology studies with PF-07321332 (refer PK and pharmacology sections).

2.6.5.2. Main study

A single pivotal trial (C4671005 or EPIC-HR) provides data for the evaluation of efficacy. This is a phase 2/3, randomised, double-blind, placebo-controlled study.

In December 2021, the EMA issued advice on use of Paxlovid for treating COVID-19 based on the interim analysis in an Article 5(3) procedure. The results of a planned interim analysis that was conducted after approximately 45% of participants in the mITT analysis set completed Day 28 assessments and included participants randomised through 29 September 2021 (data cut-off 26 October 2021).

While the Art 5.3 was based on the primary interim analysis on the basis of which the DSMB recommended to stop the enrolment of the patient, the assessment of the marketing authorisation application is also based on the supportive final analysis; it presents the results of the primary analysis of all enrolled participants who completed the Day 34 visit.

The planned 24-weeks follow-up has not been completed yet. Those data will be provided when the 24-weeks follow-up will be completed.

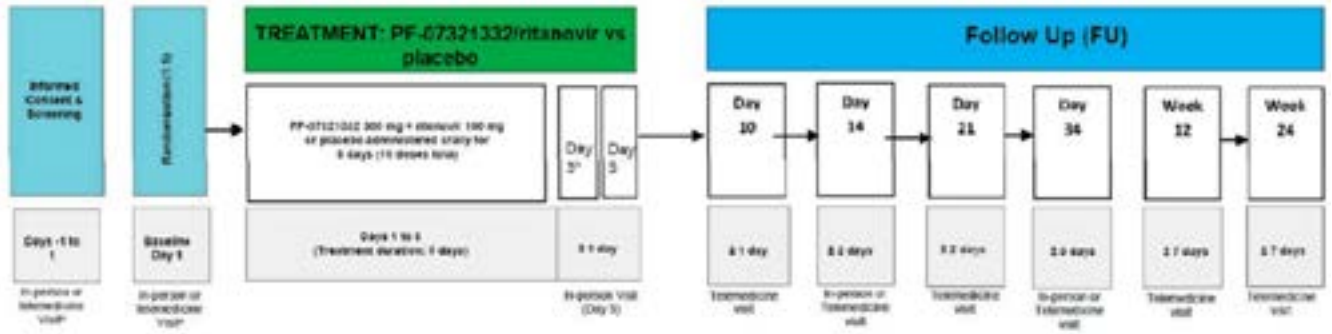
Study C4671005

Methods

This Phase 2/3, randomised, double-blind, placebo-controlled study in non-hospitalised, symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illness will determine the efficacy, safety, and tolerability of PF-07321332/ritonavir compared with placebo in a 1:1 ratio.

Participants were screened within 48 hours of randomisation. Eligible participants have received PF-07321332 plus ritonavir or placebo orally q12h for 5 days (10 doses total). The total study duration is up to 24 weeks, study intervention through Day 5 or Day 6, efficacy assessments through Day 28, a safety follow-up period through Day 34, and long-term follow-up at Weeks 12 and 24.

Figure 14. Schema of the study



- **Study Participants**

Key inclusion Criteria

Participants are eligible to be included in the study were male and female aged ≥18 years with:

Type of Participant and Disease Characteristics

- Confirmed SARS-CoV-2 infection as determined by RT-PCR in any specimen collected within 5 days prior to randomisation. RT-PCR was the preferred method; however, with evolving approaches to confirmation of SARS-CoV-2 infection, other molecular or antigen tests that detect viral RNA or protein were allowed. Participants may be enrolled based on positive results of a rapid SARSCoV-2 antigen test performed at screening.

- Initial onset of signs/symptoms attributable to COVID-19 within 5 days prior to the day of randomisation and at least 1 of the specified signs/symptoms attributable to COVID-19 present on the day of randomisation:

  Cough, Shortness of breath or difficulty breathing, Fever (>38°C), Chills or shivering, Fatigue, Muscle or body aches, Diarrhoea, Nausea, Vomiting, Headache, Sore throat, Stuffy or runny nose.

- Has at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19 including:

  - ≥60 years of age;
  - BMI >25;
  - Current smoker (cigarette smoking within the past 30 days) and history of at least 100 lifetime cigarettes;
  - Immunosuppressive disease (e.g., bone marrow or organ transplantation or primary immune deficiencies) OR prolonged use of immune-weakening medications:
    - Has received corticosteroids equivalent to prednisone ≥20 mg daily for at least 14 consecutive days within 30 days prior to study entry.
    - Has received treatment with biologics (e.g., infliximab, ustekinumab), immunomodulators (e.g., methotrexate, 6MP, azathioprine) or cancer chemotherapy within 90 days prior to study entry.
    - HIV infection with CD4 cell count <200 mm3 and a viral load less than400 copies/mL
  - Chronic lung disease (if asthma, requires daily prescribed therapy);
  - Known diagnosis of hypertension;
  - CVD, defined as history of any of the following: myocardial infarction, stroke, TIA, HF, angina with prescribed nitroglycerin, CABG, PCI, carotid endarterectomy, and aortic bypass;
  - Type 1 or Type 2 diabetes mellitus;
  - CKD provided the participant does not meet Exclusion Criterion 5;
  - Sickle cell disease;
  - Neurodevelopmental disorders (e.g., cerebral palsy, Down's syndrome) or other conditions that confer medical complexity (e.g., genetic or metabolic syndromes and severe congenital anomalies);
  - Active cancer, other than localised skin cancer, including those requiring treatment as long as the treatment is not among the prohibited medications that must be administered/continued during the trial period;
  - Medical-related technological dependence (e.g., CPAP [not related to COVID-19]).

<u>Key exclusion Criteria</u>

Main exclusion criteria were:

<u>Medical Conditions</u>

- History of hospitalisation for the medical treatment of COVID-19.

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- Current need for hospitalisation or anticipated need for hospitalisation within 48 hours after randomisation in the clinical opinion of the site investigator.
- Prior to current disease episode, any confirmed SARS-CoV-2 infection, as determined by a molecular test (antigen or nucleic acid) from any specimen collection.
- Known medical history of active liver disease (other than non-alcoholic hepatic steatosis), including chronic or active hepatitis B or C infection, primary biliary cirrhosis, Child-Pugh Class B or C, or acute liver failure.
- Receiving dialysis or have known moderate to severe renal impairment.
- Known HIV infection with a viral load greater than 400 copies/mL or taking prohibited medications for HIV treatment (from known medical history within past 6 months of the screening visit).
- Suspected or confirmed concurrent active systemic infection other than COVID-19 that may interfere with the evaluation of response to the study intervention.
- Any comorbidity requiring hospitalisation and/or surgery within 7 days prior to study entry, or that is considered life threatening within 30 days prior to study entry, as determined by the investigator.

Diagnostic Assessments

- Oxygen saturation of <92% on room air obtained at rest within 24 hours prior to randomisation.

Prior/Concomitant Therapy

- Current or expected use of any medications or substances that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations may be associated with serious and/or life-threatening events during treatment and for 4 days after the last dose of PF-07321332/ritonavir.
- Concomitant use of any medications or substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to first dose of PF-07321332/ritonavir and during study treatment.
- Has received or is expected to receive convalescent COVID-19 plasma.
- Has received or is expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit.

As a note, throughout the study period, provision was made to allow study visits to be conducted at a participant's home or at another non-clinic location approved by the investigator where possible when participants are unwilling or unable to attend a clinic visit.

- **Treatments**

The dosing instruction were:

- 2 tablets of PF-07321332 150 mg (or 3 tablets of 100 mg for some participants in the sentinel cohort) or placebo for PF-07321332 q12h
- 1 capsule of ritonavir 100 mg or placebo for ritonavir q12h.

The treatment was administered for 5 days (10 doses in total).

- **Objectives and outcomes/endpoints**

The primary objective and endpoint were:

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Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To compare the efficacy of PF-07321332/ritonavir to placebo for the treatment of COVID-19 in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28.	The difference in proportions of patients experiencing COVID-19-related hospitalization or death from any cause through Day 28 in nonhospitalized adult patients with symptomatic COVID-19 who are at increased risk of progression to severe disease, who did not receive COVID-19 therapeutic mAb treatment and were treated ≤3 days after COVID-19 symptom onset. This will be estimated without regard to adherence to randomized treatment.

The primary endpoint was the proportion of participants with COVID-19 related hospitalisation or death from any cause through Day 28.

Hospitalisation was defined as >24 hours of acute care, in a hospital or similar acute care facility, including Emergency Rooms or temporary facilities instituted to address medical needs of those with severe COVID-19 during the COVID-19 pandemic. This included specialised acute medical care unit within an assisted living facility or nursing home. This did not include hospitalisation for the purposes of public health and/or clinical trial execution.

The analysis was conducted in the modified intent-to-treat (mITT) analysis set [all treated subjects with onset of symptoms ≤3 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic monoclonal antibody (mAb) treatment], the mITT1 analysis set (all treated subjects with onset of symptoms ≤ 5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment), and the complementary population of analysis represented in mITT2 comprised all treated subjects with onset of symptoms ≤5 days).

Of note the CHMP has considered that the mITT1 was of particular relevance since in line with the SmPC recommendation of posology. Consequently, the results of this population of analysis were to be highlighted in a dedicated table in the section 5.1 of the SmPC while the results from the primary population of analysis (mITT) and the complementary one (mITT2) were to be covered through corresponding statements.

The secondary objectives and endpoints were as follows:

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Secondary:	Secondary:	Secondary:
• To describe the safety and tolerability of PF-07321332/ritonavir relative to placebo in the treatment of nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Incidence of TEAEs. • Incidence of SAEs and AEs leading to discontinuations.	Not applicable.
• To compare the efficacy of PF-07321332/ritonavir to placebo for the treatment of COVID-19 in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28.	The difference in proportions of patients experiencing COVID-19-related hospitalization or death from any cause through Day 28 in nonhospitalized adult patients with symptomatic COVID-19 who are at increased risk of progression to severe
		disease and who did not receive COVID-19 therapeutic mAb treatment. This will be estimated without regard to adherence to randomized treatment.
• To compare PF-07321332/ritonavir to placebo for the duration and severity of signs and symptoms in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Time (days) to sustained alleviation of all targeted signs/symptoms through Day 28. • Proportion of participants with severe signs/symptoms attributed to COVID-19 through Day 28. • Time (days) to sustained resolution of all targeted signs/symptoms through Day 28. • Duration of each targeted COVID-19 sign/symptom. • Progression to a worsening status in 1 or more self-reported COVID-19-associated symptoms through Day 28. • Proportion of participants with a resting peripheral oxygen saturation ≥95% at Days 1 and 5.	The absolute difference in median time to sustained alleviation or resolution of symptoms for all nonhospitalized adult patients with COVID-19 who are at increased risk of progression to severe disease. This will be estimated irrespective of adherence to randomized treatment.
• To compare PF-07321332/ritonavir to placebo for all-cause mortality in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Proportion of participants with death (all cause) through Week 24.	• Not applicable.
• To determine the PK of PF-07321332 in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• PF-07321332 PK in plasma and whole blood (if feasible).	• Not applicable.
• To describe the viral load in nasal samples over time in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Viral titers measured via RT-PCR in nasal swabs over time.	• Not applicable.
• To compare PF-07321332/ritonavir to placebo for COVID-19-related medical visits in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Number of COVID-19 related medical visits through Day 28.	• Not applicable.
• To compare PF-07321332/ritonavir to placebo for COVID-19-related hospitalizations in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Number of days in hospital and ICU stay in participants with COVID-19 related hospitalization.	• Not applicable.

In terms of efficacy, only the Proportion of participants with COVID-19-related hospitalisation or death from any cause through Day 28, with the different estimands, and the Viral titres measured via RT-PCR in nasal swabs over time have been analysed at the interim analysis, as planned in the protocol.

- **Sample size**

This study was designed to have 90% statistical power to show a difference of 3.5% in the proportion of participants hospitalised/dying who did not receive COVID-19 therapeutic mAb between the treatment arms (PF07321332/ritonavir versus placebo) and were treated ≤3 days after COVID-19 symptom onset, using a 2-sided Type I error rate of 5%. The proportion of hospitalisation/death in the placebo arm was assumed to be 7%.

The sample size needed to detect a 3.5% difference with 90% power at a 2-sided significance level of 5% was determined to be 1717 randomised participants. Enrolment of participants who at baseline had received or were expected to receive COVID-19 therapeutic mAb treatment was estimated to be approximately 20% of participants and limited/capped to 25% enrolment. Enrolment of participants that had COVID-19 symptom onset >3 days prior to randomisation was expected to be approximately 25% and was to be limited to approximately 1000 participants. Assuming a 5% dropout rate, the total sample size for this study was to be approximately 3100 participants.

To allow for a 5% dropout rate, enrolment was to be stopped after approximately 1870 participants had been enrolled to ensure at least 1779 participants were available for the primary analysis.

- **Randomisation and blinding (masking)**

Eligible participants with a confirmed diagnosis of SARS-CoV-2 infection were randomised (1:1) to receive PF-07321332 and ritonavir or placebo orally q12h for 5 days (10 doses total).

Randomisation was stratified by geographic region and by whether participants had received/were expected to receive treatment with COVID-19 therapeutic mAbs (yes/no) based on the site investigator's assessment at time of randomisation.

Randomisation for the strata where participants had received or were expected to receive COVID-19 therapeutic mAb treatment was to be capped at a maximum of 25% enrolment.

This is a double-blind study. The majority of sponsor staff were blinded to study intervention allocation. There was an unblinded team supporting the interactions with, and the analyses for, the E-DMC while the study was on-going. The team consisted of medical monitor/clinicians, reporting statistician and reporting programmer(s) and was separate from the direct members of the study team. After all participants completed the Day 34 visit (or Early Termination (ET) prior to Day 34 visit), the study was to be unblinded and analyses through Day 34, including the primary efficacy endpoint analyses, was to be conducted. However, a blinded study team is to manage the completion of the study until all participants had completed the Week 24 visit (or ET prior to the Week 24 visit). The blinded team was to be separate from the unblinded team.

- **Statistical methods**

<u>Interim analysis</u>

A planned IA for efficacy and futility with a potential sample size-re-estimation was conducted and reviewed by an independent E-DMC after approximately 45% overall participants had completed the Day 28 assessments in the mITT analysis set (i.e., 28 days after randomisation).

A second IA for efficacy and futility was planned after approximately 70% of participants in the mITT analysis set completed the Day 28 assessments (i.e., 28 days after randomisation).

Subsequent to the planned interim analyses, there were 2 analyses planned for reporting the results of this study. The primary analysis was to be performed after all participants had completed the Day 34 visit. The follow-up analysis was to be performed after all participants had completed the Week 24 visit.

The nominal significance level for the 2 planned interim and final proportion of hospitalisation/death analyses was determined by means of the Lan-DeMets procedure with an O'Brien-Fleming stopping boundary. Further details are provided in the statistical methods section under multiplicity adjustment procedures.

Changes after interim analysis results

Following the availability of the first interim analysis results, the protocol was amended (Amendment 4, 20 November 2021) to remove the second interim analysis as the planned interim analysis objective was achieved. The sample size was also updated from 3100 to approximately 3000 participants due to the removal of the second interim analysis.

Analysis populations for the interim analysis

The efficacy analysis sets are described in the table below.

Analysis set	**Description**
Modified Intent-To-Treat (mITT)	All participants randomly assigned to study intervention, who take at least 1 dose of study intervention, with at least 1 post-baseline visit through Day 28 visit, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were treated ≤3 days of COVID-19 onset. Participants will be analysed according to the study intervention to which they were randomised.
Modified Intent-To-Treat 1 (mITT1)	All participants randomly assigned to study intervention, who take at least 1 dose of study intervention, with at least 1 post-baseline visit through Day 28 visit and who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment. Participants will be analysed according to the study intervention to which they were randomised.
Modified Intent-To-Treat 2 (mITT2)	All participants randomly assigned to study intervention, who take at least 1 dose of study intervention, and with at least 1 post-baseline visit through Day 28. Participants will be analysed according to the study intervention to which they were randomised.

Other analysis sets were used for disposition, baseline or safety summaries.

Full Analysis Set (FAS): All participants randomly assigned to study intervention regardless of whether or not study intervention was administered.

Safety Analysis Set (SAS): All participants who receive at least 1 dose of study intervention. Participants were analysed according to the intervention they actually received.

Analysis populations for the final analysis

The mITT, mITT1 and mITT2 populations were updated as part of SAP version 1.4 for the final analysis (no longer requiring at least 1 post-baseline visit through Day 28 visit), following an FDA request.

Analysis set	Description
Modified Intent-To-Treat (mITT)	All participants randomly assigned to study intervention, who take at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were treated ≤3 days of COVID-19 onset. Participants will be analysed according to the study intervention to which they were randomised.
Modified Intent-To-Treat 1 (mITT1)	All participants randomly assigned to study intervention, who take at least 1 dose of study intervention, and who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment. Participants will be analysed according to the study intervention to which they were randomised.
Modified Intent-To-Treat 2 (mITT2)	All participants randomly assigned to study intervention, who take at least 1 dose of study intervention. Participants will be analysed according to the study intervention to which they were randomised.

The definitions for the FAS and the SAS remained the same.

A **Per Protocol** set was also defined for the final analysis: All participants in the mITT set without important protocol deviations considered to impact the interpretation of the primary efficacy endpoint.

Hypothesis testing and multiplicity adjustment

The primary hypothesis to be tested was whether or not there is a difference in proportion of participants with COVID-19 related hospitalisation or death from any cause through Day 28 between PF-7321332/ ritonavir and placebo. The statistical hypothesis was as follows:

$$H_o: \pi_{PF\text{-}7321332} - \pi_{placebo} = 0$$

versus

$$H_a: \pi_{PF\text{-}7321332} - \pi_{placebo} \neq 0$$

Where $p_{PF\text{-}7321332}$ and $p_{placebo}$ are the proportions of participants with hospitalisation or death through Day 28. The hypotheses will be tested at an overall significant level of 5% (2-sided).

Following the positive test of the primary endpoint, sequential testing was to be performed for the following 2 secondary endpoints:

1. Proportion of participants with COVID-19 related hospitalisation or death from any cause through Day 28 who did not receive COVID-19 therapeutic mAb treatment, regardless of their onset of COVID-19 related signs and symptoms.
2. Time (days) to sustained alleviation of all targeted signs/symptoms through Day 28.

Other secondary endpoints listed below were to be subsequently tested following the Hochberg procedure:

a) Time (days) to sustained resolution of all targeted signs/symptoms through Day 28.

b) Proportion of participants with a resting peripheral oxygen saturation ≥95% at Days 1 and 5.

c) Number of COVID-19 related medical visits through Day 28.

The nominal significance level for the 2 planned interim and final proportion of hospitalisation/death analyses was determined by means of the Lan-DeMets procedure with an O'Brien-Fleming stopping boundary, with an overall 2-sided type I error rate of 5%. For the first IA (45%), O'Brien-Fleming

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approach was used for decision making, i.e., reject H0 with 2-sided p-value ≤0.002, or reject H1 with 2-sided p-value >0.9184. The actual stopping boundaries depended on the exact timing of the IA.

For the second IA (70%), O'Brien-Fleming approach was to be used for decision making, ie, reject H0 with 2-sided p-value ≤0.014, or reject H1 with 2-sided p-value >0.337. The actual stopping boundaries were to depend on the available percentage of information.

A sample size re-estimation was to be conducted during the first interim analysis based on conditional power. The sample size could have been adjusted one time and the increase was to be capped at 30%. The Cui, Hung, and Wang (1999) method would be used to control the Type I error probability.

Primary endpoint

The cumulative proportion of participants who experienced a COVID-19-related hospitalisation or death due to any cause during the first 28 days of the study was estimated for each treatment group of the mITT analysis set using the Kaplan-Meier method to consider losses to follow-up and patients who discontinued early.

The estimand was the difference of the proportions in the 2 treatment groups and its 95% confidence interval was presented, as well as, the associated two-sample proportion test. For the 95% CI, the corresponding estimate of the standard error was computed using Greenwood's formula (Kalbfleisch and Prentice; 1980). The Greenwood's formula to estimate the variance of the difference of proportions at Day 28 is sqrt[Var(S_{PF}(28))+Var($S_{Placebo}$(28))]. Instead of dealing with S(t_i) the log-log approach to CI was used. The 95% CI was computed for the estimate of L(t)= log(-log(S(t))), the hazard function.

$$Var\left(\hat{L}(t)\right) = Var\left[log\left(-log\left(\hat{S}(t)\right)\right)\right]$$

The CI will be in right range when transforming back to S(t) = exp (-exp (L(t)). Antilogging this confidence interval gives a 95% confidence interval for the difference itself.

The above primary analysis was to be conducted for the 2 planned interim analyses as well. Two-sided 95% CI (adjusted for the 2 planned interim analyses) and associated p-value (two-sample proportion test) for the null hypothesis of no difference between treatment groups were to be presented. Significance level was to be determined using the O'Brien-Fleming approach at the interim analysis and the final analysis. The overall significance level was set at 5% (2 sided).

For participants who completed Day 28 efficacy assessment (Day 34 visit), they were censored at their last visits. For participants who discontinued before Day 28 assessment or are lost to follow-up, they were censored at the last known date in the study.

Participants were analysed under the mAb stratum assigned at randomisation/baseline.

The proportion of participants with COVID-19 related hospitalisation or death from any cause through Day 28 were summarised.

Sensitivity analyses of the primary endpoint

A sensitivity analysis of the primary endpoint was performed using the mITT2 analysis set.

Two additional sensitivity analyses were performed: 1) excluding all data from Indian sites and additional participants from a non-compliant US site. 2) excluding participants from the sentinel cohort of the study treated with active treatment (3 doses of 100 mg).

A post-hoc sensitivity analysis was performed using the mITT analysis set whereby participants that did not have follow-up data through Day 21 were hypothetically assumed to experience both COVID-19-related hospitalisation and death in a worst-case scenario.

Secondary endpoints

Proportion of participants with COVID-19 related hospitalisation or death due to any cause through Day 28 in the mITT1 analysis set

The analysis of the proportion of participants with COVID-19 related hospitalisation or death due to any cause through Day 28 in the mITT1 analysis set was similar to the primary endpoint analysis.

Time (days) to Sustained Alleviation and Time to Resolution of Targeted COVID-19 Sign/Symptoms through Day 28

The time (days) to sustained alleviation and time to resolution were defined for all targeted COVID-19 associated symptoms based on self-assessment.

Sustained alleviation of all targeted COVID-19 signs/symptoms was defined as the event occurring on the first of 4 consecutive days when all symptoms scored as moderate or severe at study entry are scored as mild or absent AND all symptoms scored mild or absent at study entry are scored as absent. The first day of the 4 consecutive-day period is considered the First Event Date.

Sustained resolution is defined as when all targeted symptoms are scored as absent for 4 consecutive days. The first day of the 4 consecutive-day period is considered the First Event Date.

For symptoms with no reported severity in baseline, the symptom was to be absent in order to be counted as sustained alleviated/resolved (missing severity at baseline were treated as mild).

Day 25 is the last possible day the symptom alleviation and resolution endpoints can be achieved (definition includes data from the subsequent three days) and Day 28 is the last day participants report their daily signs and symptoms.

The time to sustained symptom alleviation/resolution for the purpose of this study is defined as:

- For a participant with sustained symptom alleviation/resolution (event), time to event is calculated as (First Event Date) – (First Dose Date) +1.
- For a participant that either completes Day 28 of the study or discontinues from the study before Day 28 without sustained symptom alleviation/resolution (censored), censoring date is at the last date on which symptom alleviation/resolution is assessed, and time is calculated as (Censoring Date) – (First Dose Date) +1 or Day 25 whichever occurs first.

The decision to require 4 consecutive days with all targeted symptoms absent was based on exploratory analyses of data from the ACTIV-2/A5401 study, which suggested that this choice (rather than requiring fewer consecutive days) better captured sustained symptom resolution with low probability of subsequent relapse.

Participants who are hospitalised for the treatment of COVID-19 or death from any cause during the 28-day period were classified as not achieving sustained symptom alleviation/resolution and were censored at day 25.

Cox proportional hazard model analyses were used for time to sustained symptom alleviation/resolution. Cox proportional hazard model included treatment and region effect as independent variables. In addition, the stratification variables were added to the model analyses depending of the analysis population.

Number of COVID-19 Related Medical Visits Through Day 28

The number of COVID-19 related medical visits through Day 28 were analysed with a negative-binomial regression model, using the log-total number of days of data collection as the participant

offset variable. The resulting analysis shows the difference in estimated rate of medical visits between treatment groups. The analyses were done using mITT, mITT1, and mITT2 populations.

Subgroup analyses

Pre-specified subgroup analyses of the primary and first key secondary endpoints using the mITT and mITT1 analysis sets, respectively, were conducted by age (<65, ≥65 years), gender, race, BMI (<25, 25-29, ≥30 kg/m2), baseline serology status (antibody negative, antibody positive), baseline viral load ([<104, ≥104 copies/mL] and [<107, ≥107 copies/mL]), baseline comorbidities and number of baseline comorbidities present (0-1, 2-3, ≥4).

Changes to planned analyses

Several important changes were made to the planned analyses as part of protocol amendments 2, 3 and 4. Most relevant modifications are briefly described in the table below.

Protocol amendment	Change in planned analyses
Amendment 2 02 August 2021	The primary analysis set (mITT) has been refined to include just those participants who were treated ≤3 days after COVID-19 symptom onset (symptom onset window reduced from <5 days to ≤3 days). Other impacts include: 1. Key secondary endpoint added as a consequence on mITT1 population, i.e. regardless of COVID-19 symptom onset 2. Sample size increased from 2260 to approximately 3000 (adjusted for updated primary efficacy analysis) 3. Enrolment of participants that had COVID-19 symptom onset > 3 days prior to randomisation expected to be approximately 25% and limited to 1000 participants
Amendment 3 26 October 2021	Additional planned interim analysis for efficacy and futility to be done after approximately 70% of participants in the mITT analysis set complete the Day 28 assessments (i.e., 28 days after randomisation). Other impacts include: 4. Modification of first interim analysis to be planned for efficacy and futility (rather than efficacy and safety) 5. Sample size increased from 3000 to 3100 participants due to addition of second interim analysis
Amendment 4 20 November 2021	Second interim analysis removed because the planned interim objective was achieved, and sample size reduced from 3100 to 3000 as a result.

Several changes were also implemented by SAP amendments. Key changes were:

- A sensitivity analysis of the primary endpoint based on mITT2 in the SAP (v1.1; 12 October 2021) was initially described as a secondary analysis of the primary endpoint (in protocol amendment 2, 2 August 2021)
- The POC analysis of viral load was specified in the SAP.

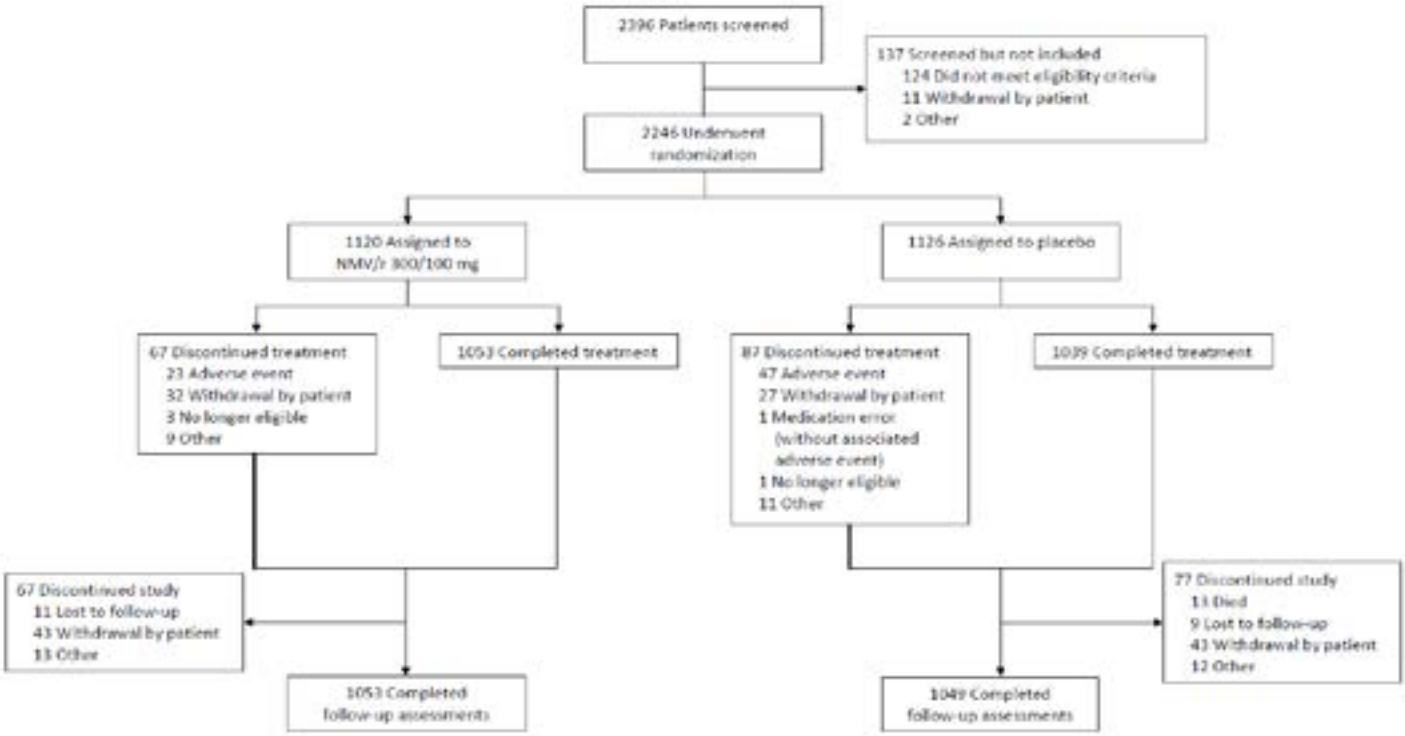
- mITT, mITT1 and mITT2 populations updated for the final analysis as requested by the FDA. They are no longer required to provide at least one post-baseline measurement through Day 28 visit.

Results

- **Participant flow**

Of the 2396 participants screened for entry into the study, 2246 participants were randomised and 137 participants did not fulfil all eligibility criteria at screening. The most common reason for screen failure was not having a confirmed SARS-CoV-2 infection as determined by RT-PCR collected within 5 days of randomisation.

Figure 15. Participant flow



- **Recruitment**

The study was conducted in 343 sites in Argentina, Brazil, Bulgaria, Colombia, Czech Republic, Hungary, India, Japan, Republic of Korea, Malaysia, Mexico, Poland, Puerto Rico, Russian Federation, South Africa, Spain, Taiwan, Thailand, Turkey, Ukraine, United States. The trial began on 16 July 2021 and the and the primary completion date was 09 December 2021.

Halt of centre's recruitment

The applicant made a data driven decision to halt recruitment (22 September 2021, total of 193 participants randomised) in India due to observations in a blinded data review of a >90% rate of serology positive participants at baseline (92% versus 45% in patients from India versus ROW, respectively), with corresponding low levels of viral load measured at baseline from a blinded assessment (mean baseline viral load [Log10 copies/mL] = 2.36 versus 5.25 copies/mL in patients from India versus ROW, respectively), and the high frequency of participants experiencing mild COVID-19 symptoms at baseline (73% versus 15% of participants with only mild symptoms at baseline, India versus ROW, respectively).

- **Conduct of the study**

Protocol Amendments

The applicant indicates that the permitted window in the inclusion criteria for a positive RT-PCR test prior to randomisation was updated from 3 days to 5 days (Protocol Amendment 1, 02 July 2021) (For other mains protocol amendment, please see Statistical methods' section).

Deviation

Overall, the most frequently reported important protocol deviations occurred within the Procedures/Tests, Investigational Product, and Laboratory categories. All other categories occurred in ≤2.5% of participants.

- In the Procedures/Test category, most deviations (18.3% participants) were due to the participant missing more than 25% of their COVID-19-related symptoms diary entries.
- In the Investigational Product category, most deviations (≥1% participants) were: PF 07321332/placebo and ritonavir/placebo were taken > 5 minutes apart (9.5%), dose window more than +/- 4 hours (4.2 %), and compliance >115% (1.0%).
- In the Laboratory category, most deviations (5.0% participants) were NP/nasal swab not done.

The applicant considers that protocol deviations were comparable between both treatment groups.

GCP noncompliance

A US site, terminated for GCP noncompliance, reported a total of 12 important protocol deviations in 12 of 37 enrolled participants at the site: 8 participants in PF-07321332/ritonavir arm and 4 participants in placebo arm. Important protocol deviations by category include:

- Inclusion/Exclusion criteria (PF-07321332/ritonavir: 3 participants; placebo: 0 participants)
- Investigational Product (PF-07321332/ritonavir: 3 participants; placebo: 1 participant)
- Procedures/Tests (PF-07321332/ritonavir: 2 participants; placebo: 3 participants).

Stop of the study

On 03 November 2021, the E-DMC reviewed data from the 45% interim analysis and determined that the pre-specified criteria for stopping the trial due to overwhelming efficacy had been achieved (PF-07321332/ritonavir is superior to placebo in the mITT analysis set for reduction in hospitalisation/death; p<0.0001, the pre-specified p-value per protocol to stop the trial for efficacy was p<0.002). Further enrolment in the study was stopped.

- **Baseline data**

The baseline demographics characteristics were overall equally distributed across treatment arms (**Table 25**).

Table 25. Demographic and Baseline Characteristics - Full Analysis Set

	PF-07321332 300 mg + Ritonavir 100 mg (N=1120)	Placebo (N=1126)	Total (N=2246)
Age (Years), n (%)			
< 18	0	0	0
18 - 44	556 (49.6)	517 (45.9)	1073 (47.8)

	PF-07321332 300 mg + Ritonavir 100 mg (N=1120)	Placebo (N=1126)	Total (N=2246)
45 - 59	338 (30.2)	349 (31.0)	687 (30.6)
60 - 64	86 (7.7)	112 (9.9)	198 (8.8)
65 - 74	104 (9.3)	117 (10.4)	221 (9.8)
≥ 75	36 (3.2)	31 (2.8)	67 (3.0)
Mean (SD)	45.33 (15.40)	46.34 (15.51)	45.84 (15.46)
Median (range)	45.00 (18.00, 86.00)	46.50 (18.00, 88.00)	46.00 (18.00, 88.00)
Gender, n (%)			
Male	566 (50.5)	582 (51.7)	1148 (51.1)
Female	554 (49.5)	544 (48.3)	1098 (48.9)
Race, n (%)			
White	800 (71.4)	807 (71.7)	1607 (71.5)
Black or African American	60 (5.4)	50 (4.4)	110 (4.9)
Asian	154 (13.8)	161 (14.3)	315 (14.0)
American Indian or Alaska Native	96 (8.6)	95 (8.4)	191 (8.5)
Native Hawaiian or other Pacific Islander	0	0	0
Multiracial	1 (<0.1)	2 (0.2)	3 (0.1)
Other	0	0	0
Not reported	8 (0.7)	9 (0.8)	17 (0.8)
Unknown	1 (<0.1)	2 (0.2)	3 (0.1)
Ethnicity, n (%)			
Hispanic or Latino	499 (44.6)	505 (44.8)	1004 (44.7)
Not Hispanic or Latino	616 (55.0)	614 (54.5)	1230 (54.8)
Not reported	5 (0.4)	7 (0.6)	12 (0.5)
Unknown	0	0	0
Weight (kg)			
Mean (SD)	81.39 (17.51)	82.28 (18.85)	81.84 (18.19)
Median (range)	80.00 (42.00, 158.3)	80.00 (42.00, 173.0)	80.00 (42.00, 173.0)
Height (cm)			
Mean (SD)	167.1 (9.64)	167.5 (10.24)	167.3 (9.94)
Median (range)	167.0 (136.9, 196.0)	167.6 (125.2, 207.3)	167.6 (125.2, 207.3)
BMI (kg/m^2), n (%)			
< 25	220 (19.6)	217 (19.3)	437 (19.5)
25 - < 30	492 (43.9)	489 (43.4)	981 (43.7)
30 - < 35	276 (24.6)	268 (23.8)	544 (24.2)
35 - < 40	78 (7.0)	88 (7.8)	166 (7.4)
≥ 40	53 (4.7)	63 (5.6)	116 (5.2)
Mean (SD)	29.09 (5.50)	29.25 (5.74)	29.17 (5.62)
Median (range)	28.20 (16.58, 58.07)	28.34 (16.05, 59.07)	28.30 (16.05, 59.07)
Duration since first diagnosis (Days), n (%)			
≤ 3	1044 (93.2)	1072 (95.2)	2116 (94.2)

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	PF-07321332 300 mg + Ritonavir 100 mg (N=1120)	Placebo (N=1126)	Total (N=2246)
> 3	76 (6.8)	54 (4.8)	130 (5.8)
Mean (SD)	1.30 (1.29)	1.31 (1.23)	1.30 (1.26)
Median (range)	1.00 (0.00, 5.00)	1.00 (0.00, 9.00)	1.00 (0.00, 9.00)
Duration since first symptom (Days), n (%)			
≤ 3	754 (67.3)	735 (65.3)	1489 (66.3)
> 3	366 (32.7)	391 (34.7)	757 (33.7)
Mean (SD)	2.93 (1.12)	2.99 (1.09)	2.96 (1.10)
Median (range)	3.00 (0.00, 7.00)	3.00 (0.00, 9.00)	3.00 (0.00, 9.00)
Number of risk factors of interest, n (%)			
0	2 (0.2)	0	2 (<0.1)
1	449 (40.1)	425 (37.7)	874 (38.9)
2	393 (35.1)	408 (36.2)	801 (35.7)
3	183 (16.3)	192 (17.1)	375 (16.7)
4	77 (6.9)	75 (6.7)	152 (6.8)
> 4	16 (1.4)	26 (2.3)	42 (1.9)
Comorbidities, n (%)			
Cardiovascular disorder	42 (3.8)	50 (4.4)	92 (4.1)
Chronic kidney disease	6 (0.5)	8 (0.7)	14 (0.6)
Chronic lung disease	62 (5.5)	41 (3.6)	103 (4.6)
Cigarette smoker	428 (38.2)	448 (39.8)	876 (39.0)
Diabetes mellitus	135 (12.1)	138 (12.3)	273 (12.2)
Hypertension	359 (32.1)	380 (33.7)	739 (32.9)
Immunosuppression	6 (0.5)	7 (0.6)	13 (0.6)
Cancer	5 (0.4)	6 (0.5)	11 (0.5)
Neurodevelopmental disorder	2 (0.2)	1 (<0.1)	3 (0.1)
Sickle cell disease	0	0	0
HIV infection	0	1 (<0.1)	1 (<0.1)
Device dependence	4 (0.4)	3 (0.3)	7 (0.3)
COVID-19 mAb treatment, n (%)			
Received/expected to receive	70 (6.3)	70 (6.2)	140 (6.2)
Not received/not expected to receive	1050 (93.8)	1056 (93.8)	2106 (93.8)
Geographic region, n (%)			
United States	463 (41.3)	465 (41.3)	928 (41.3)
Europe	334 (29.8)	335 (29.8)	669 (29.8)
India	95 (8.5)	98 (8.7)	193 (8.6)
Rest of World	228 (20.4)	228 (20.2)	456 (20.3)
Serology status, n (%)			
Negative	518 (46.3)	537 (47.7)	1055 (47.0)
Positive	581 (51.9)	568 (50.4)	1149 (51.2)
Unknown	21 (1.9)	21 (1.9)	42 (1.9)
Viral load (Log_{10} copies/mL), n (%)			
0	191 (17.1)	184 (16.3)	375 (16.7)
< 2.7	300 (26.8)	332 (29.5)	632 (28.1)

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	PF-07321332 300 mg + Ritonavir 100 mg (N=1120)	Placebo (N=1126)	Total (N=2246)
< 4	406 (36.3)	413 (36.7)	819 (36.5)
≥ 4	677 (60.4)	676 (60.0)	1353 (60.2)
≥ 5	583 (52.1)	582 (51.7)	1165 (51.9)
≥ 6	442 (39.5)	441 (39.2)	883 (39.3)
< 7	783 (69.9)	814 (72.3)	1597 (71.1)
≥ 7	300 (26.8)	275 (24.4)	575 (25.6)
≥ 8	118 (10.5)	113 (10.0)	231 (10.3)
≥ 9	4 (0.4)	5 (0.4)	9 (0.4)
≥ 10	0	0	0
Mean (SD)	4.67 (2.88)	4.59 (2.86)	4.63 (2.87)
Median (range)	5.41 (0.00, 9.16)	5.30 (0.00, 9.15)	5.35 (0.00, 9.16)

Age at Screening (years) = (date of given informed consent - date of birth + 1)/365.25.
The denominator to calculate percentages is N, the number of participants in the full analysis set within each treatment group.
Risk Factors include Age ≥ 60, BMI > 25 and Verbatims from pre-specified Medical History (Cigarette Smoker, Immunosuppression, Chronic Kidney Disease,Hypertension, Diabetes Mellitus, Cardiovascular Disorder, Chronic Lung Disease, HIV Infection, Sickle Cell Disease, Neurodevelopmental Disorder, Cancer and Device Dependence).
Duration since First Diagnosis is days from qualifying positive SARS-CoV-2 test.
Duration since first diagnosis and duration since first symptom are computed from the start of dosing.
Missing category is not included in the table.
Rest of World: Argentina, Brazil, Colombia, Japan, Malaysia, Mexico, Peru, Russian Federation, South Africa, Republic of Korea, Taiwan, Thailand, and Turkey.

A total of 2,246 participants were randomised to receive either Paxlovid or placebo in the supportive final analysis.

All participants had a laboratory confirmed SARS-CoV-2 diagnosis, with 94.2% of participants having a qualifying SARS CoV-2 positive test collected within 3 days of first dose of study intervention.

Across treatment groups:

- 93.8% participants did not receive or were not planning to receive mAbs for the disease under study at the time of randomisation.
- 53.0% of participants were serological positive at baseline.
- 60.2% participants had baseline viral load ≥4.0 Log10 copies/mL and 25.6% of participants had a very high baseline viral load (≥7.0 log10 copies/mL)

The most common risks factor at baseline were across treatment groups:

- BMI >25 kg/m^2: 80.5% (BMI >30 kg/m2: 36.8%)
- Cigarettes smokers: 39.0%
- Hypertension: 32.9%

Across treatment groups, 38.9% and 35.7% had respectively 1 and 2 risk factors.

As a significant caveat, immunosuppressed patients were poorly represented in the clinical study (<1%). This is notably specified in the description of the study population in section 5.1. The mean age of the whole population was 46 years with 13% of participants 65 years of age and consequently the population of patients older than 75 was very limited (3%) with an expected scarce number of patients 75 years of age and older; 66% of participants had onset of symptoms ≤3 days from initiation of study treatment; 37% were obese, which is limited since the inclusion criteria was also compatible for the inclusion of overweight patients (BMI > 25 kg/m2), this has unfortunately somewhat diluted the obese

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patients (BMI > 30 kg/m2); 12% had diabetes mellitus. It is noteworthy that a high proportion (51%) were serological positive while not expected to be vaccinated neither to have prior COVID-19 and only a limited proportion of participants (6.2%) either received or were expected to receive COVID-19 therapeutic mAb treatment at the time of randomisation and were excluded from the mITT and mITT1 analyses.

Overall, the demographic and baseline characteristics are consistent across the interim and the final analysis.

Variants of concern

An analysis was conducted to examine the prevalence of VOCs by treatment and by treatment failure. The primary variant across both treatment arms was Delta (98.53%) and was distributed in high prevalence as subvariants Delta/21J (74.15%), Delta/21I (15.95%) and Delta/21A (8.43%). In the group receiving PF-07321332/ritonavir, 7 participants experienced TF, and all were infected with the Delta (21J) subvariant.

Concomitant medication

During the study treatment and follow-up periods (through Day 34), concomitant medications reported by participants included the following:

- 38 (1.7%) participants received mAb for COVID-19 treatment (bamlanivimab, etesevimab, casirivimab, imdevimab, and regdanvimab), which is lower than what was reported in the 6.2% of participants who were expected to receive mAb at the time of randomisation (baseline). Of the participants who received mAb for COVID-19 treatment, 12 (1.1%) participants were in the PF-07321332/ritonavir group and 26 (2.3%) participants were in the placebo group (Table 14.4.2.1).
- 61 (2.7%) participants received favipiravir: (27 [2.4%] participants for PF-07321332/ritonavir and 34 [3.0%] for placebo).
- 19 (0.9%) participants received remdesivir (2 [0.2%] for PF-07321332/ritonavir and 17 [1.5%] for placebo).
- 186 (8.4%) participants received corticosteroids with ATC2 classification of "Corticosteroids for systemic use" (69 [6.2%] for PF-07321332/ritonavir and 117 [10.5%] for placebo). Corticosteroids were administered for any reason, such as underlying conditions (e.g., rheumatoid arthritis, asthma) and COVID-19

The proportion of participants who took a prohibited concomitant medication/vaccine was higher in the placebo group compared with the PF-07321332/ritonavir group (1.5% and 0.6%, respectively).

Supplemental Oxygen

Participants who required oxygen supplementation for COVID-19 during the C4671005 study were able to continue study treatment. During the study, 9 participants were administered supplemental oxygen for COVID-19 in the PF-07321332 group; of these, 5 (55.6%) participants had an event (hospitalisation). Within the placebo group, 55 participants were administered supplemental oxygen for COVID-19; of these, 47 participants (85.5%) had an event of hospitalisation or death.

Serostatus

Patients were considered seropositive at baseline if they had evidence of antibodies to either the S or the N antigen. Serology testing did not discriminate between IgG or IgM. Given the current turnaround time, serology testing was not part of the screening process prior to enrolment. Participants may have been unaware of prior (potentially asymptomatic) SARS-CoV-2 infection and tested seropositive at baseline. Additional exploratory testing is planned to further characterize the immune response to

SARS-CoV-2 at baseline and over time (including cytokine, immune cell markers and neutralising antibody responses).

Additionally, the population enrolled in Study C4671005 was limited to unvaccinated patients at high risk of progression to severe COVID-19. However, study C4671002 is running in parallel, and is recruiting both unvaccinated patients without risk factors for severe COVID-19 as well as fully vaccinated patients with risk factors for severe COVID-19. In a pre-planned interim analysis of data from this trial, an additional reduction in viral load of ~1.0 log10 copies/mL relative to placebo at Day 5 was observed, similar to what has been characterised in unvaccinated/high risk patients from Study C4671005. These results suggest that the antiviral activity of PF-07321332/ritonavir is consistent across vaccinated and unvaccinated patients, as would be anticipated with an antiviral with an intracellular target. Some further insights might be obtained from the smaller sample sized study in patients at standard risk of developing severe COVID-19 including patients vaccinated or non-vaccinated against SARS-CoV-2. However, the added value of this additional C4671002 or EPIC-SR study performed in patients at standard risk is uncertain given that study of lower sample size failed on its primary endpoint. As immunity to SARS-CoV-2 wanes and/or is compromised by emerging variants of concern, risk of hospitalisation/death in vaccinated patients may increase and become more reflective of the C4671005 unvaccinated patient population. Therefore, data from both C4671002 and C4671005 will inform the anticipated efficacy of treatment in both vaccination and unvaccinated patients.

Moreover, the CHMP requested to investigate the high proportion of patients with seropositive status having in mind that those patients were not expected to receive vaccine against SARS-CoV-2 nor had prior episode of COVID-19. The applicant specified that investigations were ongoing to this purpose.

- **Numbers analysed**

The analysis of efficacy was performed using the mITT, mITT1, and mITT2 sets as follow.

Table 26. Participant Evaluation Groups - All Screened Participants (Protocol C4671005)

	PF-07321332 300 mg + Ritonavir 100 mg (N=1120) n (%)	Placebo (N=1126) n (%)	Total (N=2246) n (%)
Screened: 2396			
Screened failure: 137			
Not screen failure but not randomized: 13			
Assigned to treatment	1120 (100.0)	1126 (100.0)	2246 (100.0)
Treated	1109 (99.0)	1115 (99.0)	2224 (99.0)
Not treated	11 (1.0)	11 (1.0)	22 (1.0)
Safety analysis set	1109 (99.0)	1115 (99.0)	2224 (99.0)
Full analysis set	1120 (100.0)	1126 (100.0)	2246 (100.0)
mITT analysis set	697 (62.2)	682 (60.6)	1379 (61.4)
mITT1 analysis set	1039 (92.8)	1046 (92.9)	2085 (92.8)
mITT2 analysis set	1109 (99.0)	1115 (99.0)	2224 (99.0)
Per-protocol analysis set	680 (60.7)	658 (58.4)	1338 (59.6)

PFIZER CONFIDENTIAL SDTM Creation: 11DEC2021 (22:19) Source Data: adsl Table Generation: 12DEC2021 (11:42)
(Data cutoff date : 11DEC2021 Database snapshot date : 11DEC2021) Output File: ./nda/C4671005_EUA/adsl_s002
Table 14.1.1.1 PF-07321332 is for Pfizer internal use.

A total of 13 participants who were not screen failures were not randomised. Further examination of those 13 participants showed all but 2 withdrew consent. One participant did not come to the Day 1 visit within 48 hours after screening and the other participant decided not to complete the baseline. Generally, the treatment duration was compliant with what is required in the Protocol.

- **Outcomes and estimation**

Primary analysis

COVID-19-Related Hospitalisation or Death from Any Cause (mITT)

This analysis was conducted in patients who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were treated ≤3 days of COVID-19 onset. Through Day 28, there were 9 deaths in the placebo group and none in the PF-07321332/ritonavir group.

Table 27. Primary Analysis of Proportion of Participants with COVID-19-Related-Hospitalisation or Death From any Cause Through Day 28 - mITT, Kaplan-Meier Method

	PF-07321332 300 mg + Ritonavir 100 mg	Placebo
N	697	682
Participants with event, n (%)	5 (0.717)	44 (6.452)
Participants with COVID-19 hospitalisation	5 (0.717)	44 (6.452)
Participants with death	0	9 (1.320)
Average time at risk for event (Days)[a]	27.288	26.188
Average study follow-up (Days)[b]	27.448	27.245
Estimated proportion (95% CI), %	0.723 (0.302, 1.729)	6.531 (4.901, 8.676)
Difference from Placebo (SE)	-5.807 (1.005)	
95% CI of difference	-7.777, -3.837	
p-value	<.0001	

N = number of participants in the analysis set.
The cumulative proportion of participants hospitalised for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.
a. Average time at risk for event is computed as time to first event, or time to last day of participation, or Day 28, whichever is earlier.
b. Average study follow-up is computed as time to last day of participation, or Day 28, whichever is earlier.

Interim analysis - COVID-19-Related Hospitalisation or Death from Any Cause (mITT)

The primary analysis from the interim report is presented below.

Table 28. Primary Analysis of Proportion of Participants with COVID-19-Related-Hospitalisation or Death From any Cause Through Day 28 - mITT, Kaplan-Meier Method

	PF-07321332 300 mg + Ritonavir 100 mg	Placebo
N	389	385
Participants with event, n (%)	3 (0.8)	27 (7.0)
Participants with COVID-19 hospitalization	3 (0.8)	27 (7.0)
Participants with death	0	7 (1.8)
Average time at risk for event (Days)[a]	27.2	25.9
Average study follow-up (Days)[b]	27.3	26.9
Estimated proportion (95% CI), %	0.776 (0.251, 2.386)	7.093 (4.919, 10.174)
Difference from Placebo (SE)	-6.317 (1.390)	
95% CI of difference	-9.041, -3.593	
p-value	<.0001	

N – number of participants in the analysis set.
The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.
a. Average time at risk for event is computed as time to first event, or time to last day of participation, or Day 28, whichever is earlier.
b. Average study follow-up is computed as time to last day of participation, or Day 28, whichever is earlier.

Sensitivity Analyses

At the request of FDA, a post-hoc sensitivity analysis of the mITT analysis set was performed whereby participants who did not have follow-up data through Day 21 were hypothetically assumed to have experience both COVID-19-related hospitalisation and death in a worst-case scenario:

- 2 participants in the PF-07321332/ritonavir group and 1 participant in the placebo group were assumed to have had a primary endpoint event.
- A 5.66% (95% CI: -7.69% to -3.63%; p<0.0001) absolute reduction, reducing the primary endpoint event rate from 6.68% to 1.02%, with PF-07321332/ritonavir in comparison with placebo treatment.

Additionally, to evaluate whether the results in the primary analysis were affected by data from India and a non-compliant US site, the analysis was repeated while excluding data from these sites.

- 5 participants in the PF-07321332/ritonavir group and 44 participants in the placebo group were assumed to have had a primary endpoint event.
- A 5.87% (95% CI: 7.86% to -3.88%; p<0.0001) absolute reduction, reducing the primary endpoint event rate from 6.60% to 0.73%, with PF-07321332/ritonavir in comparison with placebo treatment.
- It is to note that, of 193 participants from India randomised, none progressed to hospitalisation or death.

The results of an additional sensitivity analysis that excluded participants from the sentinel cohort of the study treated with active treatment (3 x 100 mg PF-07321332 tablets) were consistent with those observed in the primary analysis.

Sensitivity Analyses using mITT2

This analysis aimed to assess the treatment effect in a population including participants who received mAb treatment or planned to receive mAb treatment (as a note, one participant in each treatment

group had received mAb treatment). The population includes patients regardless they received treatment within 3 days and after 3 days since onset of symptom.

Table 29. Proportion of Participants with COVID-19-Related-Hospitalisation or Death From any Cause Through Day 28 - mITT2, Kaplan-Meier Method

	PF-07321332 300 mg + Ritonavir 100 mg	Placebo
N	1109	1115
Participants with event, n (%)	9 (0.812)	68 (6.099)
Participants with COVID-19 hospitalisation	9 (0.812)	67 (6.009)
Participants with death	0	12 (1.076)
Average time at risk for event (Days)[a]	27.057	26.040
Average study follow-up (Days)[b]	27.216	27.083
Estimated proportion (95% CI), %	0.822 (0.429, 1.574)	6.185 (4.909, 7.779)
Difference from Placebo (SE)	-5.363 (0.776)	
95% CI of difference	-6.884, -3.842	
p-value	<.0001	

N = number of participants in the analysis set.
The cumulative proportion of participants hospitalised for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.
a. Average time at risk for event is computed as time to first event, or time to last day of participation, or Day 28, whichever is earlier.
b. Average study follow-up is computed as time to last day of participation, or Day 28, whichever is earlier.
PFIZER CONFIDENTIAL SDTM Creation: 12DEC2021 (10:10) Source Data: adtte Table Generation: 12DEC2021 (11:37) (Data cutoff date : 11DEC2021 Database snapshot date : 11DEC2021) Output File: ./nda/C4671005_EUA/adtteh_s001_mitt2

The results of the analyses were consistent with the mITT primary analysis and conclusions remain unchanged:

- when participants who received a therapeutic COVID-19 mAb treatment postbaseline were considered to have experienced a primary endpoint event, treatment with PF-07321332/ritonavir reduced the primary event rate from 6.678 to 0.867%, showing a 5.811% absolute reduction relative to placebo (p<.0001). Two participants in the PF-07321332/ritonavir group and 3 participants in the placebo group received mAb treatment postbaseline.

Secondary Efficacy Analysis

1) Proportion of participants with COVID-19 related hospitalisation or death from any cause through Day 28 (mITT-1)

This secondary analysis assessed the treatment effect in a population including participants who have received treatment within 3 days of symptom onset and those who have received treatment after 3 days. Through Day 28, there were 12 deaths in the placebo group and none in the PF-07321332/ritonavir group.

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Table 30. Proportion of Participants with COVID-19-Related-Hospitalisation or Death From any Cause Through Day 28 – mITT1, Kaplan-Meier Method

	PF-07321332 300 mg + Ritonavir 100 mg	Placebo
N	1039	1046
Participants with event, n (%)	8 (0.770)	66 (6.310)
Participants with COVID-19 hospitalisation	8 (0.770)	65 (6.214)
Participants with death	0	12 (1.147)
Average time at risk for event (Days)[a]	27.048	25.972
Average study follow-up (Days)[b]	27.203	27.046
Estimated proportion (95% CI), %	0.781 (0.391, 1.556)	6.400 (5.063, 8.075)
Difference from Placebo (SE)	-5.619 (0.810)	
95% CI of difference	-7.207, -4.031	
p-value	<.0001	

N = number of participants in the analysis set.
The cumulative proportion of participants hospitalised for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.
a. Average time at risk for event is computed as time to first event, or time to last day of participation, or Day 28, whichever is earlier.
b. Average study follow-up is computed as time to last day of participation, or Day 28, whichever is earlier.

Interim analysis - Proportion of participants with COVID-19 related hospitalisation or death from any cause through Day 28 (mITT-1)

The first secondary analysis from the interim report is presented below.

Table 31. Proportion of Participants with COVID-19-Related-Hospitalisation or Death From any Cause Through Day 28 – mITT1, Kaplan-Meier Method

	PF-07321332 300 mg + Ritonavir 100 mg	Placebo
N	607	612
Participants with event, n (%)	6 (1.0)	41 (6.7)
Participants with COVID-19 hospitalization	6 (1.0)	41 (6.7)
Participants with death	0	10 (1.6)
Average time at risk for event (Days)[a]	27.0	25.9
Average study follow-up (Days)[b]	27.2	26.8
Estimated proportion (95% CI), %	0.999 (0.450, 2.209)	6.764 (5.025, 9.074)
Difference from Placebo (SE)	-5.765 (1.098)	
95% CI of difference	-7.917, -3.613	
p-value	<.0001	

N – number of participants in the analysis set.
The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.
a. Average time at risk for event is computed as time to first event, or time to last day of participation, or Day 28, whichever is earlier.
b. Average study follow-up is computed as time to last day of participation, or Day 28, whichever is earlier.

2) Time to Sustained Alleviation of All Targeted Signs/Symptoms Through Day 28 (mITT)

Because statistical significance was achieved in the analyses of both the primary and first secondary endpoints, the time to sustained alleviation in all targeted signs/symptoms through Day 28 was analysed with an alpha level of 5% in the sequential testing procedure. The median time to sustained alleviation in the placebo group was 15 days and was reduced to 13 days in the PF-07321332/ritonavir group.

Table 32. Time to Sustained Alleviation of All Targeted Signs and Symptoms Through Day 28 - mITT Analysis Set (Protocol C4671005)

		PF-07321332 300 mg + Ritonavir 100 mg (N=697)	Placebo (N=682)
Parameter			
Time to sustained alleviation (Days)	N1	686	674
	Participants with event, n (%)	526 (76.676)	463 (68.694)
	Median (95% CI)	12.000 (12.000, 13.000)	15.000 (13.000, 16.000)
	Q1, Q3	8.000, 21.000	9.000, -
	Hazard ratio (95% CI) versus Placebo	1.269 (1.117, 1.442)	
	p-value	0.0002	
	Proportional hazard assumption p-value	0.5252	

3) Time to Sustained Resolution of All Targeted Signs/Symptoms Through Day 28 (mITT)

The median time to sustained resolution in the placebo group was 19 days and was reduced to 16 days in the PF-07321332/ritonavir group.

Table 33. Time to Sustained Resolution of All Targeted Signs and Symptoms Through Day 28 - mITT Analysis Set (Protocol C4671005)

		PF-07321332 300 mg + Ritonavir 100 mg (N=697)	Placebo (N=682)
Parameter			
Time to sustained resolution (Days)	N1	686	674
	Participants with event, n (%)	464 (67.638)	414 (61.424)
	Median (95% CI)	16.000 (15.000, 17.000)	18.000 (17.000, 20.000)
	Q1, Q3	10.000, -	11.000, -
	Hazard ratio (95% CI) versus Placebo	1.201 (1.049, 1.375)	
	p-value	0.0080	
	Proportional hazard assumption p-value	0.5137	

3) Proportion of Participants with a Resting Peripheral Oxygen Saturation ≥95% at Days 1 and 5 (mITT)

Participants who had a resting peripheral oxygen saturation ≥95% at baseline (Day 1) were more likely to maintain those levels at Day 5 than those with a resting peripheral oxygen saturation <95% at baseline but the treatment difference was not significant (p=0.2331).

Table 34. Proportion of Participants With Resting Peripheral Oxygen Saturation >= 95% at Days 1 and 5 - mITT1 Analysis Set, Breslow-Day Test (Protocol C4671005)

	PF-07321332 300 mg + Ritonavir 100 mg (N=697)	Placebo (N=682)
Participants with Day 1 < 95%, n (%)	45 (6.456)	52 (7.625)
< 95% at Day 5	11 (24.444)	13 (25.000)
≥ 95% at Day 5	31 (68.889)	35 (67.308)
Participants with Day 1 ≥ 95%, n (%)	652 (93.544)	630 (92.375)
< 95% at Day 5	11 (1.687)	22 (3.492)
≥ 95% at Day 5	607 (93.098)	565 (89.683)
Odds ratio for Day 5 vs Day 1 (95% CI)	19.581 (7.879, 48.661)	9.539 (4.435, 20.518)
p-value from Breslow-Day test: homogeneity of odds ratios across treatment groups	0.2331	

N = number of participants in the analysis set.
Breslow-Day test was applied for testing homogeneity of odds ratio.

4) Number of COVID-19 related medical visits (mITT)

Compared with the PF-07321332/ritonavir group, there were approximately 5 times as many participants in the placebo group who had COVID-19 related medical visits (52 vs 10). The total number of visits was approximately 4 times as high in the placebo group (81 vs 22).

Table 35. Analysis of COVID-19 Related Medical Visits - mITT Analysis Set (Protocol C4671005)

	PF-07321332 300 mg + Ritonavir 100 mg (N=697)	Placebo (N=682)
Proportion of participants with COVID-19 related medical visits, n (%)[a]	10 (1.435)	52 (7.625)
Total number of medical visits across all participants	22	81
Analysis of number of medical visits		
Mean (SD)	0.032 (0.342)	0.119 (0.541)
Median (range)	0.000 (0.000, 7.000)	0.000 (0.000, 9.000)
Number of medical visits per day[b]		
Mean (SD)	0.0009 (0.0094)	0.0054 (0.0290)
Median (range)	0.0000 (0.0000, 0.1892)	0.0000 (0.0000, 0.5000)
LS mean	0.0008	0.0029
95% CI	(0.0004,0.0014)	(0.0017,0.0049)
Versus Placebo		
LS mean ratio	0.263	
95% CI for LS mean ratio	(0.130,0.532)	
p-value	0.0002	

N = number of participants in the analysis set.
a. Medical Visits include emergency room, practitioner's office, home healthcare services, urgent care, telephone consultation, outpatient infusion center, other, COVID-19-Related-Hospitalization (ICU and non-ICU stays). The Medical Visits and Hospitalization events are limited through Day 34 visit.
b. Number of medical visits per day = Number of medical visits/Number of days follow up limited to Day 37
Negative binomial regression model includes main effects of treatment, geographic region, baseline SARS-CoV-2 serology status and baseline viral load (< 4 log10 copies/mL, >= 4 log10 copies/mL) , and the log number of days follow up as the participant offset variable.

- **Ancillary analyses**

Subgroup analysis

1) Serological status

Subgroup analysis by serology status performed in mITT-1 are presented below.

Table 36. Proportion of Participants with COVID-19-Related-Hospitalisation or Death From any Cause Through Day 28, by Subgroup of Serology Status - mITT1, Kaplan-Meier Method

Subgroup		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
Negative	N	487	505
	Participants with event, n (%)	7 (1.437)	58 (11.485)
	Participants with COVID-19 hospitalization	7 (1.437)	57 (11.287)
	Participants with death	0	11 (2.178)
	Average time at risk for event (Days) *	25.760	24.691
	Average study follow-up (Days) *	27.076	26.584
	Estimated proportion (95% CI), %	1.466 (0.702, 3.051)	11.713 (9.179, 14.887)
	Difference from Placebo (SE)	-10.247 (1.547)	
	95% CI of difference	-13.279, -7.214	
	p-value	<.0001	
Positive	N	540	528
	Participants with event, n (%)	1 (0.185)	8 (1.515)
	Participants with COVID-19 hospitalization	1 (0.185)	8 (1.515)
	Participants with death	0	1 (0.189)
	Average time at risk for event (Days) *	27.289	27.199
	Average study follow-up (Days) *	27.302	27.515
	Estimated proportion (95% CI), %	0.185 (0.026, 1.307)	1.522 (0.764, 3.021)
	Difference from Placebo (SE)	-1.337 (0.565)	
	95% CI of difference	-2.445, -0.229	
	p-value	0.0180	

2) Number of baseline comorbidities

Subgroup analysis by number of baseline comorbidities performed in mITT-1 are presented below.

Table 37. Proportion of Participants with COVID-19-Related-Hospitalisation or Death From any Cause Through Day 28, by Subgroup of number of baseline comorbidities - mITT1, Kaplan-Meier Method

Subgroup		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
0-1	N	829	832
	Participants with event, n (%)	4 (0.483)	43 (5.168)
	Participants with COVID-19 hospitalization	4 (0.483)	42 (5.048)
	Participants with death	0	5 (0.601)
	Average time at risk for event (Days) *	27.191	26.067
	Average study follow-up (Days) *	27.268	26.983
	Estimated proportion (95% CI), %	0.491 (0.185, 1.303)	5.254 (3.923, 7.019)
	Difference from Placebo (SE)	-4.763 (0.818)	
	95% CI of difference	-6.365, -3.160	
	p-value	<.0001	
2-3	N	206	211
	Participants with event, n (%)	4 (1.942)	23 (10.900)
	Participants with COVID-19 hospitalization	4 (1.942)	23 (10.900)
	Participants with death	0	7 (3.318)
	Average time at risk for event (Days) *	26.456	25.569
	Average study follow-up (Days) *	26.927	27.280
	Estimated proportion (95% CI), %	1.978 (0.747, 5.185)	10.936 (7.405, 15.997)
	Difference from Placebo (SE)	-8.958 (2.364)	
	95% CI of difference	-13.592, -4.323	
	p-value	0.0002	
≥ 4	N	4	3
	Participants with event, n (%)	0	0
	Participants with COVID-19 hospitalization	0	0
	Participants with death	0	0
	Average time at risk for event (Days) *	28.000	28.000
	Average study follow-up (Days) *	28.000	28.000
	Estimated proportion (95% CI), %	0.000 (0.000, 0.000)	0.000 (0.000, 0.000)
	Difference from Placebo (SE)	0.000 (0.000)	
	95% CI of difference	0.000, 0.000	
	p-value	-	

3) Age

Subgroup analysis by age performed in mITT-1 are presented below.

Table 38. Proportion of Participants with COVID-19-Related-Hospitalisation or Death From any Cause Through Day 28, by Subgroup of Age - mITT1, Kaplan-Meier Method

Subgroup		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
Age < 65 years	N	908	909
	Participants with event, n (%)	7 (0.771)	46 (5.061)
	Participants with COVID-19 hospitalization	7 (0.771)	46 (5.061)
	Participants with death	0	4 (0.440)
	Average time at risk for event (Days) *	27.100	26.160
	Average study follow-up (Days) *	27.249	27.121
	Estimated proportion (95% CI), %	0.782 (0.374, 1.634)	5.133 (3.870, 6.794)
	Difference from Placebo (SE)	-4.351 (0.794)	
	95% CI of difference	-5.907, -2.795	
	p-value	<.0001	
Age ≥ 65 years	N	131	137
	Participants with event, n (%)	1 (0.763)	20 (14.599)
	Participants with COVID-19 hospitalization	1 (0.763)	19 (13.869)
	Participants with death	0	8 (5.839)
	Average time at risk for event (Days) *	26.687	24.730
	Average study follow-up (Days) *	26.885	26.547
	Estimated proportion (95% CI), %	0.763 (0.108, 5.295)	14.697 (9.742, 21.847)
	Difference from Placebo (SE)	-13.933 (3.129)	
	95% CI of difference	-20.066, -7.800	
	p-value	<.0001	

4) Gender

Subgroup analysis by gender performed in mITT-1 are presented below.

Table 39. Proportion of Participants with COVID-19-Related-Hospitalisation or Death From any Cause Through Day 28, by Subgroup of Gender - mITT1, Kaplan-Meier Method

Subgroup		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
Male	N	520	540
	Participants with event, n (%)	4 (0.769)	41 (7.593)
	Participants with COVID-19 hospitalization	4 (0.769)	41 (7.593)
	Participants with death	0	8 (1.481)
	Average time at risk for event (Days) *	27.133	25.746
	Average study follow-up (Days) *	27.302	27.028
	Estimated proportion (95% CI), %	0.781 (0.294, 2.066)	7.706 (5.733, 10.321)
	Difference from Placebo (SE)	-6.926 (1.220)	
	95% CI of difference	-9.317, -4.534	
	p-value	<.0001	
Female	N	519	506
	Participants with event, n (%)	4 (0.771)	25 (4.941)
	Participants with COVID-19 hospitalization	4 (0.771)	24 (4.743)
	Participants with death	0	4 (0.791)
	Average time at risk for event (Days) *	26.963	26.213
	Average study follow-up (Days) *	27.104	27.065
	Estimated proportion (95% CI), %	0.781 (0.294, 2.067)	5.007 (3.411, 7.321)
	Difference from Placebo (SE)	-4.226 (1.051)	
	95% CI of difference	-6.286, -2.167	
	p-value	<.0001	

5) BMI

Subgroup analysis by BMI performed in mITT-1 are presented below.

Table 40. Proportion of Participants with COVID-19-Related-Hospitalisation or Death From any Cause Through Day 28, by Subgroup of BMI - mITT1, Kaplan-Meier Method

Subgroup		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
< 25 kg/m [1]	N	209	207
	Participants with event, n (%)	1 (0.478)	9 (4.348)
	Participants with COVID-19 hospitalization	1 (0.478)	9 (4.348)
	Participants with death	0	1 (0.483)
	Average time at risk for event (Days) [a]	26.459	26.523
	Average study follow-up (Days) [b]	26.579	27.493
	Estimated proportion (95% CI), %	0.483 (0.068, 3.379)	4.365 (2.255, 8.221)
	Difference from Placebo (SE)	-3.882 (1.502)	
	95% CI of difference	-6.826, -0.937	
	p-value	0.0098	
25 - < 30 kg/m [2]	N	458	466
	Participants with event, n (%)	3 (0.655)	28 (6.009)
	Participants with COVID-19 hospitalization	3 (0.655)	28 (6.009)
	Participants with death	0	4 (0.858)
	Average time at risk for event (Days) [a]	27.378	26.039
	Average study follow-up (Days) [b]	27.537	27.157
	Estimated proportion (95% CI), %	0.658 (0.213, 2.027)	6.095 (4.248, 8.705)
	Difference from Placebo (SE)	-5.436 (1.179)	
	95% CI of difference	-7.747, -3.126	
	p-value	<.0001	

6) Hypertension

Subgroup analysis by hypertension status performed in mITT-1 are presented below.

Table 41. Proportion of Participants with COVID-19-Related-Hospitalisation or Death From any Cause Through Day 28, by Subgroup of hypertension status - mITT1, Kaplan-Meier Method

Subgroup		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
Hypertension = Yes	N	338	351
	Participants with event, n (%)	5 (1.479)	42 (11.966)
	Participants with COVID-19 hospitalization	5 (1.479)	41 (11.681)
	Participants with death	0	11 (3.134)
	Average time at risk for event (Days) [a]	26.901	24.869
	Average study follow-up (Days) [b]	26.932	26.799
	Estimated proportion (95% CI), %	1.508 (0.630, 3.586)	12.123 (9.106, 16.047)
	Difference from Placebo (SE)	-10.614 (1.877)	
	95% CI of difference	-14.294, -6.935	
	p-value	<.0001	
Hypertension = No	N	700	695
	Participants with event, n (%)	3 (0.429)	24 (3.453)
	Participants with COVID-19 hospitalization	3 (0.429)	24 (3.453)
	Participants with death	0	1 (0.144)
	Average time at risk for event (Days) [a]	27.363	26.532
	Average study follow-up (Days) [b]	27.333	27.186
	Estimated proportion (95% CI), %	0.434 (0.140, 1.340)	3.500 (2.359, 5.177)
	Difference from Placebo (SE)	-3.066 (0.745)	
	95% CI of difference	-4.526, -1.605	
	p-value	<.0001	

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7) Diabetes mellitus

Subgroup analysis by diabetes mellitus status performed in mITT-1 are presented below.

Table 42. Proportion of Participants with COVID-19-Related-Hospitalisation or Death From any Cause Through Day 28, by Subgroup of diabetes mellitus status - mITT1, Kaplan-Meier Method

Subgroup		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
Diabetes mellitus = Yes	N	125	127
	Participants with event, n (%)	2 (1.600)	9 (7.087)
	Participants with COVID-19 hospitalization	2 (1.600)	9 (7.087)
	Participants with death	0	4 (3.150)
	Average time at risk for event (Days) *	26.830	26.197
	Average study follow-up (Days) *	27.024	27.189
	Estimated proportion (95% CI), %	1.607 (0.404, 6.271)	7.119 (3.769, 13.235)
	Difference from Placebo (SE)	-5.512 (2.550)	
	95% CI of difference	-10.510, -0.515	
	p-value	0.0306	
Diabetes mellitus = No	N	913	919
	Participants with event, n (%)	6 (0.657)	57 (6.202)
	Participants with COVID-19 hospitalization	6 (0.657)	56 (6.094)
	Participants with death	0	8 (0.871)
	Average time at risk for event (Days) *	27.081	25.941
	Average study follow-up (Days) *	27.227	27.026
	Estimated proportion (95% CI), %	0.668 (0.300, 1.480)	6.301 (4.896, 8.092)
	Difference from Placebo (SE)	-5.634 (0.853)	
	95% CI of difference	-7.305, -3.963	
	p-value	<.0001	

8) Cigarette smoker

Subgroup analysis by cigarette smoker performed in mITT-1 are presented below.

Table 43. Proportion of Participants with COVID-19-Related-Hospitalisation or Death From any Cause Through Day 28, by Subgroup of cigarette smoker - mITT1, Kaplan-Meier Method

Subgroup		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
Cigarette smoker = Yes	N	405	424
	Participants with event, n (%)	4 (0.988)	17 (4.009)
	Participants with COVID-19 hospitalization	4 (0.988)	17 (4.009)
	Participants with death	0	2 (0.472)
	Average time at risk for event (Days) *	27.081	26.752
	Average study follow-up (Days) *	27.323	27.486
	Estimated proportion (95% CI), %	0.998 (0.376, 2.636)	4.043 (2.533, 6.423)
	Difference from Placebo (SE)	-3.045 (1.061)	
	95% CI of difference	-5.164, -0.926	
	p-value	0.0049	
Cigarette smoker = No	N	632	622
	Participants with event, n (%)	4 (0.633)	49 (7.878)
	Participants with COVID-19 hospitalization	4 (0.633)	48 (7.717)
	Participants with death	0	10 (1.608)
	Average time at risk for event (Days) *	27.024	25.441
	Average study follow-up (Days) *	27.123	26.746
	Estimated proportion (95% CI), %	0.646 (0.243, 1.711)	8.026 (6.126, 10.481)
	Difference from Placebo (SE)	-7.380 (1.146)	
	95% CI of difference	-9.627, -5.134	
	p-value	<.0001	

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 44. Summary of efficacy for trial C4671005

Title: An Interventional Efficacy and Safety, Phase 2/3, Double-Blind, 2-Arm Study to Investigate Orally Administered PF-07321332/Ritonavir Compared With Placebo in Non-hospitalised Symptomatic Adult Participants With COVID-19 Who are at Increased Risk of Progressing to Severe Illness				
Study identifier	C4671005			
Design	This Phase 2/3, randomised, double-blind, placebo-controlled study in non-hospitalised, symptomatic adult participants with COVID-19 at increased risk of progressing to severe illness determined the efficacy, safety, and tolerability of PF-07321332/ritonavir compared with placebo. Eligible participants with a confirmed diagnosis of SARS-CoV-2 infection were randomised (1:1) to receive PF-07321332/ritonavir or placebo orally q12h for 5 days (10 doses total). Randomisation was stratified by geographic region and whether participants had received/were expected to receive COVID-19 therapeutic mAb treatment (yes/no) based on the site investigator's assessment at the time of randomisation.			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks not applicable not applicable	
Hypothesis	Superiority			
Treatments groups	Intervention group		PF-07321332/ritonavir. 5 days, 1120 participants randomised	
	Control group		Placebo. 5 days, 1126 participants randomised	
Endpoints and definitions	Primary endpoint	Proportion of participants With COVID-19 related hospitalisation or death from any cause through Day 28.	The difference in proportions of patients experiencing COVID-19-related hospitalisation or death from any cause through Day 28 in non-hospitalised adult patients with symptomatic COVID-19 who are at increased risk of progression to severe disease, who did not receive COVID-19 therapeutic mAb treatment and were treated ≤3 days after COVID-19 symptom onset. This will be estimated without regard to adherence	
	First secondary endpoint	Proportion of participants With COVID-19 related hospitalisation or death from any cause through Day 28.	The difference in proportions of patients experiencing COVID-19-related hospitalisation or death from any cause through Day 28 in non-hospitalised adult patients with symptomatic COVID-19 who are at increased risk of progression to severe disease and who did not receive COVID-19 therapeutic mAb treatment. This will be estimated without regard to adherence to randomised treatment.	
Database lock	09 December 2021			
Results and Analysis				
Analysis description	**Primary Analysis (interim analysis)**			
Analysis population and time point description	Modified Intent to treat (patients treated ≤3 days after COVID-19 symptom onset) Day 28			
Descriptive statistics and estimate variability	Treatment group	PF-07321332 300 mg + Ritonavir 100 mg	Placebo	
	Number of subjects	697	682	

Title: An Interventional Efficacy and Safety, Phase 2/3, Double-Blind, 2-Arm Study to Investigate Orally Administered PF-07321332/Ritonavir Compared With Placebo in Non-hospitalised Symptomatic Adult Participants With COVID-19 Who are at Increased Risk of Progressing to Severe Illness				
Study identifier	C4671005			
	Participants with event, n (%)	5 (0.717)	44 (6.452)	
	Estimated proportion of Participants With COVID-19-Related-Hospitalisation or Death From Any Cause, %	0.723	6.531	
	95% CI	0.302, 1.729	4.901, 8.676	
Effect estimate per comparison	Primary endpoint	Comparison groups	PF-07321332 300 mg + Ritonavir 100 mg vs Placebo	
		Difference from Placebo (SE)	-5.807 (1.005)	
		95% CI of difference	-7.777, -3.837	
		P-value	<.0001	
Notes	Sensitivity and supplemental analysis are consistent with the primary analysis. Through Day 28, there were 9 deaths in the placebo group and none in the PF-07321332/ritonavir group.			
Analysis description	**First secondary analysis (supportive final analysis)**			
Analysis population and time point description	Modified Intent to treat 1 (patients treated ≤3 and > 3 days after COVID-19 symptom onset) Day 28			
Descriptive statistics and estimate variability	Treatment group	PF-07321332 300 mg + Ritonavir 100 mg	Placebo	
	Number of subjects	1039	1046	
	Participants with event, n (%)	8 (0.770)	66 (6.310)	
	Estimated proportion of Participants With COVID-19-Related-Hospitalisation or Death From Any Cause, %	0.781	6.400	
	95% CI	0.391, 1.556	5.063, 8.075	
Effect estimate per comparison	Primary endpoint	Comparison groups	PF-07321332 300 mg + Ritonavir 100 mg vs Placebo	
		Difference from Placebo (SE)	-5.619 (0.810)	
		95% CI of difference	-7.207, -4.031	
		P-value	<.0001	
Notes	Through Day 28, there were 12 deaths in the placebo group and none in the PF-07321332/ritonavir group.			

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical study in support of this procedure was a phase 2/3, randomised, double-blind, placebo-controlled study (C4671005 or EPIC-HR study) to compare the efficacy, safety, and tolerability of PF-07321332/ritonavir versus placebo in non-hospitalised, symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illness. The total study duration was up to 24 weeks, study intervention through Day 5 or Day 6, efficacy assessments through Day 28, a safety follow-up period through Day 34, and long-term follow-up at Weeks 12 and 24.

The general design of this phase 2/3 clinical trial appears appropriate. Additionally, considering the pandemic context and the need of curative treatments for the COVID-19, supporting the MAA with a single pivotal study is deemed acceptable.

The selection criteria are globally consistent with the target population. To be enrolled, positive RT-PCR, or other molecular or antigen tests, and initial onset signs/symptoms attributable to COVID-19 were needed, both within 5 days prior randomisation. This seems reasonable to define symptomatic patients with COVID-19, as well as the list of the specified signs/symptoms.

Risk factors of progressing to severe illness were predefined. Some inclusion criteria were not sufficiently stringent and thus have somewhat diluted the population at the highest risk of progressing to severe disease. Patients were to be enrolled on the basis of being overweight (BMI >25 kg/$m^{2,}$), likely referring to CDC, and not necessarily requiring obesity (BMI >30 kg/m^2) based on WHO's criteria and ECDC. Additionally, the lower bound for age regardless of comorbidities was >60 y/o, and not > 65 y/o, hence not enriching the population with very old patients.

In absence or further stratification factors, it is not fully clear in which extent both subpopulations, patients with mild-illness and patients with moderate illness, are sufficiently represented and well balanced across the treatment groups. Additionally, the selection criteria allowed to enrol patients with oxygen saturation of ≥92% on room air, while SpO2 <94% is one of the criteria to define severe illness. Nonetheless, current need for hospitalisation or anticipated need for hospitalisation within 48 hours after randomisation was an exclusion criterion, as such it might be unlikely that patients with severe illness were recruited at screening.

Considering that the applicant has not provided a definition of 'mild to moderate disease patients' and also considering that non-severe patients are best defined as not requiring O2, the CHMP requested that the indication be updated to not state 'mild to moderate' but rather 'not requiring O2', when describing the target population. The indication was updated accordingly.

Regarding prior and concomitant medication, drug-drug interactions related to CYP3A4, due to the administration of ritonavir, was taken into account.

It should also be highlighted that subjects were not vaccinated (allowed only from Day 34, while primary timepoint is at Day 28) but could receive mAb.

Regarding the study treatment, patients were instructed to take 2 tablets of PF-07321332 150 mg (or 3 tablets of 100 mg for some participants in the sentinel cohort) plus 1 capsule of ritonavir 100 mg q12h. Taking into consideration the assessment of pharmacodynamics and Scientific Advice provided by CHMP, the rationale for dose selection, based on reaching unbound Ctrough values above EC90 and assuming an inflated intrasubject variability, can be agreed, all the more in view of the clinical results with this selected dose. Further scrutiny will apply once the results of the updated PopPK model will be submitted.

The treatment duration, 5 days (10 doses), was defined by the company based on other antiviral agents used in the treatment of acute respiratory infections, such as remdesivir for SARS-CoV-2 and oseltamivir for influenza. This is agreed, based on the results of the clinical study with this tested treatment duration. This should be further explored in immunodeficient patients characterised by a prolonged clearance of the virus (potentially resulting in emergence of resistance). Even though the CHMP considered it was not feasible to proceed with a clinical study in immunocompromised patients, this issue should be monitored post-authorisation.

The choice of placebo as comparator is considered appropriate. The study designed allowed the use of mAb as considered standard of care for COVID-19 patients requiring oxygen and at increased risk of progressing to severe COVID-19. Enrolment of participants that had received or were expected to receive COVID-19 therapeutic mAb treatment was to be limited to approximately 25% of participants.

The primary objective and the primary endpoint of percentage of increased risk patients with COVID-19 related hospitalisation or death all causes within 28 days is of particular clinical relevance. There are no objections with the proposed secondary endpoints. The time to alleviation or resolution of symptoms as part of the secondary endpoints is of limited value to substantiate the clinical benefit.

The sample size calculations appear to be in line with corresponding protocol assumptions. The assumed proportion of hospitalisation/death in the placebo arm (7%) is consistent with the observed rate at interim and final analyses.

Following the availability of the first interim analysis results, the protocol was amended to remove the second interim analysis as the planned interim analysis objective was achieved.

Randomisation was stratified by geographic region and by whether participants had received/were expected to receive treatment with COVID-19 therapeutic mAbs (yes/no) based on the site investigator's assessment at time of randomisation. First, it is unclear to which extent this latter factor is appropriate to define patients most at risk of progressing to severe illness. Secondly, as the study primary analysis is restricted to patients who were treated ≤3 days after COVID-19 symptom onset, time since COVID-19 symptom onset at randomisation (≤3 vs >3 days) would have been expected as an additional stratification factor of the randomisation. The lack of stratification for the time since symptom onset could raise a concern about the preservation of the randomisation in the primary analysis population (mITT). Nevertheless, given the observed balance of treatment arms and other stratification factors in the primary analysis set, this issue is not thought to have affected the results.

Based on the SAP, all efficacy populations (mITT, mITT1 and mITT2) excluded subjects who were not treated (both interim and final analyses) or without at least 1 post-baseline visit through Day 28 (IA only). Efficacy analysis sets would be generally expected to include all randomised subjects regardless of treatment with study drug and regardless of post-baseline visit attendance. Similarly, it would be expected for the COVID-19 symptom onset criteria ≤3 days to be defined using the randomisation date, rather than using the treatment start date. The applicant did not provide additional analyses of the primary endpoint using alternative efficacy analysis sets. Nevertheless, considering the mITT, mITT1, mITT2 in the supportive final analysis to include subjects without post-baseline measurements and the relatively small frequency of untreated patients, this concern is not thought to impact the study conclusions.

The primary analysis method (proportions derived from Kaplan-Meier method with 95% CIs based on Greenwood's formula of the variance estimate) appears overall acceptable. The Lan-DeMets procedure with O'Brien-Fleming boundaries for the testing of the primary endpoint across interim and final analyses is expected to provide an appropriate control of the study type I error.

Some discrepancies were noted in the statistical analysis plan, such as the definition of analysis populations and the sequential testing of the secondary endpoints, which were clarified.

Although the primary analysis method seems acceptable, the censoring of subjects who discontinued before their Day 28 assessment or were lost to follow up could be questioned. Data from subjects who withdrew early could lead to biased estimates. As part of the assessment, the applicant provided a post-hoc sensitivity analysis with the assumption that subjects not providing follow-up data through Day 21 hypothetically experienced both COVID-19-related hospitalisation and death. This may have provided an alternative treatment effect estimate under more conservative assumptions, which was consistent with the supportive final analysis.

There were several important changes to the planned analyses that were implemented while the study was ongoing. A change in the primary analysis population and the addition of a key secondary endpoint are two key updates to the study design which could potentially raise concerns about the trial integrity. Nevertheless, these modifications were performed before unblinding the study. More importantly, the primary analysis has been repeated on all mITT, mITT1 and mITT2 populations. These alternative populations may be used to assess the robustness and consistency of the primary analysis results on wider analysis sets.

Efficacy data and additional analyses

The enrolment in the study was stopped upon recommendation by the E-DMC following the review of data from the 45% interim analysis and determined that the pre-specified criteria for stopping the trial due to efficacy had been achieved. This is acceptable.

This report included as part of this marketing authorisation includes the results from 2426 randomised participants, while 1361 participants only (n=678 for PF-07321332/ritonavir, n=683 for placebo) were included in the 45% interim analysis.

The proportion of discontinuation remained limited, with 93.1% of the randomised participants who completed the treatment phase and 93.6 % who completed the follow-up period until day 34, with well-balanced proportions across the treatment groups.

Overall, the number of important protocol deviations was comparable between the treatment groups.

Overall, demographic and baseline characteristics are balanced across the treatment groups. It should be noted that a high percentage of patients with positive serology status at baseline was observed (51.2% vs 47.0%), while the exclusion criteria included any confirmed SARS-CoV-2 infection prior the study and, participants who have received or are expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit. According to the applicant, serology testing did not discriminate between IgG or IgM. This did not allow to explore if the positive status was due to unaware of prior (potentially asymptomatic) SARS-CoV-2 infection or to immune response related to the current COVID-19 episode (at the time of the enrolment). However, the applicant is committed to provide the results of the exploratory testing planned to further characterise the immune response to SARS-CoV-2 at baseline and over time (**REC**).

Across treatment groups, 38.9% and 35.7% had respectively 1 and 2 risk factors. Main risk factors observed in the participants were overweight (80.5% with a BMI >25 kg/m2, 36.8% with a BMI >30 kg/m2), hypertension (32.9%) and diabetes mellitus (12.2%). 21.67% were older than 60 years of ages and 12.8% older than 65 years of age. Patients with immunodeficiency were poorly represented with less than 1% of the study population. There are concerns on the maintenance of the benefit in patient with immunodeficiency for which a prolonged period of viral shedding could occur. This is of importance as viral clearance might be lower in those patients with a potential risk of treatment failure and emergence of resistance with the recommended 5 days treatment. Therefore, the applicant needs to particularly monitor treatment failure in this subset of patients post approval (**REC**).

Additionally, it is noteworthy that cigarettes smokers are largely represented (39%). Cigarette smoking is not per se considered a risk factor. Thus, the applicant is committed to further elaborate in which extent participants with "cigarettes smoke" at baseline presented this solely factor or other comorbidities, and its potential impact of the results (**REC**).

60.4% participants had baseline viral load ≥4.0 Log10 copies/mL.

The population enrolled was mainly from US (41.3%) and Europe (29.8%). This appears sufficient to generalise the results of the study results to the European population.

Given the period the study was conducted, the primary variant across both treatment arms was Delta (98.53%) and was distributed in high prevalence as subvariants Delta/21J (74.15%), Delta/21I (15.95%) and Delta/21A (8.43%). As the vast majority of the participants were infected with the Delta variant, the clinical efficacy of Paxlovid is only demonstrated in this VOC. However, *in vitro* data are supportive of activity of Paxlovid against other major VOCs including the currently circulating omicron variant.

Sequencing data are available from 878 participants, completed genotyping and phenotyping analyses from the pivotal C4671005 study should be provided (refer to clinical pharmacology recommendation).

While 6.2% of the participants were expected to receive mAb at the time of randomisation, only 1.7% participants received mAb for COVID-19 treatment, 12 participants (1.1%) in the PF-07321332/ritonavir group and 26 participants (2.3%) in the placebo group, remaining a limited proportion. Additionally, 186 (8.4%) participants received corticosteroids with ATC2 classification of "Corticosteroids for systemic use" during the study period (through Day 34); 69 (6.2%) for PF-07321332/ritonavir and 117 (10.5%) for placebo which seems consistent with the observed efficacy of the study treatment.

The determination of primary efficacy was based on a planned interim analysis of 774 subjects in mITT population. The estimated risk reduction was -6.3% with unadjusted 95% CI of (9.0%, 3.6%) and a 95% CI of (-10.61%, -2.02%) when adjusting for multiplicity. The 2-sided p-value was < 0.0001 with 2-sided significance level of 0.002.

In the supporting final analysis, the primary endpoint of the study was met with a 5.807% (95% CI: -7.777% to - 3.837%; p<0.0001) absolute reduction, reducing the primary endpoint event rate from 6.531% to 0.723% at Day-28, with PF-07321332/ritonavir in comparison with placebo treatment. No patient died in the Paxlovid treatment group whereas 9 deaths occurred in the placebo group according to the mITT and 12 deaths according to the mITT1. The results are consistent with the outcomes of the interim analysis. Sensitivity analyses were also generally consistent with primary results; remove data from Indian participants and the site terminated for GCP noncompliance did not change the conclusions.

Likewise, the primary results are consistent with the analysis conducted in mITT1 and mITT2 (respectively - 5.619% [95% CI: -7.207% to -4.031%; p<0.0001] and - 5.363% [95% CI: -6.884% to -3.842; p<0.0001]).

These finding were also supported by the results in the secondary endpoint reduction in the number of COVID-19 related medical visits. While statistically significant, a limited effect was observed in the median time to sustained alleviation of all targeted signs/symptoms through day 28 and the median time to sustained resolution of all targeted signs/symptoms through day 28.

Long-term data (i.e. at Week 34) are planned to be collected in the clinical study EPIC-HR but not yet available. The applicant has committed to provide the follow-up data as soon as available to ensure no further events onset which could potentially impact the main outcomes (**REC**).

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A large proportion of participants started treatment beyond 3 days after COVID-19 onset (i.e. 38.6%) and are excluded of the mITT. If such proportion of patients failed to start the treatment within 3 days while clinical trials offer generally optimal conditions and follow-up, it is unlikely that the proportion will be better in clinical practice. Results in mITT1 may thus appear more appropriate for generalisation and more representative of the population of interest (notably encompassing patients treated within 5 days since symptoms onset). This is adequately reflected in the SmPC.

Given above considerations regarding the population of interest, together with the much larger number of subjects available in mITT1 than in mITT, subgroup analyses are assessed with mITT1 outcomes.

Overall, results were consistent in subgroup analyses for the risk factors mainly represented. It can be observed an absolute reduction of: 6.847% (95% CI: -9.823% to -3.871%; p<0.0001) in patients with a BMI >30 kg/m2, 10.614% (95% CI: -14.294% to -6.935%; p<0.0001) in patients with hypertension, 13.933% (95% CI: -20.066% to -7.800%; p<0.0001) in patients older than 65, and 5.512% (95% CI: -10.510% to -0.515%; p=0.0306) in patients with diabetes mellitus. The absolute reduction, 3.045% (95% CI: -5.164% to -0.926%; p=0.0049) in patients who are cigarettes smoker, was smaller while statistically significant.

In patients with positive serology status at baseline (55.6%), a limited, but statistically significant, absolute reduction of 1.337% (95% CI: -2.445% to -0.229%; p=0.0180) was observed. This makes it difficult to conclude on a relevant clinical efficacy. It has to be underlined that the number of events was low in the placebo group (8 hospitalisation and 1 death). As expected, the effect size is lower than the one observed in patients with seronegative status. However, given the lack of correlates of protection, the variable protection against circulating VOC, the fact that serostatus determination cannot be a prerequisite of treatment in a context of a pandemic and given the need to administer the antiviral treatment as early as possible, it is acknowledged that in practice those patients will be treated and some of them could retrieve a significant benefit. More broadly, the question therefore arises of the generalisability of the results to vaccinated patients with high risk for progression to severe COVID-19. The applicant noted that results of the study C4671002, in which vaccinated participants were enrolled, could provide supportive data. During the procedure, the applicant communicated on the failure to meet the primary endpoint of this study, preventing from formally interpreting the subgroup analyses. The applicant is committed to provide C4671002 study results as soon as available (**REC**).

Additionally, the applicant did not want to limit the indication to participants who do not require supplemental oxygen. However, oxygen supplementation for COVID-19 was an exclusion criterion and only started after randomisation in case of patient's need. Therefore, participants who required oxygen supplementation for COVID-19 were not randomised across groups and no conclusion can be drawn on the available data. Additionally, there is no reason to deviate from the harmonised wording to qualify the patients with non-severe type of COVID-19 i.e. not requiring O2. This was in fact the position adopted by the CHMP as part of the Article 5(3) procedure with the similar clinical study in support. The applicant adjusted the indication accordingly.

Finally, upon submission of the CMAA, the applicant covered in the indication the use of Paxlovid in the adolescents, on the basis of extrapolation from adults PK based on PK simulation from PopPK model only including PK data from healthy subjects (N=20) and not PK data in patients. Therefore, the applicant withdrew this age group from the indication as a response to the major objection by the CHMP due the lack of appropriate PK/PD data in high risk adolescent patients.

2.6.7. Conclusions on the clinical efficacy

The efficacy data submitted are considered sufficient to support the use of Paxlovid for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19.

While the clinical data are comprehensive, some further investigations are worth being undertaken, such as patients with seropositive status at baseline, the need to further elaborate in which extent participants with "cigarettes smoke" at baseline presented other comorbidities, further scrutiny through ongoing studies in immunocompromised patients (including chronic kidney disease, immunosuppression, cancer, or HIV infection) and the planned long-term data (i.e. at Week 34) from study C4671005.

Clinical efficacy recommendations are covered in Annex I.

2.6.8. Clinical safety

The safety data is primary based on the supportive final analysis (of the larger sample size than primary interim analysis) of the pivotal Study C4671005 (treatment in patients COVID-19 positive at High Risk, EPIC-HR) at the data cut-off date of 11 Dec 2021. Safety data from supportive Phase 1 studies 1001, 1011, 1014 and 1015 were also submitted.

As of the data cut-off (11 Dec 2021), 2246 (100.0%) participants were randomised into Study 1005, 2224 participants were included in the safety analysis set and 2102 (93.6%) participants had completed the safety follow-up (Day 34).

2.6.8.1. Patient exposure

The duration of treatment in the safety analysis set was similar across the two treatment arms (median duration of treatment of 5.00 days in both arms). A total of 94.1% in PF-07321332/ritonavir arm and 93.1% in placebo had a treatment compliance with study intervention from ≥80% to ≤115% reflecting a high adherence to treatment.

Table 45. Duration of treatment (actual dosing day) – safety analysis set (Protocol C4671005)

Table 9. Duration of Treatment (Actual Dosing Day) - Safety Analysis Set (Protocol C4671005)

	PF-07321332 300 mg + Ritonavir 100 mg (N=1109)	Placebo (N=1115)	Total (N=2224)
Duration of treatment (Days)[a]			
n	1109	1115	2224
Mean (SD)	5.01 (0.72)	5.03 (0.70)	5.04 (0.75)
Median (range)	5.00 (3.00, 6.00)	5.00 (1.00, 7.00)	5.00 (1.00, 7.00)
Category (Days)[a]			
1	15 (1.4)	11 (1.0)	26 (1.2)
2	8 (0.7)	22 (2.0)	30 (1.3)
3	17 (1.5)	24 (2.2)	41 (1.8)
4	10 (0.9)	8 (0.7)	18 (0.8)
5	871 (78.5)	856 (76.8)	1727 (77.7)
> 5	188 (17.0)	194 (17.4)	382 (17.2)

a. The Total Number of Dosing Days on which study drug was actually administered

(PFIZER CONFIDENTIAL SDTM Creation: 12DEC2021 (10:10) Source Data: adam Table Generation: 12DEC2021 (12:09)

(Data cutoff date : 11DEC2021 Database snapshot date : 11DEC2021) Output File : /sale/C4671005_EUA/adam_s001

Table 14.4.1.1 PF-07321332 is the Pfizer internal use

Study intervention compliance was assessed by site personnel by reviewing the electronic study intervention diary, discussion with the participant, and through accounting of unused study

intervention returned by the participant at the study visits. Overall, treatment compliance with study intervention (≥80% to ≤115%) was 93.6% and adherence was similar for both PF-07321332/ritonavir and placebo treatment groups. The most frequently reported important protocol deviation related to investigational product was PF-07321332/placebo and ritonavir/placebo were taken > 5 minutes apart (9.5%) which was not expected to impact the safety profile.

Overall demographic and baseline characteristics in the safety analysis set (SAS) were comparable between the two arms of study C4671005. The median age is 46.00 yrs (range 18.00 – 88.00) with a greater proportion of 18-44 (47.7%); subjects ≥65 years of age represented 12.9% of total safety database. The repartition of male and female is comparable (50.9% of male, 49.1% female). As described above, there was 36.8% of subjects with obesity (BMI ≥30) and 43% of subjects with overweight (BMI 25≤30). Patients with most reported comorbidities patients with hypertension (33.0%), with diabetes mellitus (12.2%), with chronic lung disease (4.5%) and with cardiovascular disease (4.1%). There was a significant proportion of cigarettes smokers which is disputable as being per se a risk factor unless associated with comorbidities. The other comorbidities defining the high risk of developing severe illness from COVID-19 were reported in <1% of SAS. The large majority of subjects in the SAS did not receive/not expected to receive COVID-19 mAb treatment (93.8%).

Participants with known medical history of active liver disease or acute liver failure and participants receiving dialysis or have known moderate to severe renal impairment were excluded from the pivotal study C4671005; no safety data in these populations was gained in Study C4671005.

2.6.8.2. Adverse events

- Treatment-emergent adverse events (TEAEs), All causalities

The occurrence of TEAEs in PF-07321332/Ritonavir and placebo arms was comparable, i.e. 22.6% and 23.9% respectively. Serious AEs were less reported in PF-07321332/ritonavir arm than placebo arm, i.e. 1.6% and 6.6% respectively. There were 3 additional deaths reported in the final report compared to the 45% interim analysis (none in PF-07321332/ritonavir arm and 13 in placebo arm). The majority of reported AEs in the study were low grade. Grade ≥3 TEAEs were also less reported in PF-07321332/ritonavir arm than placebo arm, i.e. 4.1% and 8.3% respectively. No AE leading to study discontinuation occurred in PF-07321332/ritonavir arm and occurred at 1.2% subjects in placebo arm. AEs leading to drug discontinuation were more reported in placebo arm than PF-1332/ritonavir arm, 4.2% and 2.1% respectively. There were no data on the AEs leading to treatment modifications.

Table 46. Treatment-Emergent Adverse Events (All Causalities) - DAIDS Grade - Safety Analysis Set (Protocol C4671005)

Number (%) of Participants	PF-07321332 300 mg + Ritonavir 100 mg n (%)	Placebo n (%)
Participants evaluable for adverse events	1109	1115
Number of adverse events	476	525
Participants with adverse events	251 (22.6)	266 (23.9)
Participants with serious adverse events	18 (1.6)	74 (6.6)
Participants with Maximum Grade 3 or 4 adverse events	45 (4.1)	93 (8.3)
Participants with Maximum Grade 5 adverse events	0	13 (1.2)
Participants discontinued from study due to adverse events[a]	0	13 (1.2)
Participants discontinued study drug due to AE and continue study[b]	23 (2.1)	47 (4.2)
Participants with dose reduced or temporary discontinuation due to adverse events	4 (0.4)	4 (0.4)

Includes AEs that started on or prior to Day 34 visit.
Except for the Number of Adverse Events participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
a. Participants who have an AE record that indicates that the AE caused the participant to be discontinued from the study.
b. Participants who have an AE record that indicates that action taken with study treatment was drug withdrawn but AE did not cause the participants to be discontinued from study.
MedDRA v24.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 12DEC2021 (10:10) Source Data: adae Table Generation: 12DEC2021 (12:02)
(Data cutoff date : 11DEC2021 Database snapshot date : 11DEC2021) Output File: /nda/C4671005_EUA/adae_t020_Table 14.3.1.2.1 PF-07321332 is for Pfizer internal use.

All-causality TEAEs were most common (reported in ≥3% of participants in PF-07321332/ritonavir group) in the SOCs of Gastrointestinal disorders (6.0% in PF-07321332/ritonavir and 4.8% in placebo), Infections and Infestations (2.1% in PF-07321332/ritonavir and 6.8% in placebo), Investigations (8.0% in PF-07321332/ritonavir and 9.3% in placebo), Nervous system disorders (7.2% in PF-07321332/ritonavir and 2.3% in placebo), and Respiratory, thoracic and mediastinal disorders (2.1% in PF-07321332/ritonavir and 3.0% in placebo).

The most frequently reported TEAEs in the PF-07321332/ritonavir group (≥1%) were Dysgeusia (5.6%), Diarrhoea (3.1%), Fibrin D-dimer increased (1.9%), Alanine aminotransferase increased (1.5%), Creatinine renal clearance decreased (1.4%), Nausea (1.4%), Headache (1.4%) and Vomiting (1.1%).

The reported TEAEs (≥0.5%) that occurred at a greater frequency in the PF-07321332/ritonavir group compared with the placebo group were Dysgeusia (5.6% vs 0.3%), Diarrhoea (3.1% vs 1.6%), Vomiting (1.1% vs 0.8%), Headache (1.4% vs 1.3%), Pyrexia (0.7% vs 0.6%), Myalgia (0.6% vs 0.2%), Hypertension (0.6% vs 0.2%), Chills (0.5% vs 0), Dyspepsia (0.5% vs 0.4%); these TEAEs were mostly Grade 1-2. In PF-07321332/ritonavir arm, a total of 34 (3.1%) subjects experienced a Grade 3 AE and 11 (1.0%) had a Grade 4 events. The majority of the Grade 3-4 events were reported in the SOC Investigations (Creatinine renal clearance decreased, Fibrin D dimer increased) and Infections and infestations (COVID-19, COVID-19 pneumonia, abscess, pyelonephritis chronic, sepsis/viral sepsis).

- Treatment-related TEAEs

Treatment-related TEAEs were highly reported in PF-1335/ritonavir arm compared to placebo, i.e. 7.8% and 3.8% respectively. Despite the higher incidence of treatment-related TEAEs with PF-1335/ritonavir, only 1 (0.1%) treatment-related TEAE was considered as serious and 5 (0.4%) were Grade ≥3.

Table 47. Treatment-Emergent Adverse Events (Treatment Related) - DAIDS Grade - Safety Analysis Set (Protocol C4671005)

Number (%) of Participants	PF-07321332 300 mg + Ritonavir 100 mg (N=1109) n (%)	Placebo (N=1115) n (%)
Participants evaluable for adverse events	1109	1115
Number of adverse events	123	52
Participants with adverse events	86 (7.8)	42 (3.8)
Participants with serious adverse events	1 (<0.1)	0
Participants with Maximum Grade 3 or 4 adverse events	5 (0.5)	5 (0.4)
Participants with Maximum Grade 5 adverse events	0	0
Participants discontinued from study due to adverse events[a]	0	0
Participants discontinued study drug due to AE and continue study[b]	9 (0.8)	7 (0.6)
Participants with dose reduced or temporary discontinuation due to adverse events	2 (0.2)	3 (0.3)

Includes AEs that started on or prior to Day 34 visit.
Except for the Number of Adverse Events participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment
a. Participants who have an AE record that indicates that the AE caused the participant to be discontinued from the study.
b. Participants who have an AE record that indicates that action taken with study treatment was drug withdrawn but AE did not cause the participants to be discontinued from study.
MedDRA v24.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 12DEC2021 (10:10) Source Data: adae Table Generation: 12DEC2021 (12:02)
(Data cutoff date : 11DEC2021 Database snapshot date : 11DEC2021) Output File: /ada/C4671005_EUA/adae_t021
Table 14.3.1.3.1 PF-07321332 is for Pfizer internal use

The most frequently reported treatment-related TEAEs in the PF-07321332/ritonavir group (≥1%) were Dysgeusia (3.7%), and Diarrhoea (1.9%).

Most of the TEAEs and treatment-related TEAEs experienced by participants in both treatment groups were mild to moderate (Grade 1-2) in severity. No Grade 4 or 5 treatment-related AEs occurred with PF-07321332/ritonavir. There was 5 (0.4%) cases of Grade 3 treatment-related TEAEs in the PF-07321332/ritonavir group: one case of palpitations (reported as serious AE, event resolved), two cases of ALAT increase, one case of ASAT increase, one case of dysgeusia and one case of rash maculo-papular. In the placebo arm, one participant had a potentially life-threatening (Grade 4) event (Blood glucose increased) that was considered related to treatment and 4 patients experienced Grade 3 treatment-related AEs (2 cases of nausea, one case of hepatic enzyme increased and one case of rash). No participant in either treatment group had an event of death related to an AE (Grade 5).

Hypertension

The proportion of hypertension events was higher in PF-07321332/ritonavir arm compared to placebo arm but reported at a low frequency (0.6% vs 0.25%). As regards this apparent imbalance, there was no case of hypertension considered as related to PF-07321332/ritonavir. Of the 7 cases of hypertension reported with PF-07321332/ritonavir, 6 were low grade (four Grade 1 events, two Grade 2 events) and resolved. Nevertheless, although not considered related, one patient not treated for hypertension, has experienced a Grade 3 hypertension on Day 5 that did not resolve, see narrative below.

A participant received study intervention from Days 1 to 3. The participant had the following risk factors: BMI >25 kg/m2, and history of Diabetes mellitus. He experienced 2 SAEs (Abscess [Grade 3] and Sepsis [Grade 4]) on Day 4. On Day 5, he had an event of Grade 3 Hypertension and Grade 3 pneumonia. On Day 6, he experienced Grade 2 Insomnia. All of the events were assessed as not related to study intervention by the investigator. All events resolved except severe Hypertension and

severe Pneumonia, which were reported as not recovered/not resolved. The participant was permanently discontinued from study intervention and did not complete the study due to withdrawal of consent on Day 11.

It is outlined that hypertension events mostly occurred during the Paxlovid treatment schedule based on the listing of AEs within PF-07321332/ritonavir, i.e. 6 of the 7 patients experiencing hypertension had an event onset between Day 2 and Day 5 and one patient had hypertension at Day 25. Based on the provided listings of AEs and on risk factors, it is observed that the majority of patients experiencing hypertension with PF-07321332/ritonavir had no history of hypertension (4 of 7 patients). Taking into account these data and the known risk of hypertension with ritonavir at a upper dosage and a long-term treatment duration (see section 4.8 of the SmPC of Ritonavir 100mg) making unclear the contributory effect of PF-07321332, it is considered necessary to further evaluate the risk of hypertension in the routine PV and follow-up questionnaires. Ongoing clinical studies notably study in standard risk population (C-4671002) of patients without having risk factor patients. Due to this sensitive issue in a population where hypertension is already a risk factor, the CHMP has asked the company to complete the preliminary safety review covering safety data from ongoing early access worldwide and notably from US (Emergency Use Authorisation) and literature data with cut-off date 31st March by April 2022 (**LEG**) awaiting for a global safety review planned to be made by the applicant on the 3 applicant's sponsored clinical studies performed (EPIC-HR, EPIC-SR and study in PEP) planned to be provided in June 2022.

Myalgia

A similar apparent imbalance (0.6 vs 0.2% for Paxlovid vs Placebo respectively) was observed for myalgia events. Given the known risk of myalgia with ritonavir at a upper dosage and a long-term treatment duration (see section 4.8 of the SmPC of Ritonavir 100mg) the contributory effect of PF-07321332 and more globally of Paxlovid 5 days treatment duration, the CHMP has also requested a safety review (**REC**).

Hepatotoxicity

Detailed narratives on all participants included in the safety population from the final analysis with hepatotoxicity in study 1005 were provided.

Hepatotoxicity cases occurred at similar rate in both arms and were reported in 11 (1.0%) subjects in PF-07321332/ritonavir arm and 16 (1.4%) subjects in placebo arm. The majority of hepatotoxicity cases reported in the safety population were hepatic transaminase elevation > 5xULN. Indeed a risk of hepatotoxicity is associated with ritonavir and mentioned in the section 4.8 of the SmPC of Ritonavir 100 mg, i.e. Hepatic transaminase elevations exceeding five times the upper limit or normal, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir alone or in combination with other antiretrovirals. Hepatotoxicity is addressed in section 4.4 of the proposed SmPC of Paxlovid considering the known risk with ritonavir which is endorsed.

Adverse drug reactions

The proposed list of adverse reactions in section 4.8 of the SmPC is as follows:

Table 48. adverse reactions with Paxlovid

System organ class	Frequency category	Adverse reactions
Nervous system disorders	Common	Dysgeusia, headache
Gastrointestinal disorders	Common	Diarrhoea, vomiting

Dysgeusia and diarrhoea were known risks with ritonavir mentioned in section 4.8 of SmPC of Ritonavir 100 mg at very common frequency and based on the safety data in study 1005 their inclusion as ADR for Paxlovid is agreed. Vomiting and headache were listed as ADR in the proposed SmPC which is supported based on their frequencies, see all causality AEs section above.

Adverse event of special interest (AESI)

1) Hemodynamic events

Vital signs measurements did not suggest clinically meaningful changes relative to hemodynamic events across treatment groups.

Table 49. Summary of Treatment-Emergent Hemodynamic Adverse Events by Decreasing Frequency (All Causalities) - Safety Analysis Set (Protocol C4671005)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=1109)	Placebo (N=1115)
Number (%) of Participants: by Preferred Term	n (%)	n (%)
Hypertension	7 (0.6)	2 (0.2)
Hypotension	1 (0.1)	4 (0.4)

2) Inflammatory events

Table 50. Summary of Treatment-Emergent Inflammatory Adverse Events by Decreasing Frequency (All Causalities) - Safety Analysis Set (Protocol C4671005)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=1109)	Placebo (N=1115)
Number (%) of Participants: by Preferred Term	n (%)	n (%)
Fibrin D dimer increased	21 (1.9)	31 (2.8)
Activated partial thromboplastin time prolonged	9 (0.8)	12 (1.1)
C-reactive protein increased	9 (0.8)	13 (1.2)
Haptoglobin increased	3 (0.3)	3 (0.3)
Prothrombin time prolonged	3 (0.3)	5 (0.4)
Leukocytosis	2 (0.2)	0
Platelet count increased	2 (0.2)	1 (0.1)
White blood cell count increased	2 (0.2)	0

3) Thyroid-related events

Table 51. Summary of Treatment-Emergent Thyroid-related Adverse Events by Decreasing Frequency (All Causalities) - Safety Analysis Set (Protocol C4671005)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=1109)	Placebo (N=1115)
Number (%) of Participants: by Preferred Term	n (%)	n (%)
Blood thyroid stimulating hormone increased	6 (0.5)	7 (0.6)
Thyroxine increased	1 (0.1)	0
Thyroxine free increased	0	1 (0.1)

No difference was observed in the incidence rates of AESI between the two treatment arms except the hypertension events for hemodynamic events reported at a greater frequency in PF-07321332/ritonavir than placebo and Fibrin D dimer increased for the inflammatory events reported at

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a greater frequency in placebo compared to PF-07321332/ritonavir (2.8% vs 1.9%) likely in relation to disease progression in the placebo arm.

2.6.8.3. Serious adverse events, deaths, and other significant events

The overall incidence of participants with all-causality treatment-emergent SAEs was lower in the PF-07321332/ritonavir treatment group (1.6%) compared with placebo (6.6%).

Table 52. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) - Safety Analysis Set (Protocol C4671005)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=1109)	Placebo (N=1115)
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)
With any adverse event	18 (1.6)	74 (6.6)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	1 (0.1)
Anaemia	0	1 (0.1)
CARDIAC DISORDERS	1 (0.1)	0
Palpitations	1 (0.1)	0
GASTROINTESTINAL DISORDERS	0	1 (0.1)
Rectal haemorrhage	0	1 (0.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.1)	0
Chest discomfort	1 (0.1)	0
INFECTIONS AND INFESTATIONS	10 (0.9)	56 (5.0)
Abscess	1 (0.1)	0
Atypical pneumonia	0	1 (0.1)
COVID-19	2 (0.2)	8 (0.7)
COVID-19 pneumonia	6 (0.5)	37 (3.3)
Pneumonia	1 (0.1)	11 (1.0)
Sepsis	1 (0.1)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	1 (0.1)
Craniocerebral injury	0	1 (0.1)
Eye injury	0	1 (0.1)
Hand fracture	0	1 (0.1)
Road traffic accident	0	1 (0.1)
Wrist fracture	0	1 (0.1)
INVESTIGATIONS	4 (0.4)	4 (0.4)
Alanine aminotransferase increased	0	1 (0.1)
Creatinine renal clearance decreased	2 (0.2)	3 (0.3)
Fibrin D dimer increased	0	1 (0.1)
Haemoglobin decreased	1 (0.1)	0
Oxygen saturation decreased	1 (0.1)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	1 (0.1)
Colon adenoma	0	1 (0.1)
NERVOUS SYSTEM DISORDERS	2 (0.2)	0
Brain stem stroke	1 (0.1)	0
Facial paralysis	1 (0.1)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.1)	18 (1.6)
Acute respiratory failure	0	5 (0.4)
Dyspnoea	1 (0.1)	3 (0.3)
Hypoxia	0	2 (0.2)
Interstitial lung disease	0	2 (0.2)
Pneumonitis	0	5 (0.4)
Pulmonary embolism	0	2 (0.2)
Respiratory failure	0	1 (0.1)
VASCULAR DISORDERS	1 (0.1)	0
Hypertensive crisis	1 (0.1)	0

The most frequently reported treatment emergent SAEs in the PF-07321332/ritonavir group (≥2 participants) were COVID-19 (2 participants, 0.3% [compared with 7 participants, 1% in the placebo group]), and COVID-19 pneumonia (4 participants, 0.6% [compared with 21 participants, 3.1% in the placebo group]). All of these SAEs were considered related to the disease under study.

Regarded the non-COVID-19 related SAEs occurring with PF-07321332/ritonavir, it was reported one case of Chest discomfort, Dyspnoea, Palpitations (resolved at Day 5), one case of Facial paralysis (recovered with sequelae at Day 37), one case of Abscess, Sepsis (resolved at Day 9), one case of Haemoglobin decreased (resolved at Day 7) and one case of Creatinine renal clearance decreased (Low creatinine was a pre-existing condition that the participant was unaware of, SAE ongoing at the time of the last available report).

Among the non-related COVID-19 SAEs reported, one case was considered as treatment related, see the narrative below.

Participant experiencing SAEs of Chest discomfort, Dyspnoea, and Palpitations resulting in permanent discontinuation from study intervention:

The participant received study intervention from Days 1 to 2. The participant had the following risk factors: BMI >25 kg/m2.

The participant started experiencing COVID-19 signs and symptoms from Day -3 and had a confirmed positive test result for SARS-CoV-2 on the same day. Further on Day 2, the participant was hospitalised due to the SAEs of Grade 2 Chest discomfort, Grade 2 Dyspnoea, and Grade 3 Palpitations. On the same day (Day 2), a chest X-ray showed left sinus infarction in lower lobe, which was related to COVID-19. The participant's ECG was normal. The participant received oxygen therapy and was treated with enoxaparin, acetylsalicylic acid, famotidine, potassium phosphate and multivitamin supplement as prophylaxis. Study intervention was permanently discontinued on Day 2 in response to the events of Chest discomfort, Dyspnoea, and Palpitations. The events of Chest discomfort, Dyspnoea, Palpitations, and Pyrexia were reported as resolved on Day 5.

In the opinion of the investigator, there was a reasonable possibility that the events of Chest discomfort, Dyspnoea, and Palpitations were related to the study intervention (ritonavir); there was not a reasonable possibility that the events were related to the study intervention (PF-07321332), concomitant drug or clinical trial procedure.

There were **no deaths in the PF-07321332 + Ritonavir arm** according to the provided data on study 1005. A total of 13 deaths were reported in the placebo arm, all related to COVID-19 and respiratory event (hypoxia, acute respiratory distress/failure).

2.6.8.4. Laboratory findings

The clinical safety laboratory tests were to be performed at baseline, Day 5 then Days 14 and 34 required only if clinically relevant abnormal laboratory values were present from a sample drawn at the previous study visit.

The overall incidence of laboratory test abnormalities occurring within 34 days of first dose was comparable between both treatment groups. No major haematological and clinical chemistry abnormalities were detected in both PF-07321332/ritonavir and placebo arms. The most frequently occurring laboratory test abnormalities (occurring in ≥5% participants in any treatment group) were fibrinogen (<0.75 x baseline; >1.25 x baseline), aPTT (>1.1 x ULN), D-Dimer (>1.5 x ULN), PT (>1.1 x ULN), bicarbonate (<0.9 x LLN), thyrotropin (>1.2 x ULN), glucose (>1.5 x ULN), creatine kinase (>2.0 x ULN), and neutrophils (>1.2 x ULN).

Elevations of hepatic transaminases >3xULN were reported at comparable rates in both PF-07321332/ritonavir and placebo arms, i.e ASAT at 1.4% in each arm; ALAT at 3.6% and 4.2% respectively.

Vital signs

Baseline values for systolic and diastolic blood pressure, heart rate, oxygen saturation (%), body temperature, and respiratory rate, were similar across both treatment groups, and there were no clinically meaningful differences between treatment groups in the mean changes from baseline in vital signs assessments.

- The mean maximum change from baseline in vital signs were comparable for participants in the PF-07321332/ritonavir treatment group compared with the placebo group.
- The incidence of participants with diastolic blood >90 mmHg, pule rate >120 bpm or systolic blood pressure >140 mmHg was comparable across treatment groups.

ECGs

Overall, few (≤5%) participants in either treatment group had clinically significant findings in Study 1005. Mean baseline values and mean changes from baseline were similar between treatment groups for all ECG parameters.

The Study 1001 Part 5 aimed to evaluate QTc of PF-07321332/ritonavir at supratherapeutic dose. The upper bounds of 90% CI for ΔΔQTcF estimates across the entire concentration range (supratherapeutic, 2 x therapeutic exposure and therapeutic exposure) were all less than 10 ms suggesting no clinically relevant effect of PF-07321332/ritonavir on QTcF interval.

2.6.8.5. Safety in special populations

At the time of the data cutoff in Study 1005 (final CSR), there was 2 reported pregnancy in the safety database. Both participants were in the placebo group and will continue to be followed for pregnancy outcomes. Please refer to nonclinical part.

2.6.8.6. Safety related to drug-drug interactions and other interactions

Refer to drug-drug interaction in the pharmacokinetic section

2.6.8.7. Discontinuation due to adverse events

- AEs leading to treatment discontinuation

The AEs leading to treatment discontinuation were more reported in placebo arm than PF-07321332/ritonavir arm, i.e. 4.2% and 2.1% respectively. The most frequently reported AEs leading to discontinuation with PF-07321332/ritonavir treatment were Nausea (0.5%), Vomiting (0.4%) and Creatinine renal clearance decreased (0.3%).

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=1109)	Placebo (N=1115)
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**
INVESTIGATIONS	9 (0.8)	9 (0.8)
Creatinine renal clearance decreased	3 (0.3)	4 (0.4)
Glomerular filtration rate decreased	2 (0.2)	2 (0.2)
White blood cell count decreased	2 (0.2)	0
Alanine aminotransferase increased	1 (0.1)	0
Aspartate aminotransferase increased	1 (0.1)	1 (0.1)
Differential white blood cell count abnormal	1 (0.1)	0
Haemoglobin decreased	1 (0.1)	0
Oxygen saturation decreased	1 (0.1)	0
Blood glucose increased	0	1 (0.1)
Glomerular filtration rate abnormal	0	1 (0.1)
GASTROINTESTINAL DISORDERS	7 (0.6)	8 (0.7)
Nausea	5 (0.5)	5 (0.4)
Vomiting	4 (0.4)	2 (0.2)
Abdominal pain lower	1 (0.1)	0
Colitis	1 (0.1)	0
Diarrhoea	1 (0.1)	1 (0.1)
Gastritis	0	1 (0.1)
NERVOUS SYSTEM DISORDERS	4 (0.4)	2 (0.2)
Dysgeusia	2 (0.2)	0
Dizziness	1 (0.1)	1 (0.1)
Headache	1 (0.1)	0
Restless legs syndrome	0	1 (0.1)
INFECTIONS AND INFESTATIONS	2 (0.2)	20 (1.8)
COVID-19	1 (0.1)	4 (0.4)
COVID-19 pneumonia	1 (0.1)	13 (1.2)
Pneumonia	0	3 (0.3)
VASCULAR DISORDERS	2 (0.2)	0
Hypertension	1 (0.1)	0
Hypertensive crisis	1 (0.1)	0
CARDIAC DISORDERS	1 (0.1)	0
Palpitations	1 (0.1)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.1)	2 (0.2)
Chest discomfort	1 (0.1)	0
Asthenia	0	1 (0.1)
Peripheral swelling	0	1 (0.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.1)	0
Myalgia	1 (0.1)	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.1)	0
Vaginal haemorrhage	1 (0.1)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.1)	9 (0.8)
Dyspnoea	1 (0.1)	1 (0.1)
Acute respiratory failure	0	1 (0.1)
Cough	0	1 (0.1)
Hypoxia	0	1 (0.1)
Interstitial lung disease	0	1 (0.1)
Pneumonitis	0	3 (0.3)
Respiratory failure	0	1 (0.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.1)	1 (0.1)
Rash maculo-papular	1 (0.1)	0
Rash	0	1 (0.1)
PSYCHIATRIC DISORDERS	0	1 (0.1)
Insomnia	0	1 (0.1)
RENAL AND URINARY DISORDERS	0	1 (0.1)
Renal impairment	0	1 (0.1)

- AEs leading to study discontinuation

No participant in the PF-07321332/ritonavir group discontinued the study due to TEAEs (all causalities) compared with 13 participants (1.2%) in the placebo group.

2.6.8.8. Supportive studies

- Study 1001 – Phase 1 study
    - Part 1 – SAD (n=13): Out of 12 TEAEs, 7 were observed in placebo (alone or enhanced with ritonavir) treatment groups, and 5 were observed in the PF-07321332 500 mg, 1500 mg and 250 mg/ritonavir treatment groups. The SOCs with participants reporting all-causality TEAEs across all treatment groups, including placebo, were Nervous system disorders (4 events; 2 placebo and 2 treated), Gastrointestinal disorders (3 events; all placebo), General disorders and administration site conditions (2 events; 1 placebo and 1 treated), Psychiatric disorders (2 events; 1 placebo and 1 treated) and Investigations (1 event; treated). None of the TEAEs in PART-1 were treatment-related. No participant had an SAE, severe AE, or dose reduced or temporary discontinuation due to AEs.
    - Part 2 – MAD (n=29): TEAEs were reported at similar rate across the 6 treatment arms in PART-2. The SOCs with the greatest number of participants reporting all-causality TEAEs were Gastrointestinal disorders (13 events; 1 placebo and 12 treated), followed by General disorder and administration site conditions (8 events; 2 placebo and 6 treated), Nervous system disorders (6 events; all treated) and Investigations (5 events; 2 placebo and 3 treated). The numbers of treatment-related TEAEs were also similar between the 6 treatment arms in PART-2. No participant had an SAE, severe AE, discontinuation from study due to AEs, or dose reduced or temporary discontinuation due to AEs in PART-2.
    - Part 3 – RBA/FE (n=12): TEAEs were reported at similar rate in PF- 07321332 250 mg (suspension), fasted and PF- 07321332 250 mg (tablet), fasted group (3/12, 25.0% in each group) and in 1/12 (8.3%) subjects included in the PF- 07321332 250 mg (tablet), fed group. The SOCs with participants reporting all-causality or treatment-related TEAEs were General disorders and administration site conditions (5 events, 1 treatment-related), and Nervous system disorders (3 events, all treatment-related). Of note the case of Chest discomfort reported with PF- 07321332 was considered as treatment-related similarly to the SAE case reported in Study 1005.
    - Part 4 – M&E (n=6): Only 1 all-causality TEAE (Nasopharyngitis) was reported in PART-4. This AE was not treatment related.
    - Part 5 – SE (n=10): The incidences of all-causality and treatment-related TEAEs were the same between the 2 groups, treated and placebo in PART-5. The most frequently reported SOC of TEAE was Gastrointestinal disorders (6 events, 2 treatment-related).
- Study 1011 (Renal impairment):

A total of 35 participants were assigned to treatment and 34 of them were treated, 8 each in mild, moderate, and severe renal impairment group and 10 in healthy control group. There was an imbalance in AEs with a higher incidence of AEs in severe renal impairment compared to patients with normal renal function and mild/moderate renal impairment. All-causality AEs were reported by 2 participants in the normal renal function group and by 1, 1 and 5 participants in the mild, moderate,

and severe renal impairment groups, respectively. Most of the all-causality AEs (17 out of 22) were reported by participants in the severe renal impairment group. One participant in the severe renal impairment had 3 SAEs, including 1 severe SAE (Pulmonary oedema), and 2 moderate SAEs (1 Acute kidney injury, 1 Pneumonia), and all 3 were considered not treatment related. This participant discontinued study due to the SAE of Acute kidney injury. There were no deaths in this study. All-causality AEs were most frequently reported under the SOCs of Gastrointestinal disorders, General disorders and administration site conditions, and Nervous system disorders.

- Study 1014

All 12 participants took at least 1 dose of study intervention and were included in the safety analysis.

In Period 1 (PF-07321332 300 mg/ritonavir 100 mg as a single oral dose), 4 AEs were reported in 4 (33.3%) participants, and 1 AE was considered treatment related. The TEAEs reported by PT were Vessel puncture site haematoma, Dysgeusia, Sciatica and Polyuria (1 participant each, 8.3%). All 4 TEAEs were mild in severity.

In Period 2 (Carbamazepine on a titration schedule for 15 days + PF-07321332 300 mg/ritonavir 100 mg as single dose at Day 14), 18 AEs were reported in 9 (75.0%) participants, and 8 AEs reported in 6 (50%) participants were considered treatment related. One participant discontinued from study due to treatment related AE. The most frequently reported all-causality TEAEs by PT, regardless of SOC, were Transaminases increased (5 participants, 41.7%). The majority of the TEAEs (17/18) were mild in severity. There was 1 moderate TEAE of Inappropriate antidiuretic hormone secretion (Hyponatremia/SIADH) leading to study discontinuation and considered treatment-related.

- Study 1015

Twelve participants received at least 1 study treatment and were thus included in the safety analysis.

All-causality 26 and 48 AEs were reported by 7 and 10 participants in Periods 1 and 2, respectively. None of the AEs were considered serious or severe by the investigator. No participants discontinued from the study or study treatment or had dose reductions due to AEs. Among the all-causality TEAEs, 24 out of 26 AEs in Period 1 and 43 out of 48 AEs in Period 2 were considered treatment related.

In Period 1, 1 participant reported Vomiting and Headache (both related to study treatment); 1 participant reported Dizziness (not related to study treatment) and Headache (related to study treatment).

In Period 2, 1 participant reported Constipation (related to study treatment); and 1 participant reported Anorectal discomfort, Constipation, Diarrhoea, and Gastrointestinal motility disorder (all related to study treatment).

One participant experienced the event of Atrioventricular block first degree on Study Day 3 in Period 1, which continued through Period 2. The event resolved on Study Day 13.

2.6.8.9. Post marketing experience

No data has been provided. Data will be presented for authorities as part of routine pharmacovigilance.

2.6.9. Discussion on clinical safety

The safety data provided by the applicant is primarily based on the final analysis of the pivotal study C4671005/EPIC-HR at the data cut-off date of 11 Dec 2021. The treatment was intended at the posology of PF-07321332 300mg and ritonavir 100mg every 12h for 5 days. As of the data cut-off, 2246 (100.0%) participants were randomised into study C4671005, 2224 participants were included in the safety analysis set and 2102 (93.6%) participants had completed the safety follow-up (Day 34).

Overall demographic and baseline characteristics in the safety analysis set (SAS) were comparable between the two arms. Participants with known medical history of active liver disease or acute liver failure, and participants receiving dialysis or have known moderate to severe renal impairment were excluded from the pivotal study C4671005; thus, no safety data in these populations was generated.

The duration of treatment in the safety analysis set was similar across the two treatment arms (median duration of treatment of 5.00 days in both arms). A total of 94.1% in PF-07321332/ritonavir arm and 93.1% in placebo had treatment compliance with study intervention from ≥80% to ≤115% reflecting a high adherence to treatment.

The incidence of TEAEs was slightly lower in PF-07321332/ritonavir compared to placebo, i.e. 22.6% and 23.9% respectively. It should be noted that the majority of the adverse events occurring in the study may be confounded with COVID-19 symptoms. The majority of reported AEs in the study were low grade. Grade ≥3 TEAEs were less reported in PF-07321332/ritonavir arm than placebo arm, i.e. 4.1% and 8.3% respectively. In PF-07321332/ritonavir arm, a total of 34 (3.1%) subjects experienced a Grade 3 AE and 11 (1.0%) had a Grade 4 events. The majority of the Grade 3-4 events were reported in the SOCs Investigations (Creatinine renal clearance decreased, Fibrin D dimer increased) and Infections and infestations (COVID-19, COVID-19 pneumonia, abscess, pyelonephritis chronic, sepsis/viral sepsis). Treatment-related TEAEs were however more reported in PF-07321332/ritonavir arm compared to placebo, i.e. 7.8% and 3.8% respectively.

The most frequently reported TEAEs in the PF-07321332/ritonavir group (≥1%) were Dysgeusia (5.6%), Diarrhoea (3.1%), Fibrin D-dimer increased (1.9%), Alanine aminotransferase increased (1.5%), Creatinine renal clearance decreased (1.4%), Nausea (1.4%), Headache (1.4%) and Vomiting (1.1%). Dysgeusia and Diarrhoea were the most frequently reported treatment-related TEAEs in the PF-07321332/ritonavir group (3.7% and 1.9% respectively). The reported TEAEs (≥0.5%) that occurred at a greater frequency in the PF-07321332/ritonavir group compared with the placebo group were Dysgeusia (5.6% vs 0.3%), Diarrhoea (3.1% vs 1.6%), Vomiting (1.1% vs 0.8%), Headache (1.4% vs 1.3%), Pyrexia (0.7% vs 0.6%), Myalgia (0.6% vs 0.2%), Hypertension (0.6% vs 0.2%), Chills (0.5% vs 0), Dyspepsia (0.5% vs 0.4%); these TEAEs were mostly Grade 1-2. There was 5 (0.4%) cases of Grade 3 treatment-related TEAEs in the PF-07321332/ritonavir group: one case of palpitations (reported as serious AE, event resolved), two cases of ALAT increase, one case of ASAT increase, one case of dysgeusia and one case of rash maculo-papular.

Hypertension occurred at a low frequency overall but with an apparent imbalance (0.6% and 0.2%, in the PF 07321332/ritonavir and placebo group, respectively). There was no case of hypertension considered as related to PF-07321332/ritonavir. Of the 7 cases of hypertension reported with PF-07321332/ritonavir, 6 were low grade (four Grade 1 events, two Grade 2 events) and resolved. Although not considered related, one patient, not treated for hypertension, experienced a Grade 3 hypertension on Day 5 that did not resolve. It is noted that hypertension events mostly occurred during the Paxlovid treatment schedule based on the listing of AEs within PF-07321332/ritonavir, i.e. 6 of the 7 patients experiencing hypertension had an event onset between Day 2 and Day 5 and one patient had hypertension at Day 25. Based on the provided listings of AEs and on risk factors, it is observed that the majority of patients experiencing hypertension with PF-07321332/ritonavir had no

history of hypertension (4 of 7 patients). Narratives of the hypertension cases occurring in PF-07321332/ritonavir were provided. Based on these observations and due to the limited number of cases, a causality with Paxlovid cannot be concluded at this stage. Additionally, the possible contributory effect of DDI with ritonavir cannot be excluded for the serious case of hypertensive crisis. Due to this sensitive issue in a population where hypertension is already a risk factor, the CHMP has asked the company to complete the preliminary safety review covering safety data from ongoing early access worldwide and notably from US (Emergency Use Authorisation) and literature data with cut-off date 31st March by April 2022, awaiting for a global safety review planned to be made by the applicant on the 3 applicant's sponsored clinical studies performed (EPIC-HR, EPIC-SR and study in PEP) planned to be provided in June 2022 **(LEG**). Additionally, this issue will be further followed-up through routine PV and follow-up questionnaires, together with the review of the upcoming safety data. The CHMP has considered that it would be premature to conclude on causality, therefore it is not reflected in section 4.8 of the SmPC.

There was also an apparent imbalance for myalgia, more reported in PF-07321332/ritonavir arm than the placebo arm (7 [0.6%] vs 2 [0.2%]). The narratives for all the myalgia cases occurring in the PF-07321332/ritonavir arm were provided. Two cases were considered related to treatment and four were considered due to COVID-19. The limited number preclude any conclusion on a correlation between myalgia and Paxlovid at this stage. Ongoing studies are expected to provide more data regarding this issue. Taking into account the imbalance of myalgia events across the treatment arms, the two PF-07321332/ritonavir related cases of myalgia reported in study C4671005 and the known risk of myalgia with ritonavir (when used for the treatment of HIV infection at a higher dosage and for a long-term treatment duration), it was agreed to further evaluate the issue of myalgia through routine PV and to review the upcoming requested safety data as part of Post Authorisation Measure based on early access worldwide and notably from US (Emergency Use Authorisation) and literature data with cut-off date 31st March by April 2022, awaiting for a global safety review planned to be made by the applicant on the 3 applicant's sponsored clinical studies performed (EPIC-HR, EPIC-SR and study in PEP) planned to be provided in June 2022 (**REC**).

There were pre-specified adverse event of special interest (AESI) including hemodynamic events, inflammatory events, and thyroid-related events. No difference was observed on the incidence rates of AESI between the two treatment arms except the hypertension events for hemodynamic events, which were reported at a greater frequency in PF-07321332/ritonavir than placebo and Fibrin D dimer increased for the inflammatory events reported at a greater frequency in placebo compared to PF-07321332/ritonavir (2.8% vs 1.9%).

Serious AEs were less reported in PF-07321332/ritonavir arm than placebo arm, i.e. 1.6% and 6.6% respectively. The SAEs were mostly related to COVID-19. The most frequently reported SAEs with PF-07321332/ritonavir were COVID-19 pneumonia, COVID-19, and creatinine renal clearance decreased and occurred less frequently compared to placebo group (0.5% vs 3.3%, 0.2% vs 0.7% and 0.2% vs 0.3% respectively). Among the non-related COVID-19 SAEs reported, one case of chest discomfort, dyspnoea and palpitations was considered by the investigator as reasonably possible to be related to the treatment. The treatment was permanently discontinued on Day 2 and the events were reported as resolved on Day 5. The SAEs occurring with PF-07321332/ritonavir treatment were manageable. The majority of the reported SAEs with PF-07321332/ritonavir were considered as resolved/recovered and 2 cases were ongoing at the time of the report (creatinine renal clearance decreased and oxygen saturation decreased).

No death occurred in the PF-07321332/ritonavir group while a total of 13 deaths (12 in the 28-day period and 1 in the safety follow-up period) were reported in the placebo arm, all related to COVID-19.

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The overall incidence of laboratory test abnormalities occurring within 34 days of first dose was comparable between both treatment groups. No major haematological and clinical chemistry abnormalities were detected in both PF-07321332/ritonavir and placebo arms.

No in-depth QT study was performed. Based on ECG data collected, the applicant did not identify any clinically relevant difference between treatment groups. In addition, the study 1001 Part 5 aimed to evaluate QTc of PF-07321332/ritonavir at supratherapeutic dose and the ΔΔQTcF estimates suggested no clinically relevant effect of PF-07321332/ritonavir on QTcF interval.

In light of the nonclinical findings, it is appropriate that Paxlovid is not recommended during pregnancy and in women of childbearing potential not using contraception.

No summary of AEs by age group was provided by the applicant. Data on safety profile of PF-07321332/ritonavir with regard to children ≥12 to <18 years of age included initially in the claimed indication was lacking. Additionally, data was also missing in patients with severe renal impairment, with severe hepatic impairment and in pregnant women and WOBPC. These issues are addressed as safety concerns in the RMP (missing information).

The AEs leading to treatment discontinuation were more reported in placebo arm than PF-07321332/ritonavir arm, i.e. 4.2% and 2.1% respectively. The most frequently reported AEs leading to discontinuation with PF-07321332/ritonavir treatment were Nausea (0.5%), Vomiting (0.4%) and Creatinine renal clearance decreased (0.3%). There was no study discontinuation due to AE with PF-07321332/ritonavir and 13 in placebo arm (subjects who died).

No notable safety signal was detected with PF- 07321332/ritonavir in the supportive studies except study 1011. An imbalance in AEs was observed in study 1011 (renal impairment) with a higher incidence of AEs in severe renal impairment compared to patients with normal renal function and mild/moderate renal impairment, which can be expected in view of the significant over-exposure observed in this study (approx. 90% in patients with moderate impairment and approx. 200% in patients with severe impairment). 5 of the 8 patients with severe renal impairment (RI) reported an AE, of which one participant who had 3 SAEs and discontinued study due to a SAE of Acute kidney injury that may be related to the severe renal impairment condition. Two participants in the normal renal function, one participant in mild renal impairment and one participant in moderate renal impairment groups experienced an AE. As expected, in view of the large increase of PK exposure in patients with severe renal impairment (+204%), an increase of AEs is observed in those patients.

One case of Atrioventricular block was reported with PF-07321332/ritonavir in study 1015 and one case of Chest discomfort was reported with PF- 07321332 in study 1001 and considered as treatment-related. Taking into account the SAE of Palpitations, Chest discomfort and dyspnoea that occurred with Paxlovid in Study 1005, a risk of cardiovascular events cannot be ruled out but the limited cases reported prevent any conclusion at this stage.

Two clinical studies sponsored by the applicant are still on-going that will provide additional information regarding the safety profile and possible rare adverse reactions of Paxlovid.

2.6.10. Conclusions on the clinical safety

Based on the provided safety data, no major concern was identified in the safety profile of Paxlovid. The most frequent adverse reactions were dysgeusia, diarrhoea, vomiting and headache which are described in section 4.8 of the SmPC. The safety profile is expected to be further substantiated with the on-going studies in treatment of patients with standard risk of COVID-19 and post exposure prophylaxis. Given that in these two studies patients are less likely to have comorbidities, the causality assessment might be facilitated.

The CHMP considers the following measures necessary to address the clinical issues:

a) A safety review for hypertension covering safety data from ongoing early access worldwide and notably from US (Emergency Use Authorisation) and literature data with cut-off date 31st March should be provided by April 2022, awaiting for a global safety review planned to be submitted covering the 3 applicant's sponsored clinical studies (EPIC-HR, EPIC-SR and study in PEP) in June 2022.

Risk of medication errors related to the co-packaged blister (including in relation to the dose adjustment in patients with moderate renal impairment), the handling of the numerous drug drug interactions by healthcare professionals in the outpatient setting less familiar than infectious diseases specialists at hospital used to handle the ritonavir driven interactions in the field of HIV infection, will be a source of particular scrutiny in post-marketing safety data as part of routine pharmacovigilance.

Clinical safety recommendations and legally binding measures are covered in Annex I.

2.7. Risk Management Plan

2.7.1. Safety concerns

The applicant has submitted an RMP including the following summary of safety concerns:

Table 53. Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	Safety in patients with hepatic impairment Safety in patients with renal impairment Safety during use in pregnancy and lactation

Risks considered important for the inclusion in the summary of safety concerns

Missing information

Safety in patients with hepatic impairment: Since participants with known medical history of active liver disease or acute liver failure were excluded from the pivotal study C467-1005 (EPIC-HR), safety in patients with hepatic impairment should be considered as missing information. Of note in the PK study in patients with hepatic impairment, the category of patients with severe hepatic impairment was not covered. In moderate hepatic impairment, the PK data did not significantly differ from the control.

Safety in patients with renal impairment: There is a lack of data in the moderate to severe renal impairment population in study C467-1005 since this population was excluded. The results of the completed PK study C4671011 showed a PF-07321332 systemic exposure (AUC and C_{max}) increase with a magnitude depending on the severity of the renal impairment: in severe renal impairment, increase of AUC by 204% leading the CHMP to propose a contraindication in this sub-population at the time of Art 5(3) prior procedure and a dose reduction by one-half is proposed in population with moderate renal impairment. However, efficacy and safety data of Paxlovid at this reduced posology is

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lacking. In addition, a higher incidence of AEs in severe renal impairment compared to patients with normal renal function and mild/moderate renal impairment was observed in study C4671011. It is therefore considered that the safety profile of PF-07321332/ritonavir in this population cannot be established yet and that the use in patients with renal impairment should be added as missing information. As per the routine risk minimisation measures, it has been considered that the inclusion in the SmPC of a warning and precaution for use of PF-07321332/ritonavir was more appropriate than a formal contra-indication, given that there is a lack of data to inform on a posology, rather than evidence of harm.

Safety during use in pregnancy and lactation: Considering that the current epidemiology data raise concerns on the SARS-CoV-2 infection for both the pregnant women and their newborns, the loss of foetal weight observed as part of the Paxlovid non-clinical findings and that clinical experience of Paxlovid is currently missing in pregnant women, it is agreed that safety during use in pregnancy and lactation is included as missing information.

Risks not considered important for inclusion in the summary of safety concerns

Hypertension: based on the final analysis of the pivotal Study C467-1005/EPIC-HR (cut-off date of 11 Dec 2021), hypertension occurred at a low frequency overall (0.6% and 0.2%, in the PF-07321332/ritonavir and placebo group, respectively) but was more frequent in the PF-07321332/ritonavir group. Most of events were low grade and none was considered treatment-related in the PF- 07321332/ritonavir group. Nevertheless, considering that the hypertension events mostly occurred with a short time to onset, the majority of patients experiencing hypertension had no history of hypertension and that hypertension is a known risk with ritonavir, it remains uncertain the causality of hypertension with Paxlovid.

This risk will be further evaluated through routine pharmacovigilance and relevant updates should be provided within the upcoming PSUR. A targeted follow-up questionnaire is to be implemented.

Myalgia: based on the final analysis of the pivotal Study C467-1005/EPIC-HR (cut-off date of 11 Dec 2021), myalgia was reported at a low frequency (0.6% and 0.2%, in the PF- 07321332/ritonavir and placebo group, respectively) but was more frequent in the PF- 07321332/ritonavir group. Since two of the seven cases reported with PF- 07321332/ritonavir were considered treatment-related and considering myalgia is a known risk of ritonavir, it remained questionable whether there is a causal relationship between myalgia and PF-07321332/ritonavir. Myalgia will be monitored through routine pharmacovigilance, including PSUR.

The applicant clarified that hypertension is monitored as an event of special interest (under 'hemodynamic events') in the ongoing development programme and both events are evaluated during safety reviews of interval and cumulative data from the clinical studies. Hypertension and myalgia will be reviewed via routine pharmacovigilance activities. Furthermore, the applicant will provide a cumulative safety review of all available data on hypertension and myalgia from available sources, including spontaneous data, compassionate use and literature (cut off-date 31sth March) by 30th April 2022 awaiting for a global safety review planned to be made by the applicant on the 3 applicant's sponsored clinical studies performed (EPIC-HR, EPIC-SR and study in PEP) planned to be provided in June 2022.

Drug-drug interactions (DDI) (with CYP3A substrates and CYP3A inducers): Paxlovid contains ritonavir, a well-known inhibitor of cytochrome P450 CYP3A (and PgP inhibitor), which may interact with other medicines leading to clinically significant reactions, including potentially life-threatening or fatal reactions, loss of therapeutic effect of Paxlovid and possible development of viral resistance. The applicant will closely monitor cases potentially indicative of drug-drug interactions via routine pharmacovigilance and present relevant data within the upcoming PSURs.

The applicant considers that the list of contraindicated medicinal products in Section 4.3, in addition to the comprehensive list of drug interactions included in Section 4.5 are sufficient to mitigate the risk of drug interactions by appropriately informing prescribers of the potential medicinal products which may interact with Paxlovid. In addition, the applicant included a QR code and website link on the PL and outer carton, which link to the MAH product website (COVID19oralRx.com) that includes a drug interaction tool. This tool will provide another mechanism to communicate the drug interactions listed in the SmPC.

Furthermore, an additional communication regarding this DDI is proposed by the EMA and will be circulated to all relevant professional societies on the day of the CHMP opinion, which is the same day that the product information is published on EMA website.

2.7.2. Pharmacovigilance plan

Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: the applicant will implement the following:

- Pregnancy follow-up questionnaires (Exposure During Pregnancy Follow-up Questionnaire for non-study cases and Exposure During Pregnancy Supplemental Form for study cases) are also utilised to collect further data on pregnancy outcome and reproductive and developmental toxicity.
- A Data Capture Aid has been created to gather data about the safety during use in lactation.
- Two further DCAs, for lack of efficacy (including fields to request information on the COVID-19 variant) and for hypertension are provided.

Monitoring of data on treatment failure due to emerging variants:

As part of the enhanced signal detection activities for the duration of the COVID-19 pandemic, monitoring of data on treatment failure due to emerging variants from all available data sources, will include (not limited to):

- Spontaneous cases (using a targeted follow-up questionnaire for lack of efficacy as stated above)
- Clinical trial data
- Literature
- Studies conducted by public health authorities

If the review of the data leads to an impact on the benefit risk of the product, a benefit-risk discussion and any warranted product information updates will be submitted within 1 month from assessment via appropriate variation procedure. Additionally, the interval and cumulative data will be summarised in a dedicated section in the PSUR.

Additional pharmacovigilance activities

The applicant proposes the following 5 studies to further evaluate safety and to address missing information in the post marketing setting.

The following table outlines proposed additional pharmacovigilance activities in RMP version 1.2.

Summary of additional Pharmacovigilance activities

Table 54. Ongoing and Planned Additional Pharmacovigilance Activities

Study (short name and title) Status	Summary of objectives	Safety concerns addressed	Milestones	*Due dates*
Category 3 - *- Required additional pharmacovigilance activities*				
Study C4671010 A Phase 1, Non-Randomised, Open-Label Study to Assess the Pharmacokinetics, Safety and Tolerability of PF-07321332 Boosted With Ritonavir in Adult Participants with Moderate Hepatic Impairment and Healthy Participants With Normal Hepatic Function. *Ongoing*	To estimate the effect of moderate hepatic impairment on the plasma PK of PF-07321332/ritonavir. To evaluate the safety and tolerability of PF-07321332 and ritonavir, following a single oral dose administration of PF-07321332 pharmacokinetically boosted with ritonavir, in participants with moderate hepatic impairment and in healthy participants with normal hepatic function.	Safety in patients with hepatic impairment	*Final report submission*	*31 March 2022*
PASS in pregnant and breastfeeding women A post-authorisation safety study of PF-07321332/ritonavir use in pregnant and breastfeeding women *Planned*	A cohort/prevalence study using secondary data from electronic health records and/or claims in European countries to assess use of PF-07321332/ritonavir during pregnancy and if feasible lactation. The study will also evaluate pregnancy outcomes (major congenital malformations, spontaneous abortions, stillbirths, small-for-gestational-age births) as feasible in data sources, and other safety events of interest in women exposed to PF-07321332/ritonavir versus not exposed to PF-07321332/ritonavir or another appropriate comparator. As feasible, maternal, and infant outcomes will be assessed in lactating women.	Safety during use in pregnancy and lactation	*Protocol submission*	*30 April 2022*
			Estimate study start	*EMA approval of protocol and PF-07321332/ritonavir commercially available*
			Progress report submission	*30 November 2022*
			Interim report 1 submission	*30 November 2023*
			Interim report 2 submission	*29 November 2024*
			Final report submission	*28 November 2025*
PK and safety study in lactating adult women A multiple dose, pharmacokinetic and	To assess penetration of PF-07321332 in human breast milk and to measure the concentration of PF-	Safety during use in pregnancy and lactation	*Estimate study start*	*EMA approval of protocol and PF-07321332/ritonavir commercially available*

Study (short name and title) Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	***Due dates***
safety study in healthy lactating adult women. *Planned*	07321332 in breastmilk in healthy women.		*Final study results submission*	*15 September 2023*
PASS in moderate and severe renal impairment A post-authorisation safety study of PF-07321332/ritonavir use in moderate and severe renal impairment. *Planned*	To assess the safety of PF-07321332/ritonavir in patients with moderate and severe renal impairment.	Safety in patients with renal impairment	*Study feasibility assessment*	*28 February 2022*
			Protocol submission	*30 April 2022*
			Estimate study start	*EMA approval of protocol and PF-07321332/ritonavir commercially available*
			Progress report submission	*30 November 2022*
			Interim report 1 submission	*30 November 2023*
			Interim report 2 submission	*29 November 2024*
			Final report submission	*30 November 2025*
PASS in moderate and severe hepatic impairment A post-authorisation safety study of PF-07321332/ritonavir use in moderate and severe hepatic impairment. *Planned*	To assess the safety of PF-07321332/ritonavir in patients with moderate and severe hepatic impairment.	Safety in patients with hepatic impairment	*Study feasibility assessment*	*28 February 2022*
			Protocol submission	*30 April 2022*
			Estimate study start	*EMA approval of protocol and PF-07321332/ritonavir commercially available*
			Progress report submission	*30 November 2022*
			Interim report 1 submission	*30 November 2023*
			Interim report 2 submission	*29 November 2024*
			Final report submission	*30 November 2025*

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2.7.3. Risk minimisation measures

Routine risk minimisation activities are proposed to manage the safety concerns of the medicinal product.

Table 55. Summary Table of Risk Minimisation Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Safety in patients with hepatic impairment	Routine risk minimisation measures: SmPC Section 4.2 *Posology and method of administration*, Section 4.4 *Special warnings and precautions for use*, and Section 5.2 *Pharmacokinetic properties*. Pack size. Medicine's legal status. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Study C4671010 (Final CSR Due date: 31 March 2022). PASS in moderate and severe hepatic impairment (Final report submission by 30 November 2025).
Safety in patients with renal impairment-	Routine risk minimisation measures: SmPC Section 4.2 *Posology and method of administration*, Section 4.4 *Special warnings and precautions for use* and Section 5.2 *Pharmacokinetic properties*. Pack size. Medicine's legal status. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS in moderate and severe renal impairment (Final report submission by 30 November 2025).
Safety during use in pregnancy and lactation	Routine risk minimisation measures: SmPC Section 4.6 *Fertility, pregnancy and lactation*. Pack size. Medicine's legal status. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Pregnancy follow-up questionnaires and DCA for lactation to collect relevant information during follow-up activities. Additional pharmacovigilance activities: PASS in pregnant and breastfeeding women (Final study results submission by 28 November 2025). PK and safety study in lactating adult women (Final study results submission by 15 September 2023)

2.7.4. Conclusion

The CHMP and PRAC considers that the risk management plan version 1.2 is acceptable.

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2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 31.12.2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons for the approval of the conditional marketing authorisation under emergency use.

The applicant has endeavoured to ensure that the package leaflet is comprehensive and supports patient adherence and understanding, especially for patients that may have limited direct access to healthcare professionals. Further adjustments have been made to the language in the PIL to support this.

The applicant commits to complete user testing and provide it as soon as possible.

2.9.2. Labelling exemptions

The following exemptions from labelling requirements have been granted on the basis of article 63.3 of Directive 2001/83/EC. In addition, the derogations granted should be seen in the context of the flexibilities described in the Labelling flexibilities for COVID-19 therapeutics (EMA/35618/2021, from 12 March 2021) document which aims at facilitating the preparedness work of COVID-19 therapeutics' developers and the associated logistics of early printing packaging activities. The ultimate goal is to facilitate the large scale and rapid deployment of COVID-19 therapeutics for EU citizens within the existing legal framework.

Considering the self-administration context and the need for the information to be readily available and understood by the users in their national language, The QRD Group agreed to a maximum of 2 months length of deviation for all of the below requests, in particular:

a) Agreed to market an outer and immediate packaging in English only for all EU markets for a maximum period of 2 months following the EC decision;

b) An English only Package Leaflet was not agreed. The applicant shall liaise with the respective national competent authorities (NCAs) and discuss the provision of a paper PL alongside the pack in the national language(s). As noted above this has to be seen in the context of self-administration. It is crucial that the user has from the start the information in their national

language.

c) Agreed to provide national translations of the package leaflet via a Quick Response (QR) code, but as a supplement to the paper package leaflet, as indicated above.

d) Agreed to use one Global GTIN within the unique identifier for all EU markets;

e) Agreed to omit the NHRN (national code) to be encoded in the Datamatrix for some countries;

f) Agreed to omit the Blue Box information and to provide it via a QR code instead;

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

2.9.3. Quick Response (QR) code

A request to include a QR code in the labelling for the purpose of ensuring easy access to the most recent versions of the product information to patients and HCPs has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code:

Based on whether they select the patient or the HCP area, the user will be sent through to the most appropriate local website which will provide them with the following:

a) The most up to date 'Package Leaflet; Information for the Patient' (formatted as a PDF)

b) The most up to date Summary of Product Characteristics (formatted as a PDF)

c) Information about how to ensure that the HCP has obtained an authentic version of the medicine, manufactured by Pfizer.

In addition, a so-called "Drug Interaction Finder." will be included which will replicate the two drug interactions tables ('Contraindicated for concomitant use' and 'Potentially significant interactions with other medicinal products') in a searchable format. This would support patient safety by allowing HCPs to more easily identify a medicine which may interact with PF-07321332 and ritonavir.

2.9.4. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Paxlovid ((1R,2S,5S)-N-((1S)-1-Cyano-2-((3S)-2-oxopyrrolidin-3-yl)ethyl)-3-((2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido) butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide /ritonavir) is included in the additional monitoring list as it contains a new active substance and the product is approved under a conditional marketing authorisation..

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

COVID-19 manifests as a wide range of illness, from asymptomatic infection to severe pneumonia, ARDS, and death. Although approximately 80% cases are asymptomatic or mild, patients who are hospitalised with COVID-19 may have significant morbidity and mortality, and are at increased risk of developing complications such as severe inflammation associated with elevations in proinflammatory cytokines, ARDS, acute cardiac injury, thromboembolic events, hypercoagulability, and/or kidney injury. Moreover, other comorbidities, such as hypertension, obesity, and diabetes, as well as older age increase the risk for worse outcomes.

3.1.2. Available therapies and unmet medical need

The therapeutic armamentarium is limited for patients infected with SARS-CoV-2, who are at increased risk of progression to severe disease and not O2 requiring, as targeted in the C4671005 patients.

While some anti-spike monoclonal antibodies have been a valuable tool, the emerging VOC with mutations in the spike protein are constantly threatening their activity. Currently, sotrovimab is almost the unique mAb that maintains activity against the currently circulating omicron variant.

Remdesivir is also indicated for the same patient population as Paxlovid. However, remdesivir is only available via intravenous administration. There is a need to have an oral antiviral effective against COVID-19 disease.

3.1.3. Main clinical studies

The clinical development is based on the single pivotal phase 2/3 C4671005/EPIC-HR study conducted in non-hospitalised, symptomatic adult patients with COVID-19 who are at increased risk of progressing to severe illnesses. It was a double-blinded, placebo-controlled trial, in a 1:1 ratio and conducted in a superiority setting.

Eligible patients have received PF-07321332 plus ritonavir or placebo orally q12h for 5 days (10 doses total). The total study duration is up to 24 weeks, study intervention through Day 5 or Day 6, efficacy assessments through Day 28, a safety follow-up period through Day 34.

3.2. Favourable effects

The determination of primary efficacy was based on a planned interim analysis of 774 subjects in mITT population. The estimated risk reduction was -6.3% with unadjusted 95% CI of (9.0%, 3.6%) and a 95% CI of (-10.61%, -2.02%) when adjusting for multiplicity. The 2-sided p-value was < 0.0001 with 2-sided significance level of 0.002.

In the supporting final analysis, the primary endpoint of the study was met with a 5.807% (95% CI: -7.777% to - 3.837%; p<0.0001) absolute reduction in proportion of COVID-19-related hospitalisation or death from any cause at Day 28, reducing the primary endpoint event rate from 6.531% to 0.723% at Day-28, with PF-07321332/ritonavir in comparison with placebo treatment, in patients who did not

receive or were expected to receive COVID-19 therapeutic mAb treatment and were treated ≤3 days after COVID-19 symptom onset (mITT). No patient died in the Paxlovid treatment group whereas 9 deaths occurred in the placebo group. Sensitivity analyses were also generally consistent with the primary results.

Similar benefit was observed in the mITT1 population of analysis with an absolute reduction of 5.619% (95% CI: -7.207% to -4.031%; p<0.0001). mITT1 includes patients treated within 5 days since symptoms onset in line with the posology recommendation. Again, no patients died in the Paxlovid treatment group whereas 12 deaths occurred in the placebo group.

In line with the study period, the primary variant across both treatment arms was Delta (98.53%) and was distributed in high prevalence as subvariants Delta/21J (74.15%). As the vast majority of the participants were infected with the Delta variant, the clinical efficacy of Paxlovid is only demonstrated in this VOC. However, *in vitro* data are supportive of activity of Paxlovid against other major VOCs including the currently circulating omicron variant.

3.3. Uncertainties and limitations about favourable effects

The identified quality issues concerning the active substance PF-07321332 manufacture and finished product control strategy, to be addressed through fulfilment of specific obligations, pose some uncertainties with regard to the batch to batch consistency between the product batches studied in pharmaceutical, preclinical and clinical development, and future commercial batches.

A high rate of patients with positive serological status at baseline was observed, which needs to be better understood. According to the applicant, serology testing at baseline did not discriminate between IgG or IgM. This did not allow to differentiate whether the positive status was due to unawareness of prior (potentially asymptomatic) SARS-CoV-2 infection or to immune response related to the current COVID-19 episode (at the time of the enrolment). The applicant indicated that exploratory testing is planned to further characterise the immune response to SARS-CoV-2 at baseline and over time.

As rather expected, a much more limited effect could be observed in patients with positive serology status at baseline. Therefore, uncertainties remain on the magnitude of the benefit in this subpopulation. More broadly, the question therefore arises of the generalisability of the results to vaccinated patients with increased risk for progression to severe COVID-19. The benefit of the treatment in the vaccinated subpopulation needs to be further substantiated.

Patients with immunodeficiency were poorly represented with less than 1% of the study population. There are concerns on the maintenance of the benefit in patients with immunodeficiency for which a prolonged period of viral shedding could occur. This could lead to potential risk of treatment failure and emergence of resistance with the recommended 5 days treatment duration. The applicant will have to particularly monitor treatment failure in this subset of patients in post-approval.

3.4. Unfavourable effects

The incidence of TEAEs was slightly lower in PF-07321332/ritonavir compared to placebo, i.e. 22.6% and 23.9% respectively. The majority of reported AEs in the study were low grade and non-serious, and no death occurred with PF-07321332/ritonavir. Grade ≥3 TEAEs were also less reported in PF-07321332/ritonavir arm than placebo arm (4.1% vs 8.3%). The most frequently reported TEAEs in the PF-07321332/ritonavir group (≥1%) were Dysgeusia (5.6%), Diarrhoea (3.1%), Fibrin D-dimer increased (1.9%), Alanine aminotransferase increased (1.5%), Creatinine renal clearance decreased (1.4%), Nausea (1.4%), Headache (1.4%) and Vomiting (1.1%). The reported TEAEs (≥0.5%) that

occurred at a greater frequency in the PF-07321332/ritonavir group compared with the placebo group were Dysgeusia, Diarrhoea, Vomiting, Headache, Pyrexia, Myalgia, Hypertension, Chills, Dyspepsia. The most frequently reported treatment-related TEAEs in the PF-07321332/ritonavir group (≥1%) were Dysgeusia (3.7%), and Diarrhoea (1.9%).

Serious AEs were less reported in PF-07321332/ritonavir arm than placebo arm (1.6% vs 6.6%). The most frequently reported SAEs with PF-07321332/ritonavir were COVID-19 pneumonia, COVID-19, and Creatinine renal clearance decreased. Among the non-related COVID-19 SAEs reported, one case of Chest discomfort, dyspnoea and palpitations was considered by the investigator as reasonably possible to be related to the treatment (ritonavir). The majority of the reported SAEs with PF-07321332/ritonavir were considered as resolved/recovered and 2 cases were ongoing at the time of the report (creatinine renal clearance decreased and oxygen saturation decreased).

Finally, the complexity of the interaction profile driven by the ritonavir booster dose co-packaged with the antiviral PF-07321332 in Paxlovid is of importance, all the more for outpatients population, having in mind that general practitioners might be less familiar with the handling DDI derived from ritonavir than healthcare professionals at hospital in the field of HIV infection. Nevertheless, it can also be acknowledged that the short 5 days treatment duration could mitigate the burden.

At this stage the CHMP has adopted to apply the list of DDI in the SmPC of ritonavir into that of Paxlovid as indicated in the SmPC as a conservative measure. In order to highlight and mitigate this issue, the CHMP has addressed a letter to several Healthcare professionals' organisations to raise awareness about the DDI with Paxlovid.

3.5. Uncertainties and limitations about unfavourable effects

There are uncertainties on the impact of hepatic impairment on the safety profile of Paxlovid. Participants with known medical history of active liver disease or acute liver failure were excluded from the pivotal study C4671005 (EPIC-HR). In the PK study in patients with hepatic impairment, the interim analysis data in moderate HI did not significantly differ from the control, nevertheless the category of patients with severe HI was not covered.

In addition, the safety profile of PF-07321332/ritonavir in patients with moderate and severe renal impairment cannot be established yet. There is a lack of data in the moderate to severe renal impairment population in study C4671005 (exclusion of this population) and the results of the completed Phase 1 study C4671011 showed a PF-07321332 systemic exposure (AUC and Cmax) increase with a magnitude depending on the severity of the renal impairment and a higher proportion of AEs in the severe renal impairment compared to the other groups.

In severe renal impairment, there was an increase of AUC by 204%. No recommendation in terms of dose adjustment could be elaborated at this stage.

For both patients with severe renal impairment and severe hepatic impairment, given that there is a lack of data to inform on a posology, rather than evidence of harm, an explicit warning has been introduced in the SmPC at this stage pending dedicated investigations (notably through an updated PopPK model).

In moderate renal impairment, a dose reduction by one-half of PF-07321332 has been proposed by the company but was not tested in clinic. The adequacy of this dose adjustment in patients and the risk of medical errors will be particularly scrutinised in post approval.

Hypertension occurred at a low frequency overall but with an apparent imbalance (0.6% and 0.2%, in the PF- 07321332/ritonavir and placebo group, respectively). Most of events were low grade and none

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was considered treatment-related in the PF- 07321332/ritonavir group. Nevertheless considering that the hypertension events mostly occurred with a short time to onset (mainly between Day 2 and Day 5), the majority of patients experiencing hypertension had no history of hypertension (4 of 7 patients) and that hypertension is a known risk with ritonavir, it remains uncertain whether there is a causal relationship between of hypertension with Paxlovid. Given this sensitive issue in a population where hypertension is already a risk factor, the CHMP requested a safety review for hypertension covering safety data from ongoing early access worldwide and notably from US (Emergency Use Authorisation) and literature data with cut-off date 31st March 2022, by April 2022 followed by the integrated safety report with its three sponsored studies (C4671005/EPIC-HR, C4671002/EPIC-SR and C467PEP) in June 2022.

Myalgia occurred at a low frequency with also an apparent imbalance (0.6% and 0.2%, in the PF-07321332/ritonavir and placebo group, respectively). Since two cases of the 7 reported with PF-07321332/ritonavir were considered treatment-related and considering myalgia is a known risk of ritonavir, again it remains uncertain whether there is a causal relationship between myalgia and Paxlovid. A safety review for myalgia was also requested covering safety data from ongoing early access worldwide and notably from US (Emergency Use Authorisation) and literature data with cut-off date 31st March 2022, by April 2022 followed by the integrated safety report with its three sponsored studies (C4671005/EPIC-HR, C4671002/EPIC-SR and C467PEP) in June 2022.

3.6. Effects Table

Table 56. Effects Table for Paxlovid in the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19 (data cut-off: 09 December 2021).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Proportion of participants With COVID-19 related hospitalisation or death from any cause through Day 28.	Primary endpoint therapeutic ≤3 days after symptom onset.				- Consistency across sensitivity and - Supported by the secondary endpoint	C4671005 Phase 2/3 study
	First key secondary endpoint (95% CI) therapeutic > 3 days after symptom	% of event	0.781 (0.391, 1.556)	6.400 (5.063, 8.075)	ensure the generalisation following subpopulation: vaccinated patients, patients with risk factors which are poorly represented in the C4671005 study and - Need to further explore the serologic status at - Efficacy analysis sets would be expected to consistently include all randomised subjects regardless of treatment with study drug or post-	
Unfavourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Grade ≥3 TEAEs	All causalities	%	4.1	8.3	Mostly reported in the SOCs Investigations and Infections and infestations	
Dysgeusia	All causalities	%	5.6	0.3	Identified AE with ritonavir	
Vomiting	All causalities	%	1.1	0.8	Identified AE with ritonavir	
Diarrhoea	All causalities	%	3.1	1.6	Identified AE with ritonavir	
Headache	All causalities	%	1.4	1.3	Identified AE with ritonavir	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The identified quality issues discussed in this report and to be addressed through fulfilment of specific obligations, raise some uncertainties with regard to the batch to batch consistency between the product batches studied in pharmaceutical, preclinical and clinical development and future commercial batches. However, the submitted data indicate that batches to date are of appropriate quality that is comparable to that of clinical development batches. Considering the emergency context of this application the above identified quality issues do not preclude granting of a CMA. However, in order to confirm that the quality of future batches will also remain appropriate and comparable to that of clinical development batches over the life cycle of the medicinal product, these issues are expected to be addressed though fulfilment of specific obligations, within the defined due dates.

The primary endpoint of the study, proportion of COVID-19-related hospitalisation or death from any cause at Day 28, was met with consistency and further supported by the results of sensitivity analyses and in the first secondary analysis in mITT1, while, based on the provided safety data, no major concern was identified in the safety profile of PF-07321332/ritonavir combination, which appears comparable to placebo at the intended dosage of 300mg/100mg Q12h for 5 days. However, the complexity of the interaction profile driven by the ritonavir booster dose could be a limiting factor for its use.

3.7.2. Balance of benefits and risks

The submitted quality data is currently not fully comprehensive, but this is considered acceptable in the emergency context and the quality package will be completed though fulfilment of specific obligations by defined due dates.

Overall, there is a clinical benefit of Paxlovid by reducing the risk of hospitalisation or death in the target population of adults with coronavirus disease 2019 (COVID-19) who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19.

Based on the provided safety data, no major concern was identified in the safety profile of PF-07321332/ritonavir combination. The most frequent adverse reactions were dysgeusia, diarrhoea, vomiting and headache which are described in section 4.8 of the SmPC.

The demonstrated benefits of Paxlovid outweigh the risks.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive quality data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment life-threatening disease. In addition, the COVID-19 pandemic constitutes an emergency situation. It is a public health threat duly recognised by the World Health Organisation as well as the EU.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data. The CHMP has identified specific obligations concerning pharmaceutical (quality) data, which are expected to provide comprehensive data for this product. No concerns have been identified with the ability to complete these specific obligations, as the applicant has indicated that they consider respective due dates as feasible.
- Unmet medical needs will be addressed, as in the framework of the ongoing COVID-19 pandemic there is an urgent need for safe and effective therapeutic interventions that can reduce viral transmission, improve time to clinical recovery and prevent the progression of infection to more severe disease, hospitalisation and death. Paxlovid has demonstrated efficacy on patient at increased risk of severe COVID-19, it is also for oral use that can be taken outside the hospital setting.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. COVID-19 inarguably represents the most significant public health emergency of our time. In this context it is considered that the benefits to public health of the immediate availability of Paxlovid outweigh the risks inherent in the fact that additional quality data are still required.

3.8. Conclusions

The overall benefit/risk balance of Paxlovid is positive, subject to the conditions stated in section 'Recommendations'

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus

that the benefit-risk balance of Paxlovid is favourable in the following indication(s):

Paxlovid is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID 19 (see section 5.1).

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
In order improve the control strategy description and to confirm a consistent impurity profile, additional details should be included in the manufacturing process proposed for the active substance PF-07321332 for commercial supply.	30 June 2022
In order ensure comprehensive control of impurities throughout the lifecycle of the product, the control strategy for the active substance PF-07321332 for the impurities including chiral impurities and the active substance should be fully established.	30 June 2022
In order ensure comprehensive control of impurities throughout the lifecycle of the product, full validation data for the HPLC method for assay and impurity testing, and	30 June 2022

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Description	Due date
for the residual solvent method used for the control of the active substance PF-07321332 should be provided.	
In order to improve the control strategy for the ritonavir film coated tablets, the limit for dissolution specification of ritonavir film coated tablets should be tightened according to the results obtained for the biobatches, e.g. to NMT 75 % (Q) in 45 min.	30 June 2022

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that the active substance (1R,2S,5S)-N-((1S)-1-Cyano-2-((3S)-2-oxopyrrolidin-3-yl)ethyl)-3-((2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido) butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

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Annex I - List of recommendations (RECs) and Legally binding measures (LEGs)

Area	Number	Description	Classification
Quality	1	To update the quality dossier. By removing references to emergency supply product; by replacing the provisional specifications with final specifications for starting materials, intermediates, both active substances and finished product. The applicant committed to provide the updated information as soon as possible at latest in 2Q 2022.	REC
Quality	2	In order to improve the quality dossier for the Active substance PF-07321332 it is recommended to update the section "2.3 Control of materials" and "2.4 Control of critical steps and intermediates" as follows: a) It is stated that some of the synthesis routes of the starting materials are still under development and being optimised which could result in changes of the synthesis routes. Therefore, the final synthesis routes for the starting materials should be provided as soon as possible at latest in 2Q 2022 as committed by the applicant. b) Section S.2.3 should be updated with information on the several suppliers for starting materials together with the update on batch genealogy. The applicant committed to provide the data by July 2022. c) Starting materials specifications should be updated based on a complete and robust batch history as soon as available preferably before commercial application as committed by the applicant. d) Comparative data will be expected by July 2022 as committed by the applicant once definitive specifications for PF-07321332 active substance are set. e) The assay limits in the starting material specifications should be raised based on batch analysis data for the starting material suppliers and taking into account the impurity limits. Accordingly revised starting material specifications should be provided as soon as possible at latest in 2Q 2022 as committed by the applicant. f) The applicant is required to submit variation for the addition of any sites and the modified active substance synthesis route prior to implementing these changes after CMA approval.	REC

Quality	3	It is recommended to update the section "3. Characterisation" of the Active substance PF-07321332 as follows: a) As the active substance is badly soluble, the polymorphic form can have an influence on the bio performance of the drug product. Therefore, it should be demonstrated that the polymorphic form does not change during storage of the active substance. The applicant committed to provide the updated information as soon as possible at latest in 2Q 2022. b) The structure of an identified impurity should be stated, and it should be classified according to ICH M7. The applicant committed to provide the updated information as soon as possible at latest in 2Q 2022. c) It is stated that the concentrations of the solvents used will be investigated on 3 consecutive production batches of the AS. The data should be submitted. This investigation should be also performed concerning potential residues of the solvent which is used in step 1. The applicant committed to provide the updated information as soon as possible at latest in 2Q 2022. d) The applicant states that the Class 1/2A elemental impurities, will be monitored in PF-07321332 active substance and an appropriate control strategy will be established at the time of registration. The applicant committed to provide the updated information as soon as possible at latest in 2Q 2022.	REC
Quality	4	The section '4. Control of drug substance' for the Active substance PF-07321332 is recommended to update as follows: a) An updated section 3.2.S.4.2 including description of the residual solvent method and the XRD method should be provided as soon as possible. Validation data which show that the XRPD method is suitable to distinguish polymorphic forms should be provided. The applicant committed to submit the data as soon as possible at latest in 2Q 2022. b) Based on the PSD of AS batches used in drug product batches used in the pivotal clinical studies the set acceptance criteria for PSD in the active substance specification cannot be accepted. Therefore, the PSD limits should be tightened unless it could be show on PK or bioavailability data that the set upper limits of the PSD have no impact on the bio performance of the drug product.	REC

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		An accordingly revised active substance specification should be provided as soon as possible at latest in 2Q 2022 as committed by the applicant. c) It is stated that microbiological quality will be evaluated for three primary stability lots at initial release and when stored under the proposed long-term storage conditions. Data will be reported at the time of registration filing. The applicant committed to submit the data as soon as possible at latest in 2Q 2022.	
Quality	5	The section '7. Stability' for the Active substance PF-07321332 should be updated as follows: a) The applicant commits to include batches of PF-07321322 active substance manufactured by earlier and current synthetic routes on stability studies. Stability data from batches manufactured by the current synthetic route and from previous routes should be provided as soon as possible at latest in 2Q 2022 as committed by the applicant. b) Forced degradation data on a batch of PF-07321332 active substance manufactured by the commercial synthetic route should be provided as soon as available at latest in 2Q 2022 as committed by the applicant.	REC
Quality	6	The section 3.2.P.2 Pharmaceutical Development for the Drug Product PF-07321332 should address the following issues: a) With respect to BCS classification, a BCS class should be definitely determined for PF-07321332 on the basis of sound analytical data. b) The particle size distribution (PSD) set for the active substance is considered premature. A discussion in depth with respect to potential PSD impact on manufacturability and bio-performance of the PF-07321332 IR film-coated tablets should be provided. Additionally, the PSD should encompass three percentile values D10, D50 and D90, unless otherwise justified. c) Data should be presented, investigating whether the polymorphic form selected for PF-07321332 drug product can remain stable under the proposed drug product manufacturing conditions and during shelf life.	REC

		d) A certain manufacturing process step needs to be addressed in detail rather than just shortly mentioned in the blend homogeneity experiments. The applicant has provided a commitment to update the above information as soon as possible at latest in 2Q 2022.	
Quality	7	The section 3.2.P.3 for the Drug Product PF-07321332 should be updated in terms of the following aspects a) The numeration of the individual process steps in the manufacturing process narrative should be brought in line with the corresponding numeration indicated in the flow chart. Further, the term 'Package' needs to be replaced with 'Co-package' or similar to adequately reflect the co-packaging of PF-07321332 with ritonavir film-coated tablets in the same blister. b) The manufacturing process description should be amended to contain more details e.g. the operating ranges worked out within the process development, fully reflecting the information level required in the Guideline on Manufacture of the Finished Dosage Form (EMA/CHMP/QWP/245074/2015). c) Critical steps are not mentioned at all but should be specified, among others the co-packaging step, which is regarded as critical, since this packaging involves the placing of two different bulk drug products into the same blister. d) Please clarify, whether hold times are intended to be applied for the PF-07321332 drug product manufacture. If any, suitable stability data as respective justification needs to be provided. e) Process validation data to full extent, considering all requirements as specified in the Guideline on Process Validation for Finished Products (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1), should be provided. In this context, it should also be shown that the four recently available emergency supply batches have been manufactured achieving acceptably reproducible results between and within batches for the respective stages of the process. The applicant has provided a commitment to update the above information as soon as possible at latest in 2Q 2022.	REC
Quality	8	The section 3.2.P.4 for the Drug Product PF-07321332 should be revised to include the details as follows	REC

		a) All excipients (compendial and non-compendial) used for manufacture of PF-07321332 150 mg film-coated tablets should be included in this section, each with a concise description including respective function. b) An adequately compiled specification considering identity etc. for the film coat system Opadry Pink should be provided, along with an analytical procedure. If non-compendial, sound validation needs to be addressed for the non-compendial test method. c) Compliance with the EU regulation 231/2012 should be confirmed for red iron oxide. d) Exemplary CoAs should be provided for the non-compendial excipient Opadry Pink. The applicant has provided a commitment to update the above information as soon as possible at the latest in 2Q 2022.	
Quality	9	The section P.5 Control of the Drug Product PF-07321332 should be updated as follows a) Additional parameters should be included in the release specification. b) Validation data should be presented concerning intermediate precision and robustness for the three methods used for identity, assay degradation products and content uniformity. c) For the method, which is used alternatively for determination of assay, the stability indicating power should be demonstrated by using appropriate stress tests with the finished product. d) For completeness of the validation data additional validation information should be submitted. e) The degradation pathway of 4 possible degradation products should be highlighted under the section 3.2.P.5.5, the link to 3.2.S.3.2 is not considered sufficient. f) The limit for assay in the shelf life specification should be tightened. Even if limited stability data are available, a widening of the limit for assay is not considered acceptable, as no degradation is observed during stability studies including stress tests performed. The applicant has provided a commitment to update the information as soon as possible at the latest in 2Q 2022.	REC

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Quality	10	The section P.7 Container closure system for the Drug Product PF-07321332 should be updated as follows: For the container closure system used appropriate food declarations should be provided. The applicant has provided a commitment to update the information as soon as possible at the latest in 2Q 2022.	REC
Quality	11	The section P.8 Stability for the Drug Product PF-07321332 should be updated as follows a) The batch size of the Primary batches used for the stability studies should be detailed. b) The method used for determination of water activity should be described and validation data should be presented. c) It should be confirmed that the precaution advice "Do not store above 25 °C" and "Do not refrigerate or freeze" will be deleted when it has been demonstrated by stability data, that these precaution advices are not necessary. d) Based on 3 months stability data submitted for the primary stability batches of the PF-07321332 tablets including the supportive stability data, a shelf life of 12 months with the precaution advice "Do not store above 25°C. Do not refrigerate or freeze" is considered acceptable provided, the stability samples will be monitored monthly, and any Out Of Specification results (OOS results) will be provided immediately to the Authorities. The applicant has provided a commitment to update the information as soon as possible at latest in 2Q 2022.	REC
Quality	12	Ritonavir Module 3.2.P.1 of should be updated as follows: The active ingredient should be included at the declared amount (100 mg). For each individual excipient, one total amount should be given. The applicant has provided a commitment to update the information as soon as possible at the latest in 2Q 2022.	REC
Quality	13	Ritonavir Module 3.2.P.2 should be updated as follows. In the context of the CMAA, the quality documentation for ritonavir film-coated tablets is considered acceptable from a risk-based perspective as the product is currently registered in several European countries with the proposed specifications. However, the requirements of EMA/CHMP/CVMP/QWP/336031/2017 apply to ritonavir film-	REC

		coated tablets as part of the CMA for Paxlovid, as this is a new drug product: a) Only fragmented information is provided in the development section, which is to be completed in line with the requirements of ICH Q8 (R2). The underlying QTPP should be disclosed, taking into account properties of the active substance ritonavir as well as published information on the reference product. The active substance's material attributes should be defined, including the potential presence of other polymorph forms or potential conversion between forms as well as their clinical relevance (physiological properties), and their impact on the CQA of the drug product. Also, the proposed particle size distribution specification should be addressed and justified and its impact on the CQA of the drug product (e.g. the dissolution specification) be evaluated. Sections 3.2.P.2.1 and 3.2.P.2.2.3 should be updated accordingly. b) Critical process parameters during manufacture are identified with specified set points. However, justification based on development data is awaited particularly for a certain step of this non-standard procedure. Particularly, the impact of different settings on the chemical purity of the drug product and on potential conversion of the polymorph form should be discussed and supported by development results. c) Justification of the dissolution conditions are awaited, particularly the choice of media and the agitation speed. Section 3.2.P.2.2.1 should be updated. The applicant has provided a commitment to update the information as soon as possible at the latest in 2Q 2022.	
Quality	14	Ritonavir Module 3.2.P.3 of should be updated as follows: a) The process descriptions should be updated to include amounts of and reaction conditions for the given batch size of both the intermediate and the film-coated tablets, as well as the in-process controls. b) Specifications for packaging material for the intermediate are awaited, along with stability data of the intermediate. c) The specification for the intermediates should be provided and /or updated. Section 3.2.P.3.4 should be updated.	REC

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		d) Validation data for the non-standard process step should be provided. Furthermore, the process optimisation study results should be disclosed. The applicant has provided a commitment to update the information as soon as possible at the latest in 2Q 2022.	
Quality	15	Ritonavir Module 3.2.P.5 should be updated as follows: a) It should be highlighted why different specification limits are outlined for dissolution testing and impurity limits under the Certificates of Analysis for some batches. Both specification limits for dissolution testing differ from that outlined under 3.2.P.5.1. Levels of impurities found for one impurity exceed the limit detailed under P.5.1. These discrepancies should be clarified. b) The applicant states that the analysis of elemental impurities is ongoing. Data of three production batches and analytical method validation will be submitted in January 2022. The applicant should commit that these data including validation report will be implemented as soon as possible and will be send to the competent Authorities when available. c) The applicant states that method validation for three batches of ritonavir active substance which have been tested for nitrosamine impurities are in progress and will be submitted in January 2022. The applicant should commit that the validation report including calculation of allowable limits of nitrosamine impurities will be implemented in the documentation and will be send to the competent Authorities when available. d) If not otherwise justified, the limit for water content, which has been set to the shelf life specification should be tightened according to the data obtained. The applicant has provided a commitment to update the information as soon as possible at the latest in 2Q 2022.	REC
Quality	16	Ritonavir Module 3.2.P.6 should be updated as follows: The purpose of the reference standard used should be highlighted. The statement that the reference standards are used for the analysis of the film coated tablets is not sufficient. Especially the purpose of the intermediate primary reference standard should be detailed. The applicant has provided a commitment to update the information as soon as possible at the latest in 2Q 2022.	REC

Quality	17	Ritonavir Module 3.2.P.8 should be updated as follows: a) Please clarify on the proposed storage declaration for the bulk tablets ("Do not store below 25 °C") and update section 3.2.P.8.1. b) As for the post-approval stability protocol and stability commitment for the co-packaged product, XRD should be included in the regular tests. It should further be confirmed that microbiological tests will be performed annually. The applicant has provided a commitment to update the information as soon as possible at the latest in 2Q 2022.	REC
Quality	18	Drug product co-packed Paxlovid: Information and data on the bulk products PF-07321332 and ritonavir film coated tablets have been provided. However, information and data concerning the final co-packed drug product Paxlovid to be marketed is reflected poorly in the dossier. The drug product ritonavir (bulk tablets), as documented in current separate Module 3.2.P, is considered as Intermediate product, which is being introduced in the last steps of manufacture of PF-07321332 tablets. Therefore, The contents of Module 3.2.P ritonavir bulk tablets should be integrated as sub-chapter in Module 3.2.P.3 of PF-07321332 tablets in order to avoid confusion and repeating of documents. The respective sections of 3.2.P PF-07321332 tablets should be updated to include the missing information for the co-packed drug product Paxlovid to be marketed. A separate Module for the co-packaged drug product would not be required. The applicant has provided a commitment to update the information as soon as possible at the latest in 2Q 2022.	REC
NC	19	The on-going whole body autoradiographic study report in rats with PF-07321332 (alone) should be provided by 31 March 2022, together with the applicant's assessment need to be submitted as soon as available.	LEG
NC	20	The final study reports of the two 1-month repeat-dose toxicity studies (21GR122 and 21GR125) should be provided by 31 January 2022.	LEG
NC	21	The final study report for the pre- and postnatal development (21GR149) should be provided by 30 April 2022. Meanwhile, in case of any new safety concern identified during the	LEG

		ongoing analysis of these data, the applicant should inform the EMA.	
NC	22	The Environmental Risk Assessment should be completed and provided by 31 December 2024	REC
NC	23	The study report for the on-going *in vivo* study with PF-07321332 in combination with ritonavir using a mouse-adapted (MA) model of SARS-CoV-2 infection (MA-SARS-CoV-2) in BALB/c mice should be provided by 28 February 2022.	REC
C (PK)	24	*In vitro* dissolution test comparing the 250 mg uncoated tablet with the film coated tablets should be provided to substantiate the bridge.	REC
C (PK)	25	The updated PopPK model results including PK data collected from the patients enrolled in the EPIC-HR study with relevant covariables and relevant update to the exposure margins should be provided by 31 March 2022	LEG
C (PK)	26	The final clinical study report for C46711010 investigating the effect of moderate hepatic impairment on the PK of PF-07321332 should be provided.	REC
C (PK)	27	The PBPK model exercise with commercial software (SimCYP) utilising compound files for metformin and rosuvastatin should be provided. The PBPK modelling robustness should be demonstrated and high level of qualification of the model should be provided (multiple substrates, multiple perpetrators, based on *in vivo* results).	REC
C (PK)	28	Two studies are currently being performed to assess the effect of PF-07321332/ritonavir on midazolam as a CYP3A4 substrate (Study 1013) and dabigatran as a P-gp substrate (Study 1012). The study results should be provided.	REC
C (PD)	29	Evaluation of *in vitro* selected resistant SARS-CoV-2 (WA) against PF-07321332 should be provided. It is also recommended to additionally conduct the resistance assay with the current circulated variants (delta and omicron).	REC
C (PD)	30	The final report of *In vitro* Virus RNA Replication Efficiency of the Recombinant SARS-CoV-2 Containing Engineered Mutations in 3CL Protease PF-07321332 should be provided.	REC
C (PD)	31	*In vitro* cell-based efficacy data of PF-07321332 against mutant viruses that showed a drop in PF-07321332 potency as measured by biochemical assay and viruses from the breakthrough cases in study C46710053CL should be provided.	REC
C (PD)	32	The full planned genotyping and phenotyping analyses at baseline and in treatment failure from the pivotal 1005 study.	REC

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		It is highly recommended to examine the impact of mutations outside of the 3CLpro gene and 3CLpro cleavage regions.	
C	33	Patients with immunodeficiency were poorly represented with less than 1% of the study population. The applicant should monitor treatment failure in this subset of patients in post-approval.	REC
C	34	Cigarettes smokers are largely represented while, in the state of art, uncertainties remain on the increase risk related to this factors. The applicant should elaborate in which extent participants with "cigarettes smoke" at baseline presented this solely risk factors or other comorbidities, and a potential impact of the results.	REC
C	35	Long-term data from study C4671005 (i.e. at Week 34) should be provided to ensure that no further events onset potentially impacting the main outcomes.	REC
C	36	The applicant is committed to provide the results of the exploratory testing planned to further characterize the immune response to SARS-CoV-2 at baseline, including serology status.	REC
C	37	The applicant is committed to provide C4671002 study results as soon as available. Additionally, the applicant is committed to elaborate on collecting post-approval data especially in patients who still remain at risk of severe disease after vaccination.	REC
C (safety)	38	A safety review for hypertension covering safety data from ongoing early access worldwide and notably from US (Emergency Use Authorisation) and literature data with cut-off date 31st March should be provided by April 2022, awaiting for a global safety review planned to be submitted covering the 3 applicant's sponsored clinical studies (EPIC-HR, EPIC-SR and study in PEP) in June 2022	LEG
C (safety)	39	A safety review for myalgia covering safety data from ongoing early access worldwide and notably from US (Emergency Use Authorisation) and literature data with cut-off date 31st March should be provided by April 2022, awaiting for a global safety review planned to be submitted covering the 3 applicant's sponsored clinical studies (EPIC-HR, EPIC-SR and study in PEP) in June 2022	REC
C	40	The user consultation with target patient groups should be carried out and the results provided.	REC

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Document 2A.7

EMA European Public Assessment Report – Product Information (Annex I-III; updated June 27 2023)

Document URL

https://www.ema.europa.eu/en/documents/product-information/paxlovid-epar-product-information_en.pdf

Reference website URL

https://www.ema.europa.eu/en/medicines/human/EPAR/paxlovid

License

Not applicable

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ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Paxlovid 150 mg + 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pink film-coated tablet contains 150 mg of nirmatrelvir.
Each white film-coated tablet contains 100 mg of ritonavir.

Excipients with known effect

Each pink 150 mg film-coated tablet of nirmatrelvir contains 176 mg of lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Nirmatrelvir

Film-coated tablet (tablet).
Pink, oval, with a dimension of approximately 17.6 mm in length and 8.6 mm in width debossed with ‘PFE’ on one side and ‘3CL’ on the other side.

Ritonavir

Film-coated tablet (tablet).
White to off white, capsule shaped tablets, with a dimension of approximately 17.1 mm in length and 9.1 mm in width, debossed with 'H' on one side and 'R9' on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Paxlovid is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19 (see section 5.1).

4.2 Posology and method of administration

Posology

The recommended dosage is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally every 12 hours for 5 days. Paxlovid should be administered as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset. Completion of the full 5-day treatment course is recommended even if the patient requires hospitalisation due to severe or critical COVID-19 after starting treatment with Paxlovid.

If the patient misses a dose of Paxlovid within 8 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more

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than 8 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose.

Special populations

Renal impairment
No dose adjustment is needed in patients with mild renal impairment (eGFR ≥ 60 to < 90 mL/min). In patients with moderate renal impairment (eGFR ≥ 30 to < 60 mL/min), the dose of Paxlovid should be reduced to nirmatrelvir/ritonavir 150 mg/100 mg every 12 hours for 5 days to avoid over-exposure (this dose adjustment has not been clinically tested). Paxlovid should not be used in patients with severe renal impairment [eGFR < 30 mL/min, including patients with End Stage Renal Disease (ESRD) under haemodialysis] (see sections 4.4 and 5.2).

Special attention for patients with moderate renal impairment
The daily blister contains two separated parts each containing two tablets of nirmatrelvir and one tablet of ritonavir corresponding to the daily administration at the standard dose.
Therefore, patients with moderate renal impairment should be alerted on the fact that only one tablet of nirmatrelvir with the tablet of ritonavir should be taken every 12 hours.

Hepatic impairment
No dose adjustment of Paxlovid is needed for patients with either mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Paxlovid should not be used in patients with severe (Child-Pugh Class C) hepatic impairment (see sections 4.4 and 5.2).

Concomitant therapy with ritonavir- or cobicistat-containing regimen
No dose adjustment of Paxlovid is needed. Patients diagnosed with human immunodeficiency virus (HIV) or hepatitis C virus (HCV) infection who are receiving ritonavir- or cobicistat-containing regimen should continue their treatment as indicated.

Paediatric population
The safety and efficacy of Paxlovid in patients below 18 years of age have not been established. No data are available.

Method of administration

For oral use.

Nirmatrelvir must be coadministered with ritonavir. Failure to correctly coadminister nirmatrelvir with ritonavir will result in plasma levels of this active substance that will be insufficient to achieve the desired therapeutic effect.

Paxlovid can be taken with or without food (see section 5.2). The tablets should be swallowed whole and not chewed, broken or crushed, as no data is currently available.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Medicinal products listed below are a guide and not considered a comprehensive list of all possible medicinal products that are contraindicated with Paxlovid.

Medicinal products that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions.

- Alpha$_1$-adrenoreceptor antagonist: alfuzosin
- Antianginal: ranolazine
- Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine

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- Antibiotics: fusidic acid
- Anticancer drugs: neratinib, venetoclax
- Anti-gout: colchicine
- Antihistamines: terfenadine
- Antipsychotics/neuroleptics: clozapine, lurasidone, pimozide, quetiapine
- Benign prostatic hyperplasia medicinal products: silodosin
- Cardiovascular medicinal products: eplerenone, ivabradine
- Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine
- GI motility agents: cisapride
- Immunosuppressants: voclosporin
- Lipid-modifying agents:
  - HMG Co-A reductase inhibitors: lovastatin, simvastatin
  - Microsomal triglyceride transfer protein (MTTP) inhibitor: lomitapide
- Migraine medicinal products: eletriptan
- PDE5 inhibitor: avanafil, sildenafil, tadalafil, vardenafil
- Sedative/hypnotics: clorazepate, diazepam, estazolam, flurazepam, oral midazolam and triazolam
- Vasopressin receptor antagonists: tolvaptan

Medicinal products that are potent CYP3A inducers where significantly reduced nirmatrelvir/ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance.

- Antibiotics: rifampicin
- Anticancer drugs: apalutamide
- Anticonvulsants: carbamazepine, phenobarbital, phenytoin
- Herbal products: St. John's wort (*Hypericum perforatum*)

Paxlovid cannot be started immediately after discontinuation of CYP3A4 inducers due to the delayed offset of the recently discontinued CYP3A4 inducer (see section 4.5).

A multi-disciplinary approach (e.g., involving physicians and specialists in clinical pharmacology) should be considered to determine the adequate timing for Paxlovid initiation taking into account the delayed offset of the recently discontinued CYP3A inducer and the need to initiate Paxlovid within 5 days of symptom onset.

4.4 Special warnings and precautions for use

Risk of serious adverse reactions due to interactions with other medicinal products

Management of drug-drug interactions (DDIs) in high-risk COVID-19 patients receiving multiple concomitant medications can be complex and require a thorough understanding of the nature and magnitude of interaction with all concomitant medications. In certain patients, a multi-disciplinary approach (e.g., involving physicians and specialists in clinical pharmacology) should be considered for management of DDIs especially if concomitant medications are withheld, their dosage is reduced, or if monitoring of side effects is necessary.

Effects of Paxlovid on other medicinal products
Initiation of Paxlovid, a CYP3A inhibitor, in patients receiving medicinal products metabolised by CYP3A or initiation of medicinal products metabolised by CYP3A in patients already receiving Paxlovid, may increase plasma concentrations of medicinal products metabolised by CYP3A (see section 4.5).

Coadministration of Paxlovid with calcineurin inhibitors and mTOR inhibitors
Consultation of a multidisciplinary group (e.g., involving physicians, specialists in immunosuppressive therapy, and/or specialists in clinical pharmacology) is required to handle the

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complexity of this coadministration by closely and regularly monitoring immunosuppressant serum concentrations and adjusting the dose of the immunosuppressant in accordance with the latest guidelines (see section 4.5).

Effects of other medicinal products on Paxlovid
Initiation of medicinal products that inhibit or induce CYP3A may increase or decrease concentrations of Paxlovid, respectively.

These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening or fatal events from greater exposures of concomitant medicinal products.
- Clinically significant adverse reactions from greater exposures of Paxlovid.
- Loss of therapeutic effect of Paxlovid and possible development of viral resistance.

See Table 1 for medicinal products that are contraindicated for concomitant use with nirmatrelvir/ritonavir and for potentially significant interactions with other medicinal products (see section 4.5). Potential for interactions should be considered with other medicinal products prior to and during Paxlovid therapy; concomitant medicinal products should be reviewed during Paxlovid therapy and the patient should be monitored for the adverse reactions associated with the concomitant medicinal products.

Hypersensitivity reactions

Anaphylaxis and other hypersensitivity reactions have been reported with Paxlovid (see section 4.8). Cases of Toxic Epidermal Necrolysis and Stevens-Johnson syndrome have been reported with ritonavir, a component of Paxlovid (refer to Norvir Summary of Product Characteristics). If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue Paxlovid and initiate appropriate medications and/or supportive care.

Severe renal impairment

No clinical data are available in patients with severe renal impairment (including patients with ESRD). Based on pharmacokinetic data (see section 5.2), the use of Paxlovid in patients with severe renal impairment could lead to over-exposure with potential toxicity. No recommendation in terms of dose adjustment could be elaborated at this stage pending dedicated investigation. Therefore, Paxlovid should not be used in patients with severe renal impairment (eGFR < 30 mL/min, including patients with ESRD under haemodialysis).

Severe hepatic impairment

No pharmacokinetic and clinical data are available in patients with severe hepatic impairment. Therefore, Paxlovid should not be used in patients with severe hepatic impairment.

Hepatotoxicity

Hepatic transaminase elevations, clinical hepatitis and jaundice have occurred in patients receiving ritonavir. Therefore, caution should be exercised when administering Paxlovid to patients with pre-existing liver diseases, liver enzyme abnormalities or hepatitis.

Elevation in blood pressure

Cases of hypertension, generally non serious and transient, have been reported during treatment with Paxlovid. Specific attention including regular monitoring of blood pressure should be paid notably to elderly patients since they are at higher risk of experiencing serious complications of hypertension.

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Risk of HIV-1 resistance development

Because nirmatrelvir is coadministered with ritonavir, there may be a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection.

Excipients

Nirmatrelvir tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Nirmatrelvir and ritonavir tablets each contain less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on Paxlovid

Nirmatrelvir and ritonavir are CYP3A substrates.

Coadministration of Paxlovid with medicinal products that induce CYP3A may decrease nirmatrelvir and ritonavir plasma concentrations and reduce Paxlovid therapeutic effect.

Coadministration of Paxlovid with medicinal product that inhibits CYP3A4 may increase nirmatrelvir and ritonavir plasma concentrations.

Effects of Paxlovid on other medicinal products

Medicinal products CYP3A4 substrates
Paxlovid (nirmatrelvir/ritonavir) is a strong inhibitor of CYP3A and increases plasma concentrations of medicinal products that are primarily metabolised by CYP3A. Thus, coadministration of nirmatrelvir/ritonavir with medicinal products highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated (see Table 1). Coadministration of other CYP3A4 substrates that may lead to potentially significant interaction (see Table 1) should be considered only if the benefits outweigh the risks.

Medicinal products CYP2D6 substrates
Based on *in vitro* studies, ritonavir has a high affinity for several cytochrome P450 (CYP) isoforms and may inhibit oxidation with the following ranked order: CYP3A4 > CYP2D6. Coadministration of Paxlovid with drug substrates of CYP2D6 may increase the CYP2D6 substrate concentration.

Medicinal products P-glycoprotein substrates
Paxlovid also has a high affinity for P-glycoprotein (P-gp) and inhibits this transporter; caution should thus be exercised in case of concomitant treatment. Close drug monitoring for safety and efficacy should be performed, and dose reduction may be adjusted accordingly, or avoid concomitant use.

Paxlovid may induce glucuronidation and oxidation by CYP1A2, CYP2C8, CYP2C9 and CYP2C19 thereby increasing the biotransformation of some medicinal products metabolised by these pathways and may result in decreased systemic exposure to such medicinal products, which could decrease or shorten their therapeutic effect.

Based on *in vitro* studies there is a potential for nirmatrelvir to inhibit MDR1, MATE1, OCT1 and OATP1B1 at clinically relevant concentrations.

Dedicated drug-drug interactions studies conducted with Paxlovid indicate that the drug interactions are primarily due to ritonavir. Hence, drug interactions pertaining to ritonavir are applicable for Paxlovid.

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Medicinal products listed in Table 1 are a guide and not considered a comprehensive list of all possible medicinal products that are contraindicated or may interact with nirmatrelvir/ritonavir.

Table 1: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
Alpha$_1$-adrenoreceptor antagonist	↑Alfuzosin	Increased plasma concentrations of alfuzosin may lead to severe hypotension and is therefore contraindicated (see section 4.3).
Amphetamine derivatives	↑Amphetamine	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of amphetamine and its derivatives. Careful monitoring of adverse effects is recommended when these medicines are coadministered with Paxlovid.
Analgesics	↑Buprenorphine (57%, 77%)	The increases of plasma levels of buprenorphine and its active metabolite did not lead to clinically significant pharmacodynamic changes in a population of opioid tolerant patients. Adjustment to the dose of buprenorphine may therefore not be necessary when the two are dosed together.
	↑Fentanyl	Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of fentanyl. Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended when fentanyl is concomitantly administered with ritonavir.
	↓Methadone (36%, 38%)	Increased methadone dose may be necessary when coadministered with ritonavir dosed as a pharmacokinetic enhancer due to induction of glucuronidation. Dose adjustment should be considered based on the patient's clinical response to methadone therapy.
	↓Morphine	Morphine levels may be decreased due to induction of glucuronidation by coadministered ritonavir dosed as a pharmacokinetic enhancer.
	↑Pethidine	Coadministration could result in increased or prolonged opioid effects. If concomitant use is necessary, consider dosage reduction of pethidine. Monitor for respiratory depression and sedation.
	↓Piroxicam	Decreased piroxicam exposure due to CYP2C9 induction by Paxlovid.

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Table 1: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
Antianginal	↑Ranolazine	Due to CYP3A inhibition by ritonavir, concentrations of ranolazine are expected to increase. The concomitant administration with ranolazine is contraindicated (see section 4.3).
Antiarrhythmics	↑Amiodarone, ↑Dronedarone, ↑Flecainide, ↑Propafenone, ↑Quinidine	Ritonavir coadministration is likely to result in increased plasma concentrations of amiodarone, dronedarone, flecainide, propafenone and quinidine and is therefore contraindicated (see section 4.3).
	↑Digoxin	This interaction may be due to modification of P-gp mediated digoxin efflux by ritonavir dosed as a pharmacokinetic enhancer. Digoxin drug concentration is expected to increase. Monitor digoxin levels if possible and digoxin safety and efficacy.
Antiasthmatic	↓Theophylline (43%, 32%)	An increased dose of theophylline may be required when coadministered with ritonavir, due to induction of CYP1A2.
Anticancer agents	↑Abemaciclib	Serum concentrations may be increased due to CYP3A4 inhibition by ritonavir. Coadministration of abemaciclib and Paxlovid should be avoided. If this coadministration is judged unavoidable, refer to the abemaciclib SmPC for dosage adjustment recommendations. Monitor for ADRs related to abemaciclib.
	↑Afatinib	Serum concentrations may be increased due to Breast Cancer Resistance Protein (BCRP) and acute P-gp inhibition by ritonavir. The extent of increase in AUC and C_{max} depends on the timing of ritonavir administration. Caution should be exercised in administering afatinib with Paxlovid (refer to the afatinib SmPC). Monitor for ADRs related to afatinib.
	↑Apalutamide	Apalutamide is a moderate to strong CYP3A4 inducer and this may lead to a decreased exposure of nirmatrelvir/ritonavir and potential loss of virologic response. In addition, serum concentrations of apalutamide may be increased when coadministered with ritonavir resulting in the potential for serious adverse events including seizure. Concomitant use of Paxlovid with apalutamide is contraindicated (see section 4.3).

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Table 1: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
	↑Ceritinib	Serum concentrations of ceritinib may be increased due to CYP3A and P-gp inhibition by ritonavir. Caution should be exercised in administering ceritinib with Paxlovid. Refer to the ceritinib SmPC for dosage adjustment recommendations. Monitor for ADRs related to ceritinib.
	↑Dasatinib, ↑Nilotinib, ↑Vinblastine, ↑Vincristine	Serum concentrations may be increased when coadministered with ritonavir resulting in the potential for increased incidence of adverse events.
	↑Encorafenib	Serum concentrations of encorafenib may be increased when coadministered with ritonavir which may increase the risk of toxicity, including the risk of serious adverse events such as QT interval prolongation. Coadministration of encorafenib and ritonavir should be avoided. If the benefit is considered to outweigh the risk and ritonavir must be used, patients should be carefully monitored for safety.
	↑Fostamatinib	Coadministration of fostamatinib with ritonavir may increase fostamatinib metabolite R406 exposure resulting in dose-related adverse events such as hepatotoxicity, neutropenia, hypertension or diarrhoea. Refer to the fostamatinib SmPC for dose reduction recommendations if such events occur.
	↑Ibrutinib	Serum concentrations of ibrutinib may be increased due to CYP3A inhibition by ritonavir, resulting in increased risk for toxicity including risk of tumour lysis syndrome. Coadministration of ibrutinib and ritonavir should be avoided. If the benefit is considered to outweigh the risk and ritonavir must be used, reduce the ibrutinib dose to 140 mg and monitor patient closely for toxicity.
	↑Neratinib	Serum concentrations may be increased due to CYP3A4 inhibition by ritonavir. Concomitant use of neratinib with Paxlovid is contraindicated due to serious and/or life-threatening potential reactions including hepatotoxicity (see section 4.3).
	↑Venetoclax	Serum concentrations may be increased due to CYP3A inhibition by ritonavir,

Table 1: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		resulting in increased risk of tumour lysis syndrome at the dose initiation and during the ramp-up phase and is therefore contraindicated (see section 4.3 and refer to the venetoclax SmPC). For patients who have completed the ramp-up phase and are on a steady daily dose of venetoclax, reduce the venetoclax dose by at least 75% when used with strong CYP3A inhibitors (refer to the venetoclax SmPC for dosing instructions).
Anticoagulants	↑Dabigatran (94%, 133%)*	Concomitant administration of Paxlovid is expected to increase dabigatran concentrations resulting in increased risk of bleeding. Reduce dose of dabigatran or avoid concomitant use. Refer to the dabigatran product label for further information.
	↑Rivaroxaban (153%, 53%)	Inhibition of CYP3A and P-gp lead to increased plasma levels and pharmacodynamic effects of rivaroxaban which may lead to an increased bleeding risk. Therefore, the use of Paxlovid is not recommended in patients receiving rivaroxaban.
	Warfarin, ↑↓S-Warfarin (9%, 9%), ↓↔R-Warfarin (33%)	Induction of CYP1A2 and CYP2C9 lead to decreased levels of R-warfarin while little pharmacokinetic effect is noted on S-warfarin when coadministered with ritonavir. Decreased R-warfarin levels may lead to reduced anticoagulation, therefore it is recommended that anticoagulation parameters are monitored when warfarin is coadministered with ritonavir.
Anticonvulsants	Carbamazepine*, Phenobarbital, Phenytoin	Carbamazepine decreases AUC and C_{max} of nirmatrelvir by 55% and 43%, respectively. Phenobarbital and phenytoin are strong CYP3A4 inducers, and this may lead to a decreased exposure of nirmatrelvir and ritonavir and potential loss of virologic response. Concomitant use of carbamazepine, phenobarbital and phenytoin with Paxlovid is contraindicated (see section 4.3).
	↓Divalproex, Lamotrigine, Phenytoin	Ritonavir dosed as a pharmacokinetic enhancer induces oxidation by CYP2C9 and glucuronidation and as a result is expected to decrease the plasma concentrations of anticonvulsants. Careful monitoring of serum levels or therapeutic effects is recommended when these

Table 1: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		medicines are coadministered with ritonavir. Phenytoin may decrease serum levels of ritonavir.
Anticorticosteroids	↑Ketoconazole (3.4-fold, 55%)	Ritonavir inhibits CYP3A-mediated metabolism of ketoconazole. Due to an increased incidence of gastrointestinal and hepatic adverse reactions, a dose reduction of ketoconazole should be considered when coadministered with ritonavir.
Antidepressants	↑Amitriptyline, Fluoxetine, Imipramine, Nortriptyline, Paroxetine, Sertraline	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of imipramine, amitriptyline, nortriptyline, fluoxetine, paroxetine or sertraline. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir (see section 4.4).
Anti-gout	↑Colchicine	Concentrations of colchicine are expected to increase when coadministered with ritonavir. Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and ritonavir (CYP3A4 and P-gp inhibition). Concomitant use of colchicine with Paxlovid is contraindicated (see section 4.3).
Anti-HCV	↑Glecaprevir/pibrentasvir	Serum concentrations may be increased due to P-gp, BCRP and OATP1B inhibition by ritonavir. Concomitant administration of glecaprevir/pibrentasvir and Paxlovid is not recommended due to an increased risk of ALT elevations associated with increased glecaprevir exposure.
Antihistamines	↑Fexofenadine	Ritonavir may modify P-gp mediated fexofenadine efflux when dosed as a pharmacokinetic enhancer resulting in increased concentrations of fexofenadine.
	↑Loratadine	Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A and as a result is expected to increase the plasma concentrations of loratadine. Careful monitoring of therapeutic and adverse effects is recommended when loratadine is coadministered with ritonavir.
	↑Terfenadine	Increased plasma concentrations of terfenadine. Thereby, increasing the risk of serious arrhythmias from this agent and

Table 1: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		therefore concomitant use with Paxlovid is contraindicated (see section 4.3).
Anti-HIV	↑Efavirenz (21%)	A higher frequency of adverse reactions (e.g., dizziness, nausea, paraesthesia) and laboratory abnormalities (elevated liver enzymes) have been observed when efavirenz is coadministered with ritonavir.
	↑Maraviroc (161%, 28%)	Ritonavir increases the serum levels of maraviroc as a result of CYP3A inhibition. Maraviroc may be given with ritonavir to increase the maraviroc exposure. For further information, refer to the Summary of Product Characteristics for maraviroc.
	↓Raltegravir (16%, 1%)	Coadministration of ritonavir and raltegravir results in a minor reduction in raltegravir levels.
	↓Zidovudine (25%, ND)	Ritonavir may induce the glucuronidation of zidovudine, resulting in slightly decreased levels of zidovudine. Dose alterations should not be necessary.
Anti-infectives	↓Atovaquone	Ritonavir dosed as a pharmacokinetic enhancer induces glucuronidation and as a result is expected to decrease the plasma concentrations of atovaquone. Careful monitoring of serum levels or therapeutic effects is recommended when atovaquone is coadministered with ritonavir.
	↑Bedaquiline	No interaction study is available with ritonavir only. Due to the risk of bedaquiline related adverse events, coadministration should be avoided. If the benefit outweighs the risk, coadministration of bedaquiline with ritonavir must be done with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended (see bedaquiline Summary of Product Characteristics).
	↑Clarithromycin (77%, 31%), ↓14-OH clarithromycin metabolite (100%, 99%)	Due to the large therapeutic window of clarithromycin no dose reduction should be necessary in patients with normal renal function. Clarithromycin doses greater than 1 g per day should not be coadministered with ritonavir dosed as a pharmacokinetic enhancer. For patients with renal impairment, a clarithromycin dose reduction should be considered: for patients with creatinine clearance of 30 to 60 mL/min the dose should be reduced by

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Table 1: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		50% (see section 4.2 for patients with severe renal impairment).
	Delamanid	No interaction study is available with ritonavir only. In a healthy volunteer drug interaction study of delamanid 100 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily for 14 days, the exposure of the delamanid metabolite DM-6705 was 30% increased. Due to the risk of QTc prolongation associated with DM-6705, if coadministration of delamanid with ritonavir is considered necessary, very frequent ECG monitoring throughout the full Paxlovid treatment period is recommended (see section 4.4 and refer to the delamanid Summary of Product Characteristics).
	↑Erythromycin, ↑Itraconazole*	Itraconazole increases AUC and C_{max} of nirmatrelvir by 39% and 19%, respectively. Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of itraconazole and erythromycin. Careful monitoring of therapeutic and adverse effects is recommended when erythromycin or itraconazole is coadministered with ritonavir.
	↑Fusidic acid	Ritonavir coadministration is likely to result in increased plasma concentrations of both fusidic acid and ritonavir and is therefore contraindicated (see section 4.3).
	↑Rifabutin (4-fold, 2.5-fold), ↑25-*O*-desacetyl rifabutin metabolite (38-fold, 16-fold)	Due to the large increase in rifabutin AUC, reduction of the rifabutin dose to 150 mg 3 times per week may be indicated when coadministered with ritonavir as a pharmacokinetic enhancer.
	Rifampicin	Rifampicin is strong CYP3A4 inducer, and this may lead to a decreased exposure of nirmatrelvir/ritonavir and potential loss of virologic response. Concomitant use of rifampicin with Paxlovid is contraindicated (see section 4.3).
	Sulfamethoxazole/trimethoprim	Dose alteration of sulfamethoxazole/trimethoprim during concomitant ritonavir therapy should not be necessary.

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Table 1: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
	↓Voriconazole (39%, 24%)	Coadministration of voriconazole and ritonavir dosed as a pharmacokinetic enhancer should be avoided unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.
Antipsychotics	↑Clozapine, ↑Pimozide	Ritonavir coadministration is likely to result in increased plasma concentrations of clozapine or pimozide and is therefore contraindicated (see section 4.3).
	↑Haloperidol, ↑Risperidone, ↑Thioridazine	Ritonavir is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of haloperidol, risperidone and thioridazine. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir.
	↑Lurasidone	Due to CYP3A inhibition by ritonavir, concentrations of lurasidone are expected to increase. The concomitant administration with lurasidone is contraindicated (see section 4.3).
	↑Quetiapine	Due to CYP3A inhibition by ritonavir, concentrations of quetiapine are expected to increase. Concomitant administration of Paxlovid and quetiapine is contraindicated as it may increase quetiapine-related toxicity (see section 4.3).
Benign prostatic hyperplasia agents	↑Silodosin	Coadministration is contraindicated due to potential for postural hypotension (see section 4.3).
β2-agonist (long acting)	↑Salmeterol	Ritonavir inhibits CYP3A4 and as a result a pronounced increase in the plasma concentrations of salmeterol is expected. Therefore, concomitant use is not recommended.
Calcium channel antagonist	↑Amlodipine, ↑Diltiazem, ↑Nifedipine	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of calcium channel antagonists. Careful monitoring of therapeutic and adverse effects is recommended when amlodipine, diltiazem or nifedipine are concomitantly administered with ritonavir.
	↑Lercanidipine	Coadministration of lercanidipine and Paxlovid should be avoided.

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Table 1: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
Cardiovascular agents	↑Eplerenone	Coadministration with eplerenone is contraindicated due to potential for hyperkalemia (see section 4.3).
	↑Ivabradine	Coadministration with ivabradine is contraindicated due to potential for bradycardia or conduction disturbances (see section 4.3).
Endothelin antagonists	↑Bosentan	Coadministration of bosentan and ritonavir may increase steady-state bosentan maximum concentrations (C_{max}) and AUC.
	↑Riociguat	Serum concentrations may be increased due to CYP3A and P-gp inhibition by ritonavir. The coadministration of riociguat with Paxlovid is not recommended (refer to riociguat SmPC).
Ergot derivatives	↑Dihydroergotamine, ↑Ergonovine, ↑Ergotamine, ↑Methylergonovine	Ritonavir coadministration is likely to result in increased plasma concentrations of ergot derivatives and is therefore contraindicated (see section 4.3).
GI motility agent	↑Cisapride	Increased plasma concentrations of cisapride. Thereby, increasing the risk of serious arrhythmias from this agent and therefore concomitant use with Paxlovid is contraindicated (see section 4.3).
Herbal products	St. John's Wort	Herbal preparations containing St John's wort (*Hypericum perforatum*) due to the risk of decreased plasma concentrations and reduced clinical effects of nirmatrelvir and ritonavir and therefore concomitant use with Paxlovid is contraindicated (see section 4.3).
HMG Co-A reductase inhibitors	↑Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin	HMG-CoA reductase inhibitors which are highly dependent on CYP3A metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when coadministered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer. Since increased concentrations of lovastatin and simvastatin may predispose patients to myopathies, including rhabdomyolysis, the combination of these medicinal products with ritonavir is contraindicated (see section 4.3). Atorvastatin is less dependent on CYP3A for metabolism. While rosuvastatin elimination is not dependent on CYP3A, an elevation of rosuvastatin exposure has been reported with ritonavir coadministration. The mechanism of this interaction is not clear, but may be the result of transporter inhibition. When used

Table 1: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		with ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent, the lowest possible doses of atorvastatin or rosuvastatin should be administered. The metabolism of pravastatin and fluvastatin is not dependent on CYP3A, and interactions are not expected with ritonavir. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.
Hormonal contraceptive	↓Ethinyl Estradiol (40%, 32%)	Due to reductions in ethinyl estradiol concentrations, barrier or other non-hormonal methods of contraception should be considered with concomitant ritonavir use when dosed as an antiretroviral agent or as a pharmacokinetic enhancer. Ritonavir is likely to change the uterine bleeding profile and reduce the effectiveness of estradiol-containing contraceptives.
Immunosuppressants	↑Voclosporin	Coadministration is contraindicated due to potential for acute and/or chronic nephrotoxicity (see section 4.3).
Immunosuppressants	Calcineurin inhibitors: ↑Cyclosporine, ↑Tacrolimus mTOR inhibitors: ↑Everolimus, ↑Sirolimus	Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of cyclosporine, everolimus, sirolimus and tacrolimus. This coadministration should only be considered with close and regular monitoring of immunosuppressant serum concentrations, to reduce the dose of the immunosuppressant in accordance with the latest guidelines and to avoid over-exposure and subsequent increase of serious adverse reactions of the immunosuppressant. It is important that the close and regular monitoring is performed not only during the coadministration with Paxlovid but is also pursued after the treatment with Paxlovid. As overall recommended for managing the drug-drug interaction, consultation of a multidisciplinary group is required to handle the complexity of this coadministration (see section 4.4).
Migraine medicinal products	↑Eletriptan	Coadministration of eletriptan within at least 72 hours of Paxlovid is contraindicated due to potential for serious adverse reactions including cardiovascular and cerebrovascular events (see section 4.3).

Table 1: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
Lipid-modifying agents	↑Lomitapide	CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Due to CYP3A inhibition by ritonavir, concentrations of lomitapide are expected to increase. Concomitant use of Paxlovid with lomitapide is contraindicated (see prescribing information for lomitapide) (see section 4.3).
Phosphodiesterase (PDE5) inhibitors	↑Avanafil (13-fold, 2.4-fold) ↑Sildenafil (11-fold, 4-fold) ↑Tadalafil (124%, ↔) ↑Vardenafil (49-fold, 13-fold)	Concomitant use of avanafil, sildenafil, tadalafil and vardenafil with Paxlovid is contraindicated (see section 4.3).
Sedatives/hypnotics	↑Alprazolam (2.5-fold, ↔)	Alprazolam metabolism is inhibited following the introduction of ritonavir. Caution is warranted during the first several days when alprazolam is coadministered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer, before induction of alprazolam metabolism develops.
	↑Buspirone	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma concentrations of buspirone. Careful monitoring of therapeutic and adverse effects is recommended when buspirone concomitantly administered with ritonavir.
	↑Clorazepate, ↑Diazepam, ↑Estazolam, ↑Flurazepam	Ritonavir coadministration is likely to result in increased plasma concentrations of clorazepate, diazepam, estazolam, and flurazepam and is therefore contraindicated (see section 4.3).
	↑Oral Midazolam (1330%, 268%)* and parenteral Midazolam	Midazolam is extensively metabolised by CYP3A4. Coadministration with Paxlovid may cause a large increase in the concentration of midazolam. Plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Therefore, coadministration of Paxlovid with orally administered midazolam is contraindicated (see section 4.3), whereas caution should be used with coadministration of Paxlovid and parenteral midazolam. Data from concomitant use of parenteral midazolam with other protease inhibitors suggests a possible 3- to 4-fold increase in midazolam plasma levels. If Paxlovid is

Table 1: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		coadministered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.
	↑Triazolam (> 20-fold, 87%)	Ritonavir coadministration is likely to result in increased plasma concentrations of triazolam and is therefore contraindicated (see section 4.3).
Sleeping agent	↑Zolpidem (28%, 22%)	Zolpidem and ritonavir may be coadministered with careful monitoring for excessive sedative effects.
Smoke cessation	↓Bupropion (22%, 21%)	Bupropion is primarily metabolised by CYP2B6. Concurrent administration of bupropion with repeated doses of ritonavir is expected to decrease bupropion levels. These effects are thought to represent induction of bupropion metabolism. However, because ritonavir has also been shown to inhibit CYP2B6 *in vitro*, the recommended dose of bupropion should not be exceeded. In contrast to long-term administration of ritonavir, there was no significant interaction with bupropion after short-term administration of low doses of ritonavir (200 mg twice daily for 2 days), suggesting reductions in bupropion concentrations may have onset several days after initiation of ritonavir coadministration.
Steroids	Budesonide, Inhaled, injectable or intranasal fluticasone propionate, Triamcinolone	Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression (plasma cortisol levels were noted to be decreased 86%) have been reported in patients receiving ritonavir and inhaled or intranasal fluticasone propionate; similar effects could also occur with other corticosteroids metabolised by CYP3A e.g., budesonide and triamcinolone. Consequently, concomitant administration of ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a

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Table 1: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		glucocorticoid, which is not a substrate for CYP3A4 (e.g., beclomethasone). Moreover, in case of withdrawal of glucocorticoids progressive dose reduction may be required over a longer period.
	↑Dexamethasone	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma concentrations of dexamethasone. Careful monitoring of therapeutic and adverse effects is recommended when dexamethasone is concomitantly administered with ritonavir.
	↑Prednisolone (28%, 9%)	Careful monitoring of therapeutic and adverse effects is recommended when prednisolone is concomitantly administered with ritonavir. The AUC of the metabolite prednisolone increased by 37% and 28% after 4 and 14 days ritonavir, respectively.
Thyroid hormone replacement therapy	Levothyroxine	Post-marketing cases have been reported indicating a potential interaction between ritonavir containing products and levothyroxine. Thyroid-stimulating hormone (TSH) should be monitored in patients treated with levothyroxine at least the first month after starting and/or ending ritonavir treatment.
Vasopressin receptor antagonists	↑Tolvaptan	Coadministration is contraindicated due to potential for dehydration, hypovolemia and hyperkalemia (see section 4.3).

Abbreviations: ATL=alanine aminotransferase; AUC=area under the curve.
* Results from DDI studies conducted with Paxlovid.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

There are no data on the use of Paxlovid in pregnant women to inform the drug-associated risk of adverse developmental outcomes; women of childbearing potential should avoid becoming pregnant during treatment with Paxlovid and as a precautionary measure for 7 days after completing Paxlovid.

Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Patients using combined hormonal contraceptives should be advised to use an effective alternative contraceptive method or an additional barrier method of contraception during treatment with Paxlovid, and until one menstrual cycle after stopping Paxlovid (see section 4.5).

Pregnancy

There are limited data from the use of Paxlovid in pregnant women.

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Animal data with nirmatrelvir have shown developmental toxicity in the rabbit (lower foetal body weights) but not in the rat (see section 5.3).

A large number of women exposed to ritonavir during pregnancy indicate no increase in the rate of birth defects compared to rates observed in population-based birth defect surveillance systems.

Animal data with ritonavir have shown reproductive toxicity (see section 5.3).

Paxlovid is not recommended during pregnancy and in women of childbearing potential not using contraception unless the clinical condition requires treatment with Paxlovid.

Breast-feeding

There are no data on the use of Paxlovid in breast-feeding women.

It is unknown whether nirmatrelvir is present in human or animal milk, and the effects of it on the breast-fed newborn/infant, or the effects on milk production. Limited published data reports that ritonavir is present in human milk. There is no information on the effects of ritonavir on the breast-fed newborn/infant or on milk production. A risk to the newborn/infant cannot be excluded. Breast-feeding should be discontinued during treatment and as a precautionary measure for 7 days after completing Paxlovid.

Fertility

There are no human data on the effect of Paxlovid (nirmatrelvir and ritonavir) or ritonavir alone on fertility. Both nirmatrelvir and ritonavir, tested separately, produced no effects on fertility in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Paxlovid is expected to have no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions reported during treatment with Paxlovid (nirmatrelvir/ritonavir 300 mg/100 mg) were dysgeusia (5.6%), diarrhoea (3.1%), headache (1.4%) and vomiting (1.1%).

Tabulated summary of adverse reactions

The safety profile of the product is based on adverse reactions reported in clinical trials and spontaneous reporting.

The adverse reactions in Table 2 are listed below by system organ class and frequency. Frequencies are defined as follows: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); not known (frequency cannot be estimated from the available data).

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Table 2: Adverse reactions with Paxlovid

System organ class	Frequency category	Adverse reactions
Immune system disorders	Uncommon	Hypersensitivity including pruritus and rash
	Rare	Anaphylaxis
Nervous system disorders	Common	Dysgeusia, headache
Vascular disorders	Uncommon	Hypertension
Gastrointestinal disorders	Common	Diarrhoea, vomiting, nausea
	Uncommon	Abdominal pain
General disorders and administration site conditions	Rare	Malaise

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Treatment of overdose with Paxlovid should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with Paxlovid.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, protease inhibitors, ATC code: J05AE30

Mechanism of action

Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (Mpro), also referred to as 3C-like protease (3CLpro) or nsp5 protease. Inhibition of the SARS-CoV-2 Mpro renders the protein incapable of processing polyprotein precursors which leads to the prevention of viral replication.

Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, thereby providing increased plasma concentrations of nirmatrelvir.

Antiviral activity

Nirmatrelvir exhibited antiviral activity against SARS-CoV-2 infection of differentiated normal human bronchial epithelial (dNHBE) cells, a primary human lung alveolar epithelial cell line (EC_{50} value of 61.8 nM and EC_{90} value of 181 nM) after 3 days of drug exposure. Nirmatrelvir had cell culture antiviral activity (with EC_{50} values in the low nanomolar range ≤3-fold relative to USA-WA1/2020) against SARS-CoV-2 isolates belonging to the Alpha (B.1.1.7), Gamma (P.1), Delta (B.1.617.2), Lambda (C.37), Mu (B.1.621) and Omicron (B.1.1.529/BA.1, BA.2, BA.2.12.1, BA.4, and BA.5) variants. The Beta (B.1.351) variant was the least susceptible tested variant with approximately 3.7-fold reduced susceptibility relative to the USA-WA1/2020 isolate.

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Antiviral resistance in cell cultures and biochemical assays
SARS-CoV-2 M^{pro} residues potentially associated with nirmatrelvir resistance have been identified using a variety of methods, including SARS-CoV-2 resistance selection, testing of recombinant SARS-CoV-2 viruses with M^{pro} substitutions, and biochemical assays with recombinant SARS-CoV-2 M^{pro} containing amino acid substitutions. Table 3 indicates M^{pro} substitutions and combinations of M^{pro} substitutions that have been observed in nirmatrelvir-selected SARS-CoV-2 in cell culture. Individual M^{pro} substitutions are listed regardless of whether they occurred alone or in combination with other M^{pro} substitutions. Note that the M^{pro} S301P and T304I substitutions overlap the P6 and P3 positions of the nsp5/nsp6 cleavage site located at the C-terminus of M^{pro}. Substitutions at other M^{pro} cleavage sites have not been associated with nirmatrelvir resistance in cell culture. The clinical significance of these substitutions is unknown.

Table 3: SARS-CoV-2 M^{pro} amino acid substitutions selected by nirmatrelvir in cell culture (with EC_{50} fold change >5)

T21I (1.1-4.6), E166V (25-267), P252L (5.9), T304I (2.1-5.5), T21I+S144A (9.4), T21I+E166V (83), T21I+T304I (3.0-7.9), L50F+E166V (34-163), L50F+T304I (5.9), F140L+A173V (10.1), A173V+T304I (20.2), T21+L50F+A193P+S301P (28.8), T21I+S144A+T304I (27.8), T21I+C160F+A173V+V186A+T304I (28.5), T21I+A173V+T304I (15), L50F+F140L+L167F+T304I (54.7)

Most single M^{pro} mutations and some double mutations identified which reduced the susceptibility of SARS-CoV-2 to nirmatrelvir resulted in an EC_{50} shift of < 5-fold compared to wild type SARS-CoV-2. In general, triple mutations and some double mutations led to EC_{50} changes of > 5-fold to that of wild type. The clinical significance of these mutations needs to be further understood.

Viral load rebound and treatment-emergent mutations

Post-treatment viral nasal RNA rebounds were observed on Day 10 and/or Day 14 in a subset of Paxlovid and placebo recipients in EPIC-HR, irrespective of COVID-19 symptoms. The incidence of viral rebound in EPIC-HR occurred in both the Paxlovid treated participants and the untreated (placebo) participants, but at higher incidence in the Paxlovid arm (6.96% vs. 4.08%). So far, viral rebounds and symptoms recurrences of COVID-19 are not associated with more severe disease or emergence of resistance.

Clinical efficacy

The efficacy of Paxlovid is based on the interim analysis and the supporting final analysis of EPIC-HR, a phase 2/3, randomised, double-blind, placebo-controlled study in non-hospitalised, symptomatic adult participants with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Eligible participants were 18 years of age and older with at least 1 of the following risk factors for progression to severe disease: diabetes, overweight (BMI > 25), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease, hypertension, sickle cell disease, neurodevelopmental disorders, active cancer, medically-related technological dependence, or were 60 years of age and older regardless of comorbidities. Participants with COVID-19 symptom onset of ≤ 5 days were included in the study. The study excluded individuals with a history of prior COVID-19 infection or vaccination.

Participants were randomised (1:1) to receive Paxlovid (nirmatrelvir/ritonavir 300 mg/100 mg) or placebo orally every 12 hours for 5 days. The primary efficacy endpoint was the proportion of participants with COVID-19 related hospitalisation or death from any cause through Day 28. The analysis was conducted in the modified intent-to-treat (mITT) analysis set (all treated participants with onset of symptoms ≤ 3 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment), the mITT1 analysis set (all treated participants with onset of symptoms ≤ 5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment), and the mITT2 analysis set (all treated participants with onset of symptoms ≤ 5 days).

A total of 2246 participants were randomised to receive either Paxlovid or placebo. At baseline, mean age was 46 years with 13% of participants 65 years of age and older (3% were 75 years of age and older); 51% were male; 72% were White, 5% were Black or African American, and 14% were Asian; 45% were Hispanic or Latino; 66% of participants had onset of symptoms ≤ 3 days before initiation of study treatment; 81% had a BMI ≥ 25 kg/m^2 (37% a BMI ≥ 30 kg/m^2); 12% had diabetes mellitus; less than 1% of the study population had immune deficiency, 47% of participants were serological negative at baseline and 51% were serological positive. The mean (SD) baseline viral load was 4.63 $\log_{10}$ copies/mL (2.87); 26% of participants had a baseline viral load of > 10^7 (copies/mL); 6.2% of participants either received or were expected to receive COVID-19 therapeutic mAb treatment at the time of randomisation and were excluded from the mITT and mITT1 analyses. The primary SARS-CoV-2 variant across both treatment arms was Delta (98%), mostly clade 21J (based on interim analysis).

The baseline demographic and disease characteristics were balanced between the Paxlovid and placebo groups.

The determination of primary efficacy was based on a planned interim analysis of 774 participants in mITT population. The estimated risk reduction was -6.3% with unadjusted 95% CI of (-9.0%, -3.6%) and a 95% CI of (-10.61%, -2.02%) when adjusting for multiplicity. The 2-sided p-value was < 0.0001 with 2-sided significance level of 0.002.

Table 4 provides results of the primary endpoint in the mITT1 analysis population for the full data set at final study completion.

Table 4: Efficacy results in non-hospitalised adults with COVID-19 dosed within 5 days of symptom onset who did not receive COVID-19 mAb treatment at baseline (mITT1 analysis set)

	Paxlovid (N=1039)	**Placebo (N=1046)**
COVID-19 related hospitalisation or death from any cause through Day 28		
n (%) Reduction relative to placebo[a] (95% CI), %	9 (0.9%) -5.52 (-7.12, -3.92)	66 (6.3%)
p-value	< 0.0001	
All-cause mortality through Day 28, %	0	12 (1.1%)

Abbreviations: CI=confidence interval; COVID-19=Coronavirus Disease 2019; mAb=monoclonal antibody; mITT1=modified intent-to-treat 1 (all participants randomly assigned to study intervention, who took at least 1 dose of study intervention, with at least 1 post-baseline visit through Day 28, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were treated ≤ 5 days after COVID-19 symptom onset).

a. The estimated cumulative proportion of participants hospitalised or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where participants without hospitalisation and death status through Day 28 were censored at the time of study discontinuation.

The estimated risk reduction was -5.8% with 95% CI of (-7.8%, -3.8%) in participants dosed within 3 days of symptom onset, and -4.9% with 95% CI of (-7.7%, -2.2%) in the mITT1 subset of participants dosed > 3 days from symptom onset.

Consistent results were observed in the final mITT and mITT2 analysis populations. A total of 1379 participants were included in the mITT analysis population. The event rates were 5/697 (0.72%) in the Paxlovid group, and 44/682 (6.45%) in the placebo group.

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Table 5: Progression of COVID-19 (hospitalisation or death) through Day 28 in symptomatic adults at increased risk of progression to severe illness; mITT1 analysis set

	Paxlovid 300 mg/100 mg	Placebo
Number of patients	N=1039	N=1046
Serology Negative	n=487	n=505
Patients with hospitalisation or death[a] (%)	8 (1.6%)	58 (11.5%)
Estimated proportion over 28 days [95% CI], %	1.47 (0.70, 3.05)	11.71 (9.18, 14.89)
Estimated reduction relative to placebo (95% CI)	-10.04 (-13.10, -6.98)	
Serology Positive	n=540	n=528
Patients with hospitalisation or death[a] (%)	1 (0.2%)	8 (1.5%)
Estimated proportion over 28 days [95% CI], %	0.19 (0.03, 1.31)	1.52 (0.76, 3.02)
Estimated reduction relative to placebo (95% CI)	-1.34 (-2.45, -0.23)	

Abbreviations: CI=confidence interval; COVID-19=Coronavirus Disease 2019; mITT1=modified intent-to-treat 1 (all participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic monoclonal antibody treatment, and were treated ≤ 5 days after COVID-19 symptom onset).
Seropositivity was defined if results were positive in a serological immunoassay specific for host antibodies to either S or N viral proteins.
The difference between the proportions in the 2 treatment groups and its 95% confidence interval based on normal approximation of the data are presented.
a. COVID-19 related hospitalisation or death from any cause.

Efficacy results for mITT1 were consistent across subgroups of participants including age (≥ 65 years) and BMI (BMI > 25 and BMI > 30) and diabetes.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Paxlovid in one or more subsets of the paediatric population in treatment of COVID-19 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of nirmatrelvir/ritonavir have been studied in healthy participants and in participants with mild-to-moderate COVID-19.

Ritonavir is administered with nirmatrelvir as a pharmacokinetic enhancer resulting in higher systemic concentrations and longer half-life of nirmatrelvir.

Upon repeat-dose of nirmatrelvir/ritonavir 75 mg/100 mg, 250 mg/100 mg, and 500 mg/100 mg administered twice daily, the increase in systemic exposure at steady-state appears to be less than dose proportional. Multiple dosing over 10 days achieved steady-state on Day 2 with approximately 2-fold accumulation. Systemic exposures on Day 5 were similar to Day 10 across all doses.

Absorption

Following oral administration of nirmatrelvir/ritonavir 300 mg/100 mg after a single dose, the geometric mean nirmatrelvir C_{max} and AUC_{inf} at steady-state was 2.21 µg/mL and 23.01 µg*hr/mL, respectively. The median time to C_{max} (T_{max}) was 3.00 hrs. The arithmetic mean terminal elimination half-life was 6.1 hours.

Following oral administration of nirmatrelvir/ritonavir 300 mg/100 mg after a single dose, the geometric mean ritonavir C_{max} and AUC_{inf} was 0.36 µg/mL and 3.60 µg*hr/mL, respectively. The median time to C_{max} (T_{max}) was 3.98 hrs. The arithmetic mean terminal elimination half-life was 6.1 hours.

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Effect of food on oral absorption
Dosing with a high fat meal increased the exposure of nirmatrelvir (approximately 61% increase in mean C_{max} and 20% increase in mean AUC_{last}) relative to fasting conditions following administration of 300 mg nirmatrelvir (2 × 150 mg)/100 mg ritonavir tablets.

Distribution

The protein binding of nirmatrelvir in human plasma is approximately 69%.

The protein binding of ritonavir in human plasma is approximately 98-99%.

Biotransformation

In vitro studies assessing nirmatrelvir without concomitant ritonavir suggest that nirmatrelvir is primarily metabolised by cytochrome P450 (CYP) 3A4. However, administration of nirmatrelvir with ritonavir inhibits the metabolism of nirmatrelvir. In plasma, the only medicinal product-related entity observed was unchanged nirmatrelvir. Minor oxidative metabolites were observed in the faeces and urine.

In vitro studies utilising human liver microsomes have demonstrated that CYP3A is the major isoform involved in ritonavir metabolism, although CYP2D6 also contributes to the formation of oxidation metabolite M–2.

Elimination

The primary route of elimination of nirmatrelvir when administered with ritonavir was renal excretion of intact medicinal product. Approximately 49.6% and 35.3% of the administered dose of nirmatrelvir 300 mg was recovered in urine and faeces, respectively. Nirmatrelvir was the predominant drug-related entity with small amounts of metabolites arising from hydrolysis reactions in excreta. In plasma, the only drug-related entity quantifiable was unchanged nirmatrelvir.

Human studies with radiolabelled ritonavir demonstrated that the elimination of ritonavir was primarily via the hepatobiliary system; approximately 86% of radiolabel was recovered from stool, part of which is expected to be unabsorbed ritonavir.

Specific populations

Age and gender
The pharmacokinetics of nirmatrelvir/ritonavir based on age and gender have not been evaluated.

Racial or ethnic groups
Systemic exposure in Japanese participants was numerically lower but not clinically meaningfully different than those in Western participants.

Patients with renal impairment
Compared to healthy controls with no renal impairment, the C_{max} and AUC of nirmatrelvir in patients with mild renal impairment was 30% and 24% higher, in patients with moderate renal impairment was 38% and 87% higher, and in patients with severe renal impairment was 48% and 204% higher, respectively.

Patients with hepatic impairment
Compared to healthy controls with no hepatic impairment, the pharmacokinetics of nirmatrelvir in participants with moderate hepatic impairment was not significantly different. Adjusted geometric mean ratio (90% CI) of AUC_{inf} and C_{max} of nirmatrelvir comparing moderate hepatic impairment (test) to normal hepatic function (reference) was 98.78% (70.65%, 138.12%) and 101.96% (74.20%, 140.11%), respectively.

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Nirmatrelvir/ritonavir has not been studied in patients with severe hepatic impairment.

Interaction studies conducted with nirmatrelvir/ritonavir

CYP3A4 was the major contributor to the oxidative metabolism of nirmatrelvir when nirmatrelvir was tested alone in human liver microsomes. Ritonavir is an inhibitor of CYP3A and increases plasma concentrations of nirmatrelvir and other drugs that are primarily metabolised by CYP3A. Despite being coadministered with ritonavir as a pharmacokinetic enhancer, there is potential for strong inhibitors and inducers to alter the pharmacokinetics of nirmatrelvir.

Nirmatrelvir does not reversibly inhibit CYP2D6, CYP2C9, CYP2C19, CYP2C8, or CYP1A2 *in vitro* at clinically relevant concentrations. *In vitro* study results showed nirmatrelvir may be inducer of CYP3A4, CYP2B6, CYP2C8 and CYP2C9. The clinical relevance is unknown. Based on *in vitro* data, nirmatrelvir has a low potential to inhibit BCRP, MATE2K, OAT1, OAT3, OATP1B3 and OCT2. There is a potential for nirmatrelvir to inhibit MDR1, MATE1, OCT1 and OATP1B1 at clinically relevant concentrations.

The effect on the pharmacokinetics of nirmatrelvir/ritonavir was assessed with itraconazole (CYP3A inhibitor) and carbamazepine (CYP3A inducer). The test/reference ratios of the adjusted geometric means for nirmatrelvir AUC_{inf} and C_{max} were 44.50% and 56.82%, respectively, following nirmatrelvir/ritonavir 300 mg/100 mg coadministration with multiple oral doses of carbamazepine. The test/reference ratios of the adjusted geometric means for nirmatrelvir AUC_{tau} and C_{max} were 138.82% and 118.57%, respectively, when nirmatrelvir/ritonavir was coadministered with multiple doses of itraconazole as compared to nirmatrelvir/ritonavir administered alone.

The effect of nirmatrelvir/ritonavir on other drugs was assessed with midazolam (CYP3A substrate) and dabigatran (P-gp substrate). The test/reference ratios of the adjusted geometric means for midazolam AUC_{inf} and C_{max} were 1430.02% and 368.33%, respectively, when midazolam was coadministered with multiple doses of nirmatrelvir/ritonavir compared to midazolam administered alone. The test/reference ratios of the adjusted geometric means for dabigatran AUC_{inf} and C_{max} were 194.47% and 233.06%, respectively, following dabigatran administration with multiple doses of nirmatrelvir/ritonavir as compared to administration of dabigatran alone.

5.3 Preclinical safety data

No nonclinical safety studies have been conducted with nirmatrelvir in combination with ritonavir.

Nirmatrelvir

Studies of repeated dose toxicity and genotoxicity revealed no risk due to nirmatrelvir. No adverse effects were observed in fertility, embryo-foetal development, or pre- and postnatal development studies in rats. A study in pregnant rabbits showed an adverse decrease in foetal body weight, in the absence of significant maternal toxicity. Systemic exposure (AUC_{24}) in rabbits at the maximum dose without adverse effect in foetal body weight was estimated to be approximately 3 times higher than exposure in humans at recommended therapeutic dose of Paxlovid.

No carcinogenicity studies have been conducted with nirmatrelvir.

Ritonavir

Repeat-dose toxicity studies of ritonavir in animals identified major target organs as the liver, retina, thyroid gland and kidney. Hepatic changes involved hepatocellular, biliary and phagocytic elements and were accompanied by increases in hepatic enzymes. Hyperplasia of the retinal pigment epithelium and retinal degeneration have been seen in all of the rodent studies conducted with ritonavir, but have not been seen in dogs. Ultrastructural evidence suggests that these retinal changes may be secondary to phospholipidosis. However, clinical trials revealed no evidence of medicinal product-induced ocular changes in humans. All thyroid changes were reversible upon

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discontinuation of ritonavir. Clinical investigation in humans has revealed no clinically significant alteration in thyroid function tests.

Renal changes including tubular degeneration, chronic inflammation and proteinurea were noted in rats and are considered to be attributable to species-specific spontaneous disease. Furthermore, no clinically significant renal abnormalities were noted in clinical trials.

Genotoxicity studies revealed no risk due to ritonavir. Long-term carcinogenicity studies of ritonavir in mice and rats revealed tumourigenic potential specific for these species, but are regarded as of no relevance for humans. Ritonavir produced no effects on fertility in rats. Developmental toxicity observed in rats (embryo-lethality, decreased foetal body weight and ossification delays and visceral changes, including delayed testicular descent) occurred mainly at a maternally toxic dosage. Developmental toxicity in rabbits (embryo-lethality, decreased litter size and decreased foetal weights) occurred at a maternally toxic dosage.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Nirmatrelvir film-coated tablets

Tablet core:
Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Colloidal silicon dioxide
Sodium stearyl fumarate

Film coat:
Hydroxypropyl methylcellulose (E464)
Titanium dioxide (E171)
Polyethylene glycol (E1521)
Iron oxide red (E172)

Ritonavir film-coated tablets

Tablet core:
Copovidone
Sorbitan laurate
Silica, colloidal anhydrous (E551)
Calcium hydrogen phosphate, anhydrous
Sodium stearyl fumarate

Film coat:
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol (E1521)
Hydroxypropyl cellulose (E463)
Talc (E553b)
Silica, colloidal anhydrous (E551)
Polysorbate 80 (E433)

6.2 Incompatibilities

Not applicable.

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6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

OPA/Al/PVC foil blister cards of 30 tablets.

Paxlovid is packaged in cartons containing 5 daily-dose blister cards of 30 tablets.

Each daily blister card contains 4 nirmatrelvir tablets and 2 ritonavir tablets for morning and evening dose.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Brussels
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1625/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 January 2022
Date of latest renewal: 28 November 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

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ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

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A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Pfizer Manufacturing Deutschland GmbH
Betriebsstätte Freiburg
Mooswaldallee 1
79090 Freiburg
Germany

Pfizer Italia S.r.L.
Localita Marino del Tronto
63100 Ascoli, Piceno
Italy

Pfizer Ireland Pharmaceuticals
Little Connell
Newbridge
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

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ANNEX III

LABELLING AND PACKAGE LEAFLET

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A. LABELLING

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PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

PAXLOVID 150 mg + 100 mg film-coated tablets
Nirmatrelvir + ritonavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pink film-coated tablet contains 150 mg of nirmatrelvir
Each white film-coated tablet contains 100 mg of ritonavir

3. LIST OF EXCIPIENTS

Contains lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

30 film-coated tablets (20 nirmatrelvir tablets + 10 ritonavir tablets)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Scan QR code for product information in the national language.
URL: https://pfi.sr/c19oralrx

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1625/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

paxlovid

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

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MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

PAXLOVID
nirmatrelvir 150 mg tablet
ritonavir 100 mg tablet

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

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B. PACKAGE LEAFLET

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Package leaflet: Information for the patient

Paxlovid 150 mg + 100 mg film-coated tablets
nirmatrelvir + ritonavir

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Paxlovid is and what it is used for

Paxlovid contains two active substances nirmatrelvir and ritonavir in two different tablets. Paxlovid is an antiviral medicine used for treating adults with COVID-19 who do not require supplemental oxygen and who are at increased risk for progressing to severe disease.

COVID-19 is caused by a virus called a coronavirus. Paxlovid stops the virus multiplying in cells and this stops the virus multiplying in the body. This can help your body to overcome the virus infection, and may prevent you from developing severe illness.

If your symptoms worsen or do not improve after 5 days, talk to your doctor.

2. What you need to know before you take Paxlovid

Do not take Paxlovid
- if you are allergic to nirmatrelvir, ritonavir or any of the other ingredients of Paxlovid (listed in section 6).
- if you are taking any of the following medicines. Taking Paxlovid with these medicines may cause serious or life-threatening side effects or affect how Paxlovid works:
  - Alfuzosin (used to treat symptoms of an enlarged prostate)
  - Ranolazine (used to treat chronic chest pain [angina])
  - Amiodarone, dronedarone, flecainide, propafenone, quinidine (used to treat heart conditions and correct irregular heartbeats)
  - Fusidic acid, rifampicin (used to treat bacterial infections)
  - Apalutamide, neratinib, venetoclax (used to treat cancer)
  - Carbamazepine, phenobarbital, phenytoin (used to prevent and control seizures)
  - Colchicine (used to treat gout)
  - Terfenadine (used to treat allergies)

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- Lurasidone (used to treat schizophrenia)
- Pimozide, clozapine, quetiapine (used to treat schizophrenia, bipolar disorder, severe depression and abnormal thoughts or feelings)
- Silodosin (used to treat enlarged prostate gland)
- Eplerenone and ivabradine (used to treat heart and/or blood vessel problems)
- Dihydroergotamine and ergotamine (used to treat migraine headaches)
- Ergonovine and methylergonovine (used to stop excessive bleeding that may occur following childbirth or an abortion)
- Cisapride (used to relieve certain stomach problems)
- St. John's wort (*Hypericum perforatum*) (a herbal remedy used for depression and anxiety)
- Voclosporin (used to treat immune disorders)
- Lovastatin, simvastatin, lomitapide (used to lower blood cholesterol)
- Eletriptan (used to treat migraine headaches)
- Avanafil, vardenafil (used to treat erectile dysfunction [also known as impotence])
- Sildenafil, tadalafil (used to treat erectile dysfunction [also known as impotence] or pulmonary arterial hypertension [high blood pressure in the pulmonary artery])
- Clorazepate, diazepam, estazolam, flurazepam, triazolam, midazolam taken orally (used to relieve anxiety and/or trouble sleeping)
- Tolvaptan used to treat hyponatremia (low sodium levels in the blood)

Warnings and precautions

Allergic reactions
Allergic reactions, including severe allergic reactions (known as 'anaphylaxis'), can happen in people taking Paxlovid, even after only 1 dose. Stop taking Paxlovid and call your doctor right away if you get any of the following symptoms of an allergic reaction:
- trouble swallowing or breathing
- swelling of the tongue, mouth, and face
- throat tightness
- hoarseness
- itching
- skin rash

Liver disease
Tell your doctor if you have or have had a liver disease. Liver enzyme abnormalities, hepatitis and jaundice have occurred in patients receiving ritonavir.

Kidney disease
Tell your doctor if you have or have had a kidney disease.

High blood pressure
Tell your doctor if you have high blood pressure. Your doctor may need to check your blood pressure before taking Paxlovid and while you are taking this medicine. There have been reports of high blood pressure in people taking Paxlovid, particularly in older individuals.

Risk of HIV-1 resistance development
If you have untreated or uncontrolled HIV infection, Paxlovid may lead to some HIV medicines not working as well in the future.

Children and adolescents
Do not give Paxlovid to children and adolescents under 18 years because Paxlovid has not been studied in children and adolescents.

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Other medicines and Paxlovid
There are other medicines that may not be taken together with Paxlovid. Tell your doctor(s) or pharmacist if you are taking, have recently taken or might take any other medicines:

- medicines used to treat cancer, such as afatinib, abemaciclib, apalutamide, ceritinib, dasatinib, encorafenib, fostamatinib, ibrutinib, nilotinib, vinblastine and vincristine
- medicines used to thin the blood (anticoagulants), such as warfarin, rivaroxaban and dabigatran
- medicines used to treat convulsions, such as divalproex, lamotrigine
- medicines used for smoking cessation, such as bupropion
- medicines used to treat allergies, such as fexofenadine and loratadine
- medicines used to treat fungal infections (antifungals), such as itraconazole and voriconazole
- medicines used to treat Cushing's syndrome—when the body produces an excess of cortisol—such as ketoconazole tablets
- medicines used to treat HIV infection, such as efavirenz, maraviroc, raltegravir and zidovudine
- medicines used to treat infections (e.g., antibiotics and antimycobacterials), such as atovaquone, clarithromycin, erythromycin, bedaquiline, rifabutin, delamanid and sulfamethoxazole/trimethoprim
- medicines used to treat mental or mood disorders, such as haloperidol, risperidone and thioridazine
- medicines used to treat high blood pressure in the blood vessels that supply the lungs, such as bosentan and riociguat
- medicines used to treat high blood pressure (hypertension), such as amlodipine, diltiazem, lercanidipine and nifedipine
- medicines used to treat heart conditions and correct irregular heartbeats, such as digoxin
- medicines used to treat hepatitis C virus infection, such as glecaprevir/pibrentasvir
- medicines used to lower blood cholesterol, such as atorvastatin, fluvastatin, pravastatin and rosuvastatin
- medicines used to suppress your immune system, such as cyclosporine, everolimus, sirolimus and tacrolimus
- medicines used to treat severe pain, such as morphine, fentanyl, methadone, buprenorphine, other morphine-like medicines, and piroxicam
- medicines used as sedatives, hypnotics, and sleeping agent, such as alprazolam, buspirone and zolpidem
- steroids including corticosteroids used to treat inflammation, such as betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, prednisolone, prednisone and triamcinolone
- medicines used to treat asthma and other lung-related problems such as chronic obstructive pulmonary disease [COPD], such as salmeterol and theophylline
- medicines used to treat depression, such as amitriptyline, fluoxetine, imipramine, nortriptyline, paroxetine and sertraline
- medicines used as thyroid replacement therapy, such as levothyroxine
- any of the following other specific medicines:
    - oral or patch contraceptive containing ethinyl estradiol used to prevent pregnancy
    - midazolam administered by injection (used for sedation [an awake but very relaxed state of calm or drowsiness during a medical test or procedure] or anaesthesia)

Many medicines interact with Paxlovid. **Keep a list of your medicines to show your doctor(s) and pharmacist.** Do not start taking a new medicine without telling your doctor(s). Your doctor(s) can tell you if it is safe to take Paxlovid with other medicines.

Pregnancy and breast-feeding
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

There is not enough information to be sure that Paxlovid is safe for use in pregnancy. If you are pregnant, it is not recommended to use Paxlovid unless your clinical condition requires this treatment. It is recommended that you refrain from sexual activity or use contraception while taking Paxlovid and

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for 7 days after completing Paxlovid as a precaution. If you are taking hormonal contraception, as Paxlovid may reduce the effectiveness of this medicine, it is recommended that a condom or other non hormonal method of contraception is used. Your doctor will advise you on the duration of this required adjustment of your contraceptive measures.

There is no information on the use of Paxlovid in breast-feeding. You should not breast-feed your baby while taking Paxlovid and for 7 days after completing Paxlovid as a precaution.

Driving and using machines
Paxlovid is expected to have no influence on the ability to drive and use machines.

Paxlovid contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Paxlovid contains sodium
Nirmatrelvir and ritonavir tablets each contain less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How to take Paxlovid

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Paxlovid consists of 2 medicines: nirmatrelvir and ritonavir. The recommended dose is 2 tablets of nirmatrelvir (pink tablet) with 1 tablet of ritonavir (white tablet) by mouth twice daily (in the morning and in the evening).

A course of treatment lasts 5 days. For each dose, take all 3 tablets together at the same time.

If you have kidney disease, please talk to your healthcare provider for an appropriate dose of Paxlovid.

Swallow the tablets whole. Do not chew, break or crush the tablets. Paxlovid can be taken with or without meals.

If you take more Paxlovid than you should
If you take too much Paxlovid, call your healthcare provider or go to the nearest hospital emergency room right away.

If you forget to take Paxlovid
If you miss a dose of Paxlovid within 8 hours of the time it is usually taken, take it as soon as you remember. If you miss a dose by more than 8 hours, skip the missed dose and take the next dose at your regular time. Do not take 2 doses of Paxlovid at the same time.

Do not take a double dose to make up for a forgotten dose.

If you stop taking Paxlovid
Even if you feel better, do not stop taking Paxlovid without talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

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4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Common: may affect up to 1 in 10 people
- Diarrhoea
- Vomiting
- Nausea
- Altered sense of taste
- Headache

Uncommon: may affect up to 1 in 100 people
- Allergic reactions (such as itching or skin rash)
- High blood pressure
- Abdominal pain

Rare: may affect up to 1 in 1000 people
- Severe allergic reaction known as 'anaphylaxis' (such as swelling of tongue, mouth and face, trouble swallowing or breathing, throat tightness, or hoarseness)
- Malaise

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Paxlovid

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton or the blister after 'EXP'. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Paxlovid contains
- The active substances in this medicine are nirmatrelvir and ritonavir.
  - Each pink film-coated nirmatrelvir tablet contains 150 mg of nirmatrelvir.
  - Each white film-coated ritonavir tablet contains 100 mg of ritonavir.
- The other ingredients in the nirmatrelvir tablet are microcrystalline cellulose, lactose monohydrate (see section 2, 'Paxlovid contains lactose'), croscarmellose sodium, colloidal silicon dioxide and sodium stearyl fumarate (see section 2, 'Paxlovid contains sodium'). The film-coating contains hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol and iron oxide red.
- The other ingredients in the ritonavir tablet are copovidone, sorbitan laurate, colloidal anhydrous silica, anhydrous calcium hydrogen phosphate, sodium stearyl fumarate. The film-coating contains hypromellose, titanium dioxide, macrogol, hydroxypropyl cellulose, talc, colloidal anhydrous silica and polysorbate 80.

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What Paxlovid looks like and contents of the pack
Paxlovid film-coated tablets are available in 5 daily-dose blister cards with a total of 30 tablets packaged in a carton.

Each daily blister card contains 4 nirmatrelvir tablets (150 mg each) and 2 ritonavir tablets (100 mg each) and indicates which tablets need to be taken in the morning and evening (sun and moon symbols).

Nirmatrelvir 150 mg film-coated tablets are pink, oval-shaped and debossed with 'PFE' on one side and '3CL' on the other side.

Ritonavir 100 mg film-coated tablets are white to off white, capsule shaped, and debossed with 'H' on one side and 'R9' on the other side.

Marketing Authorisation Holder

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Brussels
Belgium

Manufacturer

Pfizer Manufacturing Deutschland GmbH
Betriebsstätte Freiburg
Mooswaldallee 1
79090 Freiburg
Germany

Pfizer Italia S.r.L.
Localita Marino del Tronto
63100 Ascoli, Piceno
Italy

Pfizer Ireland Pharmaceuticals
Little Connell
Newbridge
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Luxembourg/Luxemburg
Pfizer NV/SA
Tél/Tel: +32 (0)2 554 62 11

България
Пфайзер Люксембург САРЛ, Клон България
Тел.: +359 2 970 4333

Česká republika
Pfizer, spol. s r.o.
Tel: +420 283 004 111

Lietuva
Pfizer Luxembourg SARL filialas Lietuvoje
Tel: +370 5 251 4000

Magyarország
Pfizer Kft.
Tel.: + 36 1 488 37 00

Malta
Vivian Corporation Ltd.
Tel: +356 21344610

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Danmark
Pfizer ApS
Tlf: +45 44 20 11 00

Deutschland
PFIZER PHARMA GmbH
Tel: +49 (0)30 550055-51000

Eesti
Pfizer Luxembourg SARL Eesti filiaal
Tel: +372 666 7500

Ελλάδα
Pfizer Ελλάς A.E.
Τηλ: +30 210 6785800

España
Pfizer, S.L.
Tel: +34 91 490 99 00

France
Pfizer
Tél: +33 (0)1 58 07 34 40

Hrvatska
Pfizer Croatia d.o.o.
Tel: +385 1 3908 777

Ireland
Pfizer Healthcare Ireland
Tel: 1800 633 363 (toll free)
+44 (0)1304 616161

Ísland
Icepharma hf.
Sími: +354 540 8000

Italia
Pfizer S.r.l.
Tel: +39 06 33 18 21

Κύπρος
Pfizer Ελλάς A.E. (Cyprus Branch)
Τηλ: +357 22817690

Latvija
Pfizer Luxembourg SARL filiāle Latvijā
Tel: + 371 670 35 775

Nederland
Pfizer bv
Tel: +31 (0)800 63 34 636

Norge
Pfizer AS
Tlf: +47 67 52 61 00

Österreich
Pfizer Corporation Austria Ges.m.b.H
Tel: +43 (0)1 521 15-0

Polska
Pfizer Polska Sp. z o.o.
Tel.: +48 22 335 61 00

Portugal
Laboratórios Pfizer, Lda.
Tel: +351 21 423 5500

România
Pfizer Romania S.R.L
Tel: +40 (0) 21 207 28 00

Slovenija
Pfizer Luxembourg SARL
Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana
Tel: +386 (0)1 52 11 400

Slovenská republika
Pfizer Luxembourg SARL,
organizačná zložka
Tel: + 421 2 3355 5500

Suomi/Finland
Pfizer Oy
Puh/Tel: +358 (0)9 430 040

Sverige
Pfizer AB
Tel: +46 (0)8 550 520 00

United Kingdom (Northern Ireland)
Pfizer Limited
Tel: +44 (0) 1304 616161

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URL: https://pfi.sr/c19oralrx

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

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Document 2A.8

EMA Article 5 (3) Assessment Report of Paxlovid (December 16, 2021)

Document URL

https://www.ema.europa.eu/en/documents/referral/paxlovid-pf-07321332-ritonavir-covid-19-article-53-procedure-assessment-report_en.pdf

Reference website URL

https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/article-53-opinions-any-scientific-matter-human-medicines#use-of-paxlovid-(pf-07321332-and-ritonavir)-for-treating-covid-19-section

License

Not applicable

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16 December 2021
EMA/783153/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure under Article 5(3) of Regulation (EC) No 726/2004

Invented name: Paxlovid

INN/active substance: PF-07321332/ritonavir

Procedure number: EMEA/H/A-5(3)/1513

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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List of abbreviations

ACE2	Angiotensin-converting enzyme 2
ALT	Alanine aminotransferase
ASMF	Active Substance Master File
AST	Aspartate aminotransferase
ATR	Attenuated total reflectance
BCS	Biopharmaceutics classification system
BID	Twice (two times) a day
BMI	Body Mass Index
CAS	Chemical Abstracts Service
CHMP	Committee for Medicinal Products Human Use
CMC	Chemistry, Manufacturing and Controls
COVID-19	Coronavirus disease 2019
CPP	Critical Process Parameter
DDI	Drug-Drug Interactions
EC	European Commission
E-DMC	External data monitoring committee
EMA	European Medicines Agency
EPIC-HR	Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients
EUA	Emergency use authorization
FDA	Food Drug Administration
FTIR	Fourier transform infrared
GC	Gas Chromatography
GFR	Glomerular filtration rate
GMP	Good Manufacturing Practice
HDPE	High-density polyethylene
hERG	human Ether-à-go-go-Related Gene
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
IC50	Half maximal inhibitory concentration
ICH	International Conference of Harmonization
ICP-MS	Inductively Coupled Plasma- Mass Spectrometry
IMPD	Investigational Medicinal Product Dossier

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IPC	In-process Controls
IR	InfraRed
IUPAC	International Union of Pure and Applied Chemistry
Ki	Inhibition constant
LC	Liquid Chromatography
LDPE	Low density polyethylene
LoQ	List of Questions
MAA	Marketing Authorisation Application
mITT	modified Intention-to-Treat
MS	Mass Spectrometry
MTBE	t-butyl methyl ether
NMR	Nuclear Magnetic Ressonance
NMT	Not more than
NPC	4-nitrophenyl chloroformate
OC	Other concern
OPA/Al/PVC	Oriented PolyAmide/Aluminum Foil/Polyvinylchloride
OSD	Oral Solid Dose/Dosage
Ph.Eur./EP	European Pharmacopea
PK	Pharmacokinetics
QOS	Quality Overall Summary
QP	Qualified Person
QTPP	Quality Target Product Profile
RT-PCR	Reverse transcription polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SM	Starting Materials
TNC	5-Thiazolyl) methyl)-(4-nitrophenyl) carbonate
TSE/BSE	Transmissible spongiform encephalopathies/Bovine spongiform encephalopathies
UFLC	Ultra-Fast Liquid Chromatography
USP	United States Pharmacopea
UV	Ultraviolet
XRPD	X-ray powder diffraction

This list is not exhaustive

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1. Information on the procedure

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus, is the causative agent of coronavirus disease 2019 (COVID-19). Early treatment of patients with confirmed COVID-19 presenting only mild symptoms could reduce the number of patients that progress to more severe disease and require hospitalisation or admittance to intensive care unit (ICU).

The European Medicines Agency (EMA) is aware of several therapeutic candidates with putative antiviral action which are currently in development for the treatment of these patients.

Amongst those treatments is Paxlovid (PF-07321332 150 mg film-coated tablets and ritonavir 100 mg film-coated tablets), an investigational SARS-CoV-2 protease inhibitor antiviral therapy, specifically designed to be administered orally so that it can be prescribed at the first sign of infection or at first awareness of an exposure, potentially helping patients avoid severe illness which can lead to hospitalization and death. PF-07321332 is designed to block the activity of the SARS-CoV-2-3CL protease, an enzyme that the coronavirus needs to replicate. Co-administration with a low dose of ritonavir as a pharmacokinetic booster helps to optimize the pharmacokinetics of this anti-protease against SARS-Cov-2 as originally considered in the therapeutic management in the field of HIV chronic infection.

PF-07321332 inhibits viral replication at a stage known as proteolysis, which occurs before viral RNA replication. In preclinical studies, PF-07321332 did not demonstrate evidence of mutagenic DNA interactions.

Paxlovid showed a significant diminution of the percentage of patients with COVID-19-related hospitalization or death from any cause in high risk patients with at least 1 post-baseline visit through Day 28, who at baseline did not receive nor were expected to receive COVID-19 therapeutic monoclonal antibody treatment, and were treated ≤ 3 days after COVID-19 symptom onset (primary endpoint) in Paxlovid arm compared to placebo arm -6.32 with a 95% unadjusted for multiplicity CI (-9.04, -3.59) $p<0.0001$ an in Interim Analysis of Phase 2/3 EPIC-HR study.

These results are of particular relevance and their application in the clinical setting before a formal marketing authorisation is considered important in view of the current pandemic situation. In that respect, there is public health interest to seek a harmonised scientific opinion at EU level on currently available information on Paxlovid and on potential conditions of use with a view to supporting national decisions.

On 19 November 2021 the Executive Director therefore triggered a procedure under Article 5(3) of Regulation (EC) No 726/2004, and requested the CHMP to give a scientific opinion on the currently available quality, preclinical and clinical data on the potential use of Paxlovid for the treatment of confirmed COVID-19 in adult patients.

2. Scientific discussion

2.1. Introduction

The causative agent of the coronavirus disease 2019 (COVID-19) pandemic, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a member of the coronavirus family. SARS-CoV-2 infects cells through the angiotensin-converting enzyme 2 (ACE2) receptor with the lung and bronchial epithelial cells as the primary sites of infection. Like other coronaviruses, SARS-CoV-2 encodes a main protease (mPro): $3CL^{pro}$.

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PF-07321332 is a selective inhibitor of the SARS-CoV-2 protease, $3CL^{pro}$, to be administered as an oral agent for the treatment of patients with COVID-19, in combination with ritonavir. Inhibition of the 3CL protease renders the protein incapable of processing polyprotein precursors which leads to the prevention of viral replication. Ritonavir is not active against SARS-CoV-2 $3CL^{pro}$ but inhibits the CYP3A-mediated metabolism of PF-07321332, thereby providing increased plasma concentrations of PF-07321332.

2.2. Quality aspects

The finished product Paxlovid consists of two separately manufactured medicinal products (PF-07321332 150 mg film-coated tablets and ritonavir 100 mg film-coated tablets), which are co-packaged together. The ritonavir 100 mg film-coated tablets co-packaged in Paxlovid have been approved in EU countries as a generic product since 2015. The reference product Norvir has been approved since 25/08/1996 via a centralized procedure EU/1/96/016/005.

The PF-07321332 immediate release film-coated tablet contains 150 mg of PF-07321332 as active substance. Other ingredients are:

Tablet core: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, colloidal silicon dioxide and sodium stearyl fumarate;

Film-coating: hydroxy propyl methylcellulose, titanium dioxide, polyethylene glycol and iron oxide red.

The ritonavir product is an immediate release film-coated tablet containing 100 mg of the active substance ritonavir. Other ingredients are:

Tablet core: copovidone, sorbitan laureate, anhydrous colloidal silica, calcium hydrogen phosphate, anhydrous and sodium stearyl fumarate;

Film-coating: hypromellose, titanium dioxide, macrogol, hydroxy propyl cellulose, talc, anhydrous colloidal silica and polysorbate 80.

The finished product Paxlovid is packaged into a composite "Oriented PolyAmide/Aluminum Foil/Polyvinylchloride foil blister" with aluminium foil lidding; each tablet is placed into an individual blister cavity.

The packaging provides the recommended dosage which is 300 mg PF-07321332 (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally twice daily for 5 days as depicted below in Figure 1:

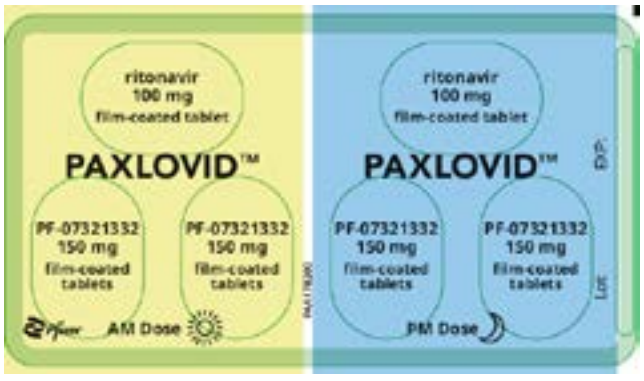

Figure 1. Paxlovid packaging configuration

Five of the blister cards are packed in a carton for 5 days treatment.

2.2.1. Active Substance (PF-07321332)

General Information

The chemical name (IUPAC) of PF-07321332 is (1R,2S,5S)-N-((1S)-1-Cyano-2-((3S)-2-oxopyrrolidin-3-yl)ethyl)-3-((2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide, corresponding to the molecular formula $C_{23}H_{32}F_3N_5O_4$. It has a molecular mass of 499.54 g/mol and the following structure (Figure 2):

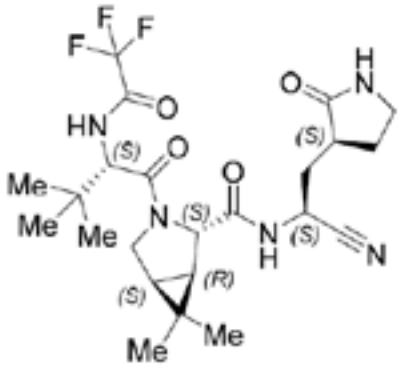

Figure 2. chemical structure of PF-07321332

The structure of PF-07321332 was elucidated by a combination of analytical methods, including 1H-NMR, 13C-NMR, High Resolution Mass Spectrometry (HRMS), UV-vis spectroscopy and attenuated total reflectance (ATR) FTIR spectroscopy. The molecular structure and absolute configuration of PF-07321332 was independently confirmed using single crystal X-ray diffraction technique.

PF-07321332 is a non hygroscopic, white to pale coloured crystalline powder. Its has low solubility in (unbuffered) water and buffered aqueous media with pH from 1.97 to 6.96 ranging between 0.98 and 1.15 mg/mL.

PF-07321332 has 6 asymmetric centres, giving 32 possible stereoisomers (azabicyclo[3.1.0]hexane moiety can only exist in the syn configuration) as could be derived from Figure 2, which shows the absolute configuration.

As an additional element of the chiral control strategy, chiral identification assays have been developed for each of the starting materials (SMs) to ensure that the correct enantiomer of each is used in the active substance synthesis.

PF-07321332 manufactured by the manufacturing process is isolated as crystalline polymorphic form 1 (anhydrous form) as confirmed by powder X-ray diffraction (XRPD). Form 2 (methyl tertiary butyl ether solvate) and Form 3 (an n-butyl acetate solvate) are further possible polymorphic forms. Form 1 is the thermodynamically most stable form at relevant temperatures and humidities.

Manufacture, process controls, characterisation and container closure

The manufacturing process consists of several chemical transformation steps. The description is acceptable in the context of this procedure, but further information and definitions are expected at the time of marketing authorisation application (MAA).

A brief description of the manufacturing process was given including reagents and solvents, some in-process controls, and yields. Appropriate in-process controls (IPC) have been established for each step. The projected commercial manufacturing scale range for PF-07321332 was defined. The company states that due to accelerated development of PF-07321332, scientific understanding of the synthesis

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and a comprehensive control strategy are not completed yet. These will be completed at time of MAA which may implicate further changes to the synthetic process, though anticipated to be minor. In the context of an Art. 5(3) submission this level of information is acceptable, but further detailed information on the manufacturing process are expected at the time of MAA.

The starting materials are structural fragments of the active substance. The provisional SM specifications, analytical procedures and summary of validation data given are acceptable for this procedure. Names and addresses for the SM manufacturers are stated. Further data and information on starting materials (justification of starting materials according to ICH Q11, confirmation of structure, description of synthesis, some tightening of specifications) will be expected at the time of MAA. Comparative data will also be expected from each proposed SM supplier.

A list of the reagents, solvents and catalysts used in the manufacturing process with identification of ICH classification for solvents as well as the respective specifications has been submitted. The specifications for raw materials are acceptable in the context of this procedure.

Provisional specifications have been established not for all isolated intermediates in the manufacturing process of PF-07321332 active substance. Detailed specifications for intermediates will be expected at the time of MAA, which should include discussion of impurity carry-over supported by batch analysis data.

A short description of the manufacturing process development is provided.

A discussion on inorganic and organic impurities (including elemental, genotoxic and chiral impurities), their carryover and control strategy has been provided and is acceptable in the context of this procedure. The residual solvents used in the final manufacturing step are specified in the active substance specifications with adequate limits according to ICH Q3C guideline.

The provided risk assessment concerning the potential presence of nitrosamines in the active substance is sufficient. Potential sources of nitrosamine impurities currently listed in EMA guidance were addressed. No risks are identified. Further data on impurities and their control strategy are expected at the time of the MAA.

PF-07321332 is packaged in two sealed, low-density polyethylene (LDPE) anti-static liners, which is then inserted in a high-density polyethylene (HDPE) drum or equivalent secondary container. A representative IR spectrum for the low-density polyethylene liner is provided as well as the corresponding specification. The provided information is acceptable in the context of this procedure, but more information and specifications are expected at the time of MAA.

Specification, analytical procedures, reference standards, batch analysis

The active substance specification includes tests for assay (HPLC), appearance, identification (IR, HPLC), impurities (HPLC), residual solvents (GC), water content (Ph. Eur.), solid state polymorphic form (PXRD), residue on ignition (Ph. Eur.), and particle size distribution (laser diffraction).

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In principle, the active substance specification contains all relevant test parameters. The justifications for the specifications, including individual specified organic impurities, qualified at toxicological levels or in line with ICH Q3A (R2), as well as the rationale for omitting chiral purity, elemental impurities and microbial enumeration, are acceptable in the context of this procedure. However, additional batch analysis data to support the impurities, specifications limits and setting of acceptance criteria are expected at time of MAA.

The descriptions of the analytical procedures and the validation data provided are acceptable in the context of this procedure, but more data are expected at the time of MAA. The quality of the reference standard for the active substance is sufficiently proven for this procedure.

Satisfactory batch analysis data are given for active substance batches used for toxicological batch and clinical batches. Additional batch analysis data for batches which support the product specification are expected at the time of MAA.

Stability

Stability data for two active substance batches produced by earlier manufacturing processes under long term conditions at 25°C/60% and under accelerated conditions at 40°C/75% RH were given showing compliance with specifications. The stability batches were packaged in double LDPE bags which are placed in HDPE drums.

No significant changes were observed. The stability batches are supportive for the proposed manufacturing process as they have the same polymorphic form, similar synthetic chemistry and same final solvents. Differences in purity profile at release are not expected to impact stability. The company has demonstrated that the active substance is photostable.

Taking into account the requirements of the ICH Q1E guideline a re-test period of 12 months at 15-30°C can be accepted. Further available data should be provided at the time of the MAA.
A commitment was given that the first three batches will be placed on stability under long-term conditions at 30°C/75% RH for 36 months and under accelerated conditions at 40°C/75% RH over 6 months.

2.2.2. Active Substance (ritonavir)

Ritonavir is an established active substance described in the Ph. Eur. The supplier of ritonavir used in the manufacture of Paxlovid is Hetero Drugs Limited. Ritonavir from Hetero is already approved for use in other medicinal products in the EU, using the Active Substance Master File (ASMF) procedure.

General Information

The chemical name (Ph.Eur.) of ritonavir is thiazol-5-ylmethyl[(1S,2S,4S)-1-benzyl-2-hydroxy-4-[[(2S)-3- methyl-2-[[methyl[[2-(1 metylethyl)thiazol-4-yl] methyl] carbamoyl] amino] butanoyl] amino]-5-phenylpentyl]carbamate, corresponding to the molecular formula C37H48N6O5S2. It has a molecular mass of 720.94 g/mol and the following structure (Figure 3):

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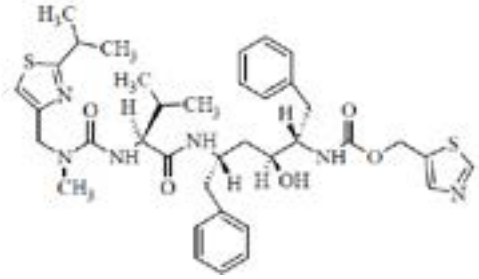

Figure 3. chemical structure of ritonavir

The molecular structure of ritonavir was investigated and confirmed by the ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, UV spectroscopy, and InfraRed spectroscopy.

Ritonavir is a white or almost-white, non hygroscopic, crystalline powder, practically insoluble in water, freely soluble in methanol and sparingly soluble in acetonitrile.

Ritonavir exhibits isomerism. It contains 4 chiral centres which are introduced selectively in the synthetic process. Enantiopurity is determined by a chiral HPLC method in the active substance specification. It also exhibits polymorphism; Hetero consistently produces polymorphic Form-I, characterised by an XRD pattern, and tested in the active substance specification.

Manufacture, process controls, characterisation and container closure

Ritonavir from Hetero is already approved in the EU using the AMSF procedure. However, a Letter of Access specifying the ASMF version (Applicant's and Restricted Part of the ASMF) has not been submitted and is required at the time of MAA to give permission to the National Competent Authorities/EMA to assess the data in the ASMF in relation to the MAA for Paxlovid. Pfizer commits to prove a Letter of Access issued by Hetero by 17-Dec-2021. In the context of this procedure, only the information presented by the company (Pfizer) were assessed.

The chemical synthesis and a brief description of manufacturing process of intermediate and final active substance were provided. The manufacturing process consists of four chemical reaction steps followed by a purification and drying step.

Information on possible impurities is provided covering Ph. Eur. impurities, additional non-Ph. Eur. impurities, residual solvents, genotoxic impurities, and elemental impurities.

Details of the impurity studies carried out considering all the above impurities and the residual solvents of Ritonavir (Form-I) were enclosed. Studies have been carried out to check the presence of the other possible impurities from the manufacturing process of Ritonavir and its starting materials.

A study has been conducted to check the possible presence of Class-I solvents in ritonavir with a validated method. From the study results it was concluded that all Class-I solvents are absent in the batches tested and therefore do not need to be controlled at the level of active substance.

Genotoxic studies: Based on the evaluation of the process, impurities were identified as potential genotoxic impurities. Studies have been carried out to check their presence in final API with a validated method. From the studies it was clear that these compounds are below detection limit in all the batches being tested.

A risk assessment for the following Class 1, 2A, 2B and 3 elemental impurities as per ICH Q3D requirement was carried out for Ritonavir production scale batches. Results from batch analysis

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obtained demonstrate that Class 1 and 2A along with intentionally added Class 2B and class 3 elemental impurities were found to be insignificant levels in Ritonavir production scale batches. Considering the manufacturing process, the potential presence of Class 1 and 2A and intentionally added Class 2B and Class 3 elemental impurities in Ritonavir (Form-I) are highly remote. It is concluded that the active substance complies with ICH Q3D and that no further controls are required.

The active substance is packaged in transparent polyethylene bag, tied with a plastic tag. This bag is placed in a black bag tied using another plastic tag. The polyethylene bags are made from LDPE (Low-Density Polyethylene) and LLDPE (Linear Low-Density Polyethylene) respectively. The bags are placed in an HDPE drum. The packaging materials complies with relevant EU regulations and Ph. Eur. requirements.

Specifications and test procedures for packing materials, IR spectrums of the polythene bags, in-house and supplier certificates of analysis for packing material and compliance certificate of packing material have been provided.

Specification, analytical procedures, reference standards, batch analysis

The proposed active substance specifications includes tests for appearance, solubility, identification (IR, HPLC), polymorphic form (XRD), related substances (HPLC), water content (Ph. Eur.), sulfated ash (Ph. Eur.), assay (HPLC), Specific rotation (Ph. Eur.) and residual solvents (GC). 4-Nitrophenyl chloroformate and [(5-Thiazolyl)methyl]- (4-nitrophenyl)carbonate content (UFLC-MS) and 1,3-Dichloroacetone (GC-MS) content are not part of the release specifications but are going to be monitored on the first batch of every year and multiple of every 10th batch.

The active substance specification contains all the requirements of the Ph. Eur. with additional requirements for polymorphic form, specific optical rotation, residual solvents, and additional non-Ph. Eur. impurities. The limits for impurities are in compliance with Ph. Eur., ICH Q3A, ICH Q3C, ICH Q3D, and ICH M7. The active substance complies with relevant EMA and ICH guidelines where appropriate.

The analytical procedures are described and their suitability was demonstrated by validation data. The reference standards are sufficiently characterised.

The provided batch data of three ritonavir batches demonstrate compliance with the active substance specification. No significant differences between the batches was observable.

Stability

Stability studies were initiated for the first three Ritonavir API validation batches, as per the ICH Q1A guideline at accelerated (40±2°C/ 75±5% RH), intermediate (30±2°C/ 65±5% RH), and long term conditions 25±2°C/ 60±5% RH. The batches were stored in the specified container closure system for 60, 12 and 6 months under long term, intermediate and accelerated conditions respectively. The methods adopted for conducting the stability studies are stability indicating which were established based on the degradation studies performed. The available stability data have been evaluated and no significant changes were observed in any of the stability batches. It has also been demonstrated that the active substance is photostable.

A forced degradation study has been performed under various stress conditions. The summary report on appearance, identification by IR and HPLC, P-XRD, related substances by HPLC, water and assay by HPLC is provided demonstrating that the methods adopted for conducting the stability studies are stability indicating.

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Based on the evaluation of stability data, the claimed retest period of 60 months at 25ºC without any recommendations for storage is endorsed.

2.2.3. Finished medicinal Product

The proposed medicinal product Paxlovid consists of PF-07321332 150 mg film-coated tablets and ritonavir 100 mg film-coated tablets, which are separately manufactured, but co-packaged on the same blister for ease of daily co-administration.

2.2.3.1 PF-07321332 150 mg film-coated tablet

Description of PF-07321332 film-coated tablets

The PF-07321332 tablets are described as oval, pink, film-coated tablets and debossed with "PFE" on one tablet side and with "3CL" on the opposite side.
The missing tablet dimensions are expected to be added to section 3.2.P.1 at time of MAA.

PF-07321332 film-coated tablet is an immediate release (IR) dosage form, containing 150 mg PF-07321332 as active substance.

Pharmaceutical Development

A Quality Target Product Profile (QTPP) in accordance with ICH Q8 was established to guide formulation and process development activities. Oriented towards this QTPP, quality attributes were derived as basis for the prospective finished product specification. Through a combination of experimental studies, risk assessments, and manufacturing experience across a range of scales and equipment types, an accelerated understanding of the formulation and process conditions and their impact on the quality attributes of the finished product was obtained.

The active substance PF-07321332 has low aqueous solubility across the physiologically relevant pH range. The solubility is pH independent, as it is a non-ionisable compound. Classification of permeability (low/high) will continue to evolve as additional data becomes available. It is tentatively classified as BCS II/IV (low solubility with permeability to-be-determined) compound. A clear BCS classification for the active PF-07321332 is expected at time of MAA.

Polymorphic forms have been identified for PF-07321332. The anhydrous crystalline form 1 is the thermodynamically most stable form under relevant manufacturing and storage conditions, and is used for all finished product development and clinical manufacture activities.

As the data set in terms of particle size distribution (PSD) is premature, a discussion in depth with respect to potential PSD impact on manufacturability and bio-performance of the PF-07321332 IR film-coated tablets is awaited at time of MAA.

Based on stability data available to date, no active substance-excipient incompatibility has been observed.

Excipients and corresponding quantities chosen are typically used for oral solid dose (OSD) products such as the film-coated tablets in question. The selected excipients are of compendial grade and comply with the requirements of the relevant Ph. Eur. monographs, with the exception of the colorant, which however comprises of compendial components.

The dissolution performance of representative PF-07321332 150 mg immediate release film-coated tablet batches was investigated in dissolution media over the physiological range. Following

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experimentation the final test conditions were found to be suitable and thus are proposed for the routine quality control (QC).

The discriminatory power of the proposed dissolution method was studied. In light of emergency supply, the aspect *in-vitro dissolution* is considered appropriately addressed.

A risk assessment considering requirements from the QTPP was conducted to identify the potential relationships between the process parameters and quality attributes. Based on this assessment, quality attributes including assay, content uniformity, dissolution, disintegration and tablet appearance were determined to be potentially impacted by the process parameters. As next step, enhanced development studies were conducted to investigate the effects of process parameters on the aforementioned quality attributes. The operating ranges studied for the process parameters at laboratory and large manufacturing scales were shown to be robust for all quality attributes studied.

As summary and conclusion, the formulation development as well as manufacturing process development have been suitably worked out in the context of emergency supply and taking into account the selected dosage form „film-coated tablet". However, at time of MAA, a number of issues need to be further addressed, and importantly an appropriate control strategy. The criticality of the proposed quality attributes and process parameters needs to be specified. Furthermore, the robustness of the proposed manufacturing process needs to be demonstrated covering the whole commercial batch size range.

Microbiological attributes for PF-07321332 150 mg film-coated have been assessed during development and complied with the harmonised USP/EP requirements for non-aqueous preparations for oral use.

The container closure system for PF-07321332 150 mg film-coated tablets and externally sourced Ritonavir 100 mg film-coated tablets consists of a foil/foil blister system made from a composite Oriented PolyAmide/Aluminum Foil/Polyvinylchloride (OPA/Al/PVC) foil blister with aluminum foil lidding where each tablet is placed into an individual blister cavity. Illustrative drawings and representative IR spectra of the packaging components are provided. More detailed information on the packaging components (specifications, analytical procedures, certificates of analysis, quality declarations) are expected to be provided at the time of the MAA.

Manufacture of the finished product and process controls

The respective manufacturing sites along with their corresponding responsibilities are clearly specified.

For the all proposed finished product manufacturing sites located in the EU, the GMP certificates are available in EudraGMDP. For the Pfizer site in USA, a written confirmation is available stating that this site had been inspected by the FDA.

The manufacturing process comprises the following steps: initial blending, screening, intra-granular lubrication, dry granulation, milling, extra-granular blending and lubrication, followed by tablet compression and film coating.

Batch formulae for batch sizes ranges were provided.

The 150 mg film-coated tablets use compendial excipients and are manufactured using conventional processing equipment. The narrative description of the manufacturing process is presented with an acceptable level of detail in the context of this procedure, by indicating the set limit of the different blending stages as well as the acceptance criteria of the in-process controls for compression. The level of detail provided on the manufacturing process is acceptable for this procedure. However, for the forthcoming MAA submission, the finished product manufacturing process needs to be described in

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greater detail, specifying all crucial aspects such as critical process parameters (CPP) and in-process controls (IPC) and holding times of intermediates.

No process validation data were presented. This is acceptable considering the fact that conventional techniques and equipment are used and also the context of this procedure. It is stated that the manufacturing & packaging process validation will be completed and provided within the MAA when final process and controls will have been identified and appropriate process understanding has been developed.

Product specification, analytical procedures, batch analysis, reference standards

The finished product specifications include appropriate tests for this kind of dosage form including appearance, identity (HPLC and IR), assay (HPLC), degradation products (HPLC), dissolution (Ph. Eur., HPLC), content uniformity (Ph. Eur.) and microbial limits (Ph. Eur.).

In principle sufficient information on specifications has been provided. However, some additional testing parameters should be included in the specifications at time of MAA. Additionally, some amendments on the acceptance criteria and a clear distinction between release and shelf-life specifications are expected to occur at the time of MAA. Revision of the limit concerning dissolution testing is awaited at time of MAA.

The impurities and degradation products have been sufficiently discussed. The finished product contains no Class 1 or Class 2 mutagenic impurities or degradation products.

An elemental impurities risk assessment is in progress. Based on the discussion presented in relation to the active substance and in view of usage of compendial, well-precedented excipients, the contributions of elemental impurities from the active substance and the excipients into the finished product should be negligible. Complete information concerning the elemental impurities risk assessment is awaited at time of MAA.

A risk assessment on the potential presence and formation of nitrosamine in the finished product was completed. The Company states, that no vulnerable amines have been identified in active substance or excipients, as well as no nitrosamine risk have been identified from the packaging material used.

Overall, the specification limits have been sufficiently justified. In addition, justification has been provided concerning exclusion of tests. Further information on justification is awaited at time of MAA.

The descriptions of the analytical procedures and their validations provided are acceptable. Some additional information is awaited at time of MAA concerning some validation parameters. Information regarding the reference standards has been provided. Further information concerning the suitability of the reference standards used for the determination of assay of the finished product is awaited at time of MAA.

Batch analysis data were provided for batches of PF-07321332 150 mg film-coated tablets manufactured according to the details described in Section P.3.3 Description of Manufacturing Process and Process Controls and tested by the methods described in Section P.5.2 Analytical Procedures. All data found were within the specifications at the time. Some clarification concerning the use of different specifications is awaited at time of MAA.

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Adventitious agents

Lactose monohydrate is the only excipient of animal origin. Relevant TSE safety confirmation is availal and accepted.

2.2.3.2 Ritonavir 100 mg film-coated tablet

Description of Ritonavir 100 mg film-coated tablets

Ritonavir 100 mg film-coated tablets are described as white to off white, capsule shaped, film-coated tablet, debossed with 'H' on one side and 'R9' on other side. Its approximate dimensions are 17.14 m x 9.13 mm.

Pharmaceutical development

The finished product has been developed as a generic to the reference product Norvir, which is authorised in the EU by AbbVie Deutschland GmbH & Co. Its qualitative composition is essentially similar to the reference product.

Ritonavir active substance is a white to light tan powder Due to its low solubility and permeability properties, it has been assigned to BCS Class IVa.

Excipients matching those of the EU reference product were chosen, all of which complying with Ph. Eur. monographs, including those contained in the non-compendial coating mixture. All excipients are common ingredients for this product type. Their compatibility with the Ritonavir premix was confirmed by stability data. At time of MAA, minor amendments should be made to the composition table as to specify the active ingredient at the declared amount (100 mg) along with one total amour of each excipient used.

The manufacturing process is described.

For commercial batches used in the bioequivalence study, *in vitro* dissolution studies were conducted and compared to the results obtained with the EU reference product.

In summary, the finished product has been shown to be comparable to the reference product with respect to key parameters *in vitro* dissolution and related substances profile/levels. However, several aspects of pharmaceutical development will need to be addressed at time of MAA, and compliance wi current ICH Q8 (R2) should be established.

The choice of container closure system for the co-packaged medicinal product is based on PF-07321332 tablets and is justified. As for the bulk tablets, the suitability of the primary container (HDPE, with polypropylene closure) was confirmed by results of accelerated stability studies for 3 months. No significant changes were observed for water content, assay, related compounds, and dissolution.

No risk of nitrosamine formation is identified originating from the packaging components. No overage are used during manufacture of Ritonavir film-coated tablets. Microbiological attributes and compatibility are not applicable for the proposed finished product.

Detailed information on the container closure system (LDPE bag placed in triple laminated aluminum bag) for Ritonavir bulk tablets was provided including specifications, analytical procedures and certificates of analysis issued by both the suppliers and the product manufacturer.

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Manufacture, process controls and characterisation

All manufacturing sites and their operations were defined.

The manufacturing process uses three stages for preparation of the premix: Stage-I (RPM-I: preparation of premix), Stage-II (RPM-II: pulverization), Stage-III (RPM-III: blending, sifting, packaging). Afterwards, the material is sifted/mixed and prepared for hot melt extrusion, milled/sifted, (pre)lubricated, before compression and coating take place. The process is considered as non-standard procedure due to the hot melt extrusion included.

Process descriptions were provided along with flow charts.

Batch formulae for production batch sizes were presented.

Overall, the process is well-described and controlled by in-process controls. Nevertheless, the applicant is expected to provide further details and justification for the control strategy employed based on development data. Besides, flow charts and in-process controls may need to be updated at time of MAA submission.

Process validation data were provided for commerical batches at both minimum and maximum batch size. Key parameter during dry mixing and lubrication was blend uniformity, monitored in individual samples taken at several locations to make sure that the active substance is evenly distributed throughout the blend. During compression and coating, it has been confirmed that the physical tablet parameters (mass variation, uniformity of dosage units, friability, hardness) comply with pre-defined requirements. The process has been shown to be reliable, robust and reproducible in order to obtain tablets that comply with the specifications and quality characteristics defined on the respective validation protocol.

Also, validation results of the manufacturing process of three batches of Ritonavir blend intermediate were provided. The results obtained demonstrate that the manufacture of Ritonavir premix is acceptable and reproducible in order to obtain mixture that comply with the specifications and quality characteristics defined on the respective validation protocol.

Product specification, analytical procedures, batch analysis, reference standards

The finished product release and shelf life specifications**Error! Reference source not found.**, include appropriate tests for this kind of dosage form including description, identification (HPLC and UV), average weight (mass), water content (KF), dissolution (Ph. Eur. - HPLC), uniformity of dosage units (content uniformity Ph. Eur.), related substances (HPLC), assay (HPLC), and microbial purity (Ph. Eur.).

In principle sufficient information on specifications has been provided. The specifications for Ritonavir 100 mg film-coated tablets are in line with the requirements of the relevant Ph. Eur. monographs, ICH guidelines and batch analysis data. However, some additional information is awaited at time of MAA.

There are no impurities in the product that are different from those present in the active substance. However, further information concerning impurity qualification is awaited at time of MAA.

A risk assessment for elemental impurities as per ICH Q3D has been provided, which sufficiently justify absence of test for elemental impurities in the finished product. The component approach has been used. However, data of three consecutive batches or six pilot batches are awaited at the time of MAA with details on the method used including LOD, LOQ of the analytical method.

A risk assessment for the presence of nitrosamines as per the requirements of EMA guidance on Information on nitrosamine for marketing authorisation holders (EMA/189634/2019 &

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CMDh/404/2019) and (EMA/428592/2019 & CMDh/405/2019) has been provided. For Ritonavir premix and Ritonavir 100 mg film-coated tablets no risk for presence of nitrosamine impurities was identified. However, for completeness of the assessment further information will be requested at the time of MAA.

If not otherwise justified, the limit for dissolution testing should be revised at time of MAA. Preferably, more than one time point should be included in the specification on *in vitro* dissolution.

The analytical methods (Ph Eur 2.2.29 & in-house analytical methods) have been sufficiently described. Method validation has been provided for almost all methods described under analytical procedures including the method used for the determination of blend assay, blend content uniformity. Further information on validation data is awaited. Validation data have been presented for the method used for determination of assay and dissolution testing as well as for identification by UV and microbial purity. For completeness of demonstration of suitability of the methods used, validation data concerning Karl Fischer method are requested at time of MAA.

Information on reference standards used including certificates of analysis has been provided. Some information is expected at time of MAA concerning the purpose of the reference standards used as well as on demonstration of suitability for the finished product.

Batch analysis data have been presented. All data were within the specifications. However, clarification concerning specification parameters is awaited at time of MAA.

Adventitious agents

There are no excipients of human or animal origin used in the manufacture Ritonavir 100 mg film-coated tablets.

Stability conclusion for the co-packaged finished product

PF-07321332 150 mg Film-coated Tablets

Due to the accelerated pharmaceutical development, limited primary stability data is currently available for the PF-07321332 150 mg film-coated tablet. In accordance with ICH guideline Q1A(R2), a primary stability study consisting of PF-07321332 150 mg film-coated tablets packaged in proposed commercial foil/foil blister packaging has been initiated.

Preliminary stability data for three primary batches of the 150 mg tablets were reported for 6 weeks at the long-term storage conditions of 30°C/75% RH and 25°C/60% RH and at the accelerated storage conditions of 40°C/75% RH. During stability, solely the stability indicating tests, appearance, assay, degradation products and dissolution were performed.

In addition, photostability (in accordance with ICH guideline Q1B) of one batch was evaluated and data was provided.

Various supportive data of early development formulations manufactured as different strength tablets packaged in several container closure systems were evaluated under different conditions. 3 months data at the long-term storage condition of 30ºC/75% RH and at the accelerated storage condition of 40ºC/75% RH for one batch of each formulation were reported. Additional supportive stability data from two developmental batches of the commercial formulation through 6 weeks storage at the long-term storage condition of 30ºC/75% RH and at the accelerated storage condition of 40ºC/75% RH were also presented.

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Forced degradation studies on PF-07321332 150 mg film-coated tablets were performed, including thermal, thermal humidity and photolysis conditions, to establish the extent and nature of potential degradation pathways and to confirm the suitability of the assay and purity method.

Stress studies on film-coated tablets stored in an open container, placed in an oven were performed. Total degradation products remained within specifications.

The overall stability data from the primary stability studies, supportive studies, stress stability studies and forced degradation stability studies, reveal that no significant changes have been observed for appearance, assay, degradation products, dissolution or water content. The levels of degradations under different conditions of temperature, humidity, light remained low.

A shelf life of 12 months was proposed for the PF-07321332 150 mg film coated tablets. According to ICH Q1E the provided stability data would support shelf-life of 6 months. However based on EMA/CHMP/QWP/545525/2017 for Investigational medicinal products in clinical trials and considering the purpose of this application (between clinical and commercial stages in the product lifecycle) it is accepted that a greater flexibility can be applied; a shelf life of 12 months is thus considered acceptable in the context of this application (see also Co-packaged Finished Product below).

The proposed storage conditions and labeling for PF-07321332 150 mg film-coated tablets are "Do not store above 25°C"; "Do not refrigerate or freeze".

Ritonavir Film-coated Tablets

Stability data for Ritonavir 100 mg tablets in the Pfizer co-packaged foil/foil blister system is currently not available. Stability studies were carried out on three full batches of Ritonavir 100 mg Film-coated tablets packed in Alu-Alu blister and stored up to 36 months at 25ºC/ 60% RH and 6 months at 40ºC/ 75% RH. No significant changes were observed in Description, Water content, Resistance to crushing of tablets, Dissolution, Related compounds, Assay, XRD and Microbiological examination of Ritonavir 100 mg film-coated tablets and the results were found to be well-within the specification.

A forced degradation study (acid, base, peroxide, thermal, photolytic and humidity) was carried out as a part of the analytical method validation in order to prove the specificity of the HPLC method for assay and related compounds of Ritonavir premix and Ritonavir 100 mg Film-coated tablets.

Stability results of Ritonavir bulk tablets were also presented. The studies were conducted with three commercial batches, stored up to 12 months at ICH long term conditions (25°C/ 60% RH). All test parameters remain within specifications. For the bulk tablets, a shelf life of 12 months has been confirmed when stored under these conditions.

The proposed shelf-life for Ritonavir 100 mg film-coated tablets is 24 months. This medicinal product does not require any special storage conditions. The commercially available Hetero Ritonavir 100 mg tablet in foil/foil blister container closure system has an approved shelf life of 24 months, which is considered appropriate for the Pfizer co-packaged presentation as well.

Co-packaged Finished Product

The final shelf-life and storage condition for the co-packaged finished product Paxlovid is based on the more stringent shelf-life and storage condition for either of the two products, which is PF-07321332 150 mg film-coated tablets. Therefore, based on overall available stability data presented for both components of the co-packaged product, the proposed shelf-life of 12 months with storage conditions "Do not store above 25°C. Do not refrigerate or freeze", as stated in the CoU (sections 5.8 and 5.9).

The twelve months stability for the drug product is acceptable provided the applicant will monitor the stability data monthly and will immediately inform the Authorities in the case of out of specification

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results. Storage conditions "Do not store above 25°C", "Do not refrigerate or freeze" is accepted provided that this storage conditions will be updated as required when further stability data are available.

2.2.4 Discussion and conclusions on chemical and pharmaceutical aspects

This procedure, triggered under Article 5(3) of Regulation (EC) No 726/2004, intends to provide a harmonised scientific opinion at EU level on currently available information on Paxlovid and on potential conditions of use with a view to supporting national decisions before a formal marketing authorisation based on the currently available quality, preclinical and clinical data on the potential use of Paxlovid for the treatment of confirmed COVID-19 in adult patients. This is particularly relevance in the clinical setting in view of the current pandemic situation and the public health interest.

The proposed medicinal product Paxlovid consists of PF-07321332 150 mg film-coated tablets and ritonavir 100 mg film-coated tablets. For ease of daily co-administration, both products (PF-07321332 150 mg film-coated tablets and Ritonavir film-coated tablets) are co-packaged on the same blister.

Information on development, manufacture and control of the active substances and the two components of the finished product (i.e. PF-07321332 150 mg film-coated tablets and ritonavir 100 mg film-coated tablets) has been presented in a satisfactory manner. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. A number of issues as detailed in the report above have been identified that require more comprehensive data for the future MAA.

The quality of this product is considered to be acceptable in the context of the present procedure, when used in accordance with the conditions defined in the Conditions of Use.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that, in the context of the present procedure, the product should have a satisfactory and uniform performance in clinical use.

The twelve months stability for the drug product is acceptable provided the applicant will monitor the stability data monthly and will immediately inform the authorities in the case of out of specification results.

Storage conditions "Do not store above 25°C", "Do not refrigerate or freeze" is accepted provided that this storage conditions will be updated as required when further stability data are available.

2.3. Non-clinical aspects

2.3.1 Pharmacology

PF-07321332 is a selective inhibitor of the SARS-CoV-2 $3CL^{pro}$. The activity of the $3CL^{pro}$ is essential for viral replication; $3CL^{pro}$ digests the virus p1a and p1ab polyproteins at multiple junctions to generate a series of proteins critical for virus replication and transcription. No close human analogues of the coronavirus $3CL^{pro}$ are known. The essential functional importance in virus replication together with the absence of closely related homologues in humans, identify the $3CL^{pro}$ as an antiviral drug target.

Primary Pharmacodynamics

In vitro

In vitro pharmacodynamic (PD) studies are reported in the clinical part of this assessment report (AR) (please see below).

In vivo

Two *in vivo* models were conducted to evaluate the anti-viral efficacy of PF-07321332 against SARS-CoV-2 using a mouse-adapted virus, SARS-CoV-2-MA10. SARS-CoV-2-MA10 is a recombinant mouse adapted strain of SARS-CoV-2 (SARS-CoV-2 MA) capable of utilizing mACE2 for viral entry by remodelling the spike and receptor binding interface via reverse genetics. In addition to the spike Q498Y/P499T substitutions engineered into the parental SARS-CoV-2 MA, SARS-CoV-2 MA10 included 5 additional nucleotide changes, all resulting in non-synonymous coding change. Disease was reflected by body weight and lung pathology.

In study 105036, SARS-CoV-2-MA10 (dose of 1 x 10^5 $CCID_{50}$) was administrated by intranasal route in BLB/c mice. Six animals/group were treated twice daily beginning four hours post infection by *per os* (PO) administration at dose levels 0, 300, 1000 mg/kg in two separate experiments. Mice were weighed prior to infection and then everyday thereafter to evaluate infection-associated weight loss. Animal were euthanized on study day 4 and lung lobes were collected for histopathology analysis and for evaluating lung virus titers. Due to the similarity of both study results, data was combined (n=12/group) and assessed. Treatment with PF-07321332 at both 300 or 1000 mg/kg oral twice (two times) a day (BID) doses significantly protected mice from weight loss and reduced virus lung titers by approximately 1.39 log or 1.91 log, respectively, compared to placebo treated group. Pharmacokinetics (PK) results (5 animal/group) revealed that the overall unbound Cmin of PF-07321332 in the BALB/c mouse was approximately 0.9x EC_{90} and 4x EC_{90} at the 300 mg/kg and 1000 mg/kg BID doses of PF-07321332. Therefore, PF-07321332 has antiviral efficacy in the mouse-adapted model of SARS-CoV-2, maintaining ~1× EC90 at Cmin. Histopathological analysis of lungs from the treated mice showed that most of the infected mice exhibited multifocal pulmonary lesions, however, this was significantly reduced in the 300 and 1000 mg/kg BID groups, respectively in the PF-07321332 treated mice compared to the untreated mice.

In study 022652, SARS-CoV-2-MA10 (dose of 2.5 x 10^4 PFU) was administrated by intranasal route in the 129-mouse strain. Six animals/group were treated twice daily beginning four hours post infection by PO administration at dose levels 0, 300, 1000 mg/kg. An additional 6 animals were treated orally with 1000 mg/kg PF-07321332 twice daily beginning twelve hours post infection. Mice were weighed prior to infection and then everyday thereafter to evaluate infection-associated weight loss. Animal were euthanized on study day 3 and lung lobes were collected for histopathology analysis and for evaluating lung virus titers. Treatment with PF-07321332 at 300, 1000 mg/kg (dosed 4h post infection), 1000 mg/kg (dosed 12h post infection) oral BID doses significantly protected mice from weight loss and reduced virus lung titers by approximately 1.1 log, 4.3 log and 4.2 log respectively, compared to placebo treated group. PK results (6 animal/group) revealed that the overall unbound Cmin of PF-07321332 was approximately 1.5x EC_{90} and 7x EC_{90} at the 300 mg/kg and 1000 mg/kg BID doses of PF-07321332. Treatment with PF-07321332 at a dose of 1000 mg/kg BID dosed 4h post infection or 1000 mg/kg BID dosed 12 h post infection significantly reduced histopathology scores (around 80% and 50%, respectively) when compared to vehicle control group. No significant reduction was observed at 300 mg/kg dosed at 4h post infection (around 16%).

Overall, only animal data with SARS-CoV-2 mouse adapted are available. No studies have been performed to evaluate effect of PF-07321332 treatment in infected animal model with the variants of SARS-CoV-2. Translability in clinic of impact on viral replication in lung in animal model warrants particular caution.

No animal studies have been performed to evaluate the reduction of viral load in the upper respiratory tract and the impact of PF-07321332 treatment on viral transmission. This could be of value for the ongoing development in prevention.

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Secondary Pharmacodynamics

In study 100054569, PF-07321332 was tested for potential secondary pharmacodynamic activity *in vitro* against a panel of enzymes, receptors and ion channels, with ≥ 50% inhibitory activity considered significant. No activity was observed when PF-07321332 was tested at 100 µM ((78x the predicted human unbound PF-07321332 Cmax at a BID dose of 300/100 mg PF-07321332/ritonavir, predicted Cmax unbound 2.56 µM).

In study 20LJ074, PF-07321332 was tested for inhibitory activity against 11 phosphodiesterase (PDE) subtypes (PDEs 1 to 11). The IC_{50} values were determined to be >200 µM for all PDE subtypes tested (78x the predicted human unbound PF-07321332 Cmax at a BID dose of 300/100 mg PF-07321332/ritonavir).

Safety Pharmacology

Five studies were conducted to address the safety pharmacology core battery, in line with the International Conference of Harmonization (ICH) guideline S7A requirements. All pivotal safety pharmacology study reports contain GLP compliance statements, indicating they have been conducted in accordance with the principles of GLP, in an OECD MAD adherent country.

- *In vitro*

Table 1 - human Ether-à-go-go-Related Gene (hERG) studies with PF-07321332

Type of study, GLP, Study no	Species, Gender and no/grp	Method of Admin, Duration of dosing	Concentrations	Safety pharmacology findings
hERG assay GLP 20LJ091 22/01/2021	*In vitro*	Human embryonic kidney cells (HEK293)	30, 300 µM Lot # PF-07321332-00-0018	Control: 2.0 ± 0.4% PF-07321332 30 µM : 2.5 ± 0.4% PF-07321332 300 µM : 5.9 ± 0.3% (statistically significant) Terfenadine 60 µM : 78.5± 2.7% IC_{50} value: > 300 µmol/L
Activity at Nav1.5 and Cav1.2 ion channels	*In vitro*	Nav1.5 and Cav1.2 ion channel expressed in CHO cells	0.003, 0.03, 0.3, 3, 30, 300 µM	IC_{50} value: > 300 µmol/L T+ Nav1.5 tetracaine : IC_{50} = 1.7 µM T+ Cav1.2 verapamil : IC_{50} = 2.9 µM

In the human ether-à-go-go-Related Gene (hERG) inhibition assay, administration of PF-07321332 at 300 µM resulted in statistically significant ($p < 0.05$) inhibition of hERG (5.9 ± 0.3%) when compared to the vehicle control (2.0 ± 0.4%),The IC_{50} for the inhibitory effect of PF-07321332 on hERG potassium current was not calculated but was estimated to be greater than 300 µM (>117x the predicted human unbound PF-07321332 Cmax at a BID dose of 300/100 mg PF-07321332/ritonavir).

The IC_{50} values for PF-07321332 inhibition of the Nav1.5 (peak) sodium and the Cav1.2 calcium channel currents were both determined to be >300 µM, the highest dose tested (>117x the predicted human unbound PF-07321332 Cmax at a BID dose of 300/100 mg PF-07321332/ritonavir).

- *Ex vivo*

Table 2 – *Ex vivo* studies

Type of study, GLP, Study no	Species, Gender and no/grp	Method of Admin, Duration of dosing	Concentrations	Safety pharmacology findings
Cardiovascular Assessment (Heart) Non-GLP 20LJ075 03/11/2020	*Ex vivo*	Guinea pig isolated Langendorff-perfused heart	0.03, 0.1, 0.3, 1, 3, 10, 30 and 100 µM Lot # PF-07321332-00-0007	No effect on cardiac contractility, left ventricular pressure, coronary perfusion pressure, PR, QRS or QT intervals
Cardiovascular Assessment (Aorta) Non-GLP 20LJ076 21/10/202O	*Ex vivo*	Rat isolated ascending aorta tissue	2 pM - 100 µM Lot # PF-07321332-00-0007	Vasoconstrictive Activity: no effect PF-07321332: IC_{50} > 100 µM Phenylephrine: IC_{50} =22.5 µM Vasorelaxant Activity: a statistically significant concentration-dependent vasorelaxation, IC_{50} = 50.3 µM

In the guinea pig isolated Langendorff-perfused heart model, PF-07321332 did not produce a statistically significant change in cardiac function or cardiac conduction at any of the concentrations tested (up to 100 µM, which is 39x the predicted human unbound PF-07321332 Cmax at a BID dose of 300/100 mg PF-07321332/ritonavir). In the rat isolated aorta tissue bath preparation, PF-07321332 produced a statistically significant concentration- dependent vasorelaxation when compared with the control. The IC_{50} was determined to be 50.3 µM, representing 20x the predicted human unbound PF-07321332 Cmax at a BID dose of 300/100 mg PF-07321332/ritonavir.

- *In vivo*

Table 3 - Safety pharmacology studies with PF-07321332

Type of study, GLP, Study no	Species, Gender and no/grp	Method of Admin, Duration of dosing	Doses (mg/kg)	Safety pharmacology findings
Pulmonary system (RR, TV, MV)	Rat/Wistar Han 6M/group	Oral gavage, Single dose 10 mL/kg (2% Polysorbate 80 in 0.5% [w/v] methylcellulose in purified water)	0, 0 (15% MTBE = 150 MTBE), 60, 1000	1000 mg/kg: ↑ RR (up to +44%), ↑ MV (+38%) (from 40-160 min)
Central nervous System (FOB, BT, LA) GLP 20GR274 26/01/2021	6M/group	Lot # PF-07321332-00-0018		FOB parameters: no effect quantitative locomotor assessment: 1000 mg/kg ↓ vertical movements (-36%) (first 5 min) ↑ horizontal (+298%) and vertical (+838%) movement (last 30 min)
Cardiovascular system (blood pressure, heart rate, ECG) GLP	Cynomolgus Monkey (telemetry) 2M/group	Oral gavage, BID 5 mL/kg (2% (v/v) Polysorbate 80 in 0.5% (w/v) methylcellulose in purified water) Lot # PF-07321332-00-0018	0, 0 (22.5 [11.5 BID] MTBE) 40 (20 BID) 150 (75 BID)	No clinical signs 0, 0 (MTBE), 40: none <u>150 mg/kg:</u> ↓ HR (-8 to -14 bpm) ↑ SBP (+4 mmHg),

20GR275 25/08/2021 (report amendment 1) Full report (12/02/2021)	Prior CV phase : at D1, all animal received one single dose of 150 (75 BID) to determine PK profile Cross over design: each animal will receive all 4 dose level at D9, D12, D16, D19	↑ DBP (+3-5 mmHg) ↑ MBP (+5 mmHg) Secondary to ↓ HR ↑ RR-I (+37-52 msec), ↑ PR-I(+3 msec), ↑ QT-I (+11-13 msec), ↓ QTc (-5 to -7 msec), ↓ LV+dP/dt max (-306 to -364 mmHg/sec) TK PK phase: 150 (75 BID) Cmax = 14.7 ± 9.24 µg/mL AUC24 = 131± 100 µg.h/ml

For the *in vivo* safety pharmacology studies, no toxicokinetics (TK) parameters were included (except one measure of plasma concentration at 150 mg/kg/day in cardiovascular monkey study 20GR275). PF-07321332 Cmax values were extrapolated from 2-week studies in rats. Exposure from a 4-week toxicity study is available; since Cmax observed in rats after 4-week administration were lower than those observed after 2-week administration, exposure margins extrapolated from the 2-week study in rat is acceptable. Exposure margins are expressed based on predicted human total PF-07321332 where a BID dose of 300/100 mg PF-07321332/ritonavir resulted in a Cmax of 4.14 µg/ml.

The central nervous system (CNS) and respiratory safety pharmacology studies were conducted in male Wistar Han rats in the same study but in different groups. Relating to the effects on pulmonary system, administration of 1000 mg/kg of PF-07321332 (Cmax 51.5 µg/ml from rat 2-wk study) single dose resulted in test article related higher respiratory rate (up to +44%) and minute volume (up to +38%) compared with vehicle controls from 40 to 160 minutes post dose. Relating to the effects on CNS, in the quantitative locomotor assessment, administration of 1000 mg/kg of PF-07321332 single dose resulted in test article-related lower number of mean vertical movement counts (-36%) during the first 5 minutes of the assessment period and higher number of mean horizontal (+298%) and vertical (+838%) movement counts during the last 30 minutes of the assessment period compared with vehicle controls. These effects on CNS and respiratory system were observed at exposures 12-fold higher than the anticipated clinical Cmax. A no observed effect level (NOEL) of 60 mg/kg is reported (Cmax 13.3 µg/ml from rat 2-wk study), associated with PF-07321332 exposures 3.2-fold higher than the anticipated clinical Cmax.

One dedicated cardiovascular safety pharmacology study was conducted in conscious telemetered male monkeys in a cross-over design. PF-07321332 administered at 150 (75 BID) mg/kg/day (Cmax = 14.7 µg/ml) produced heart rate (HR) decreases of down to -14 bpm from 0.75–16.00 HPD and increased systolic, diastolic and mean blood pressure (up to +5 mmHg) from 0.75–5.5 HPD (diastolic only) and 7.25-9.00 HPD. The RR-interval was increased by up to +52 msec 0.75–16.00 HPD, consistent with the decrease in HR during this same time. Increases in both the PR interval (+3 msec) and QT-interval (up to +13 msec) were observed during the 0.75-9.00 HPD period, which were considered secondary to the decrease in HR. When the QT interval was corrected for HR (QTc), there was a test article-related decrease (down to -7 msec) during the 7.25-16.00 HPD period. PF-07321332 at 150 (75 BID) mg/kg/day also produced decreases in LV +dP/dt max (down to -364 mmHg/sec) during the 0.75-9.00 HPD period. All measures returned to vehicle control levels within 24 HPD. These cardiovascular effects were observed at exposures 3.5-fold higher than the anticipated clinical Cmax. A no observed effect

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level (NOEL) of 40 (20 BID) mg/kg is reported, associated with PF-07321332 exposures 0.33-fold higher than the anticipated clinical Cmax.

2.3.2 Pharmacokinetics

The pharmacokinetics of PF-07321332 were determined in rats, dogs, monkeys and rabbits**.**

Absorption

Two single dose administration studies have been performed (studies 103131 in rat and 111728 in monkeys). PF-07321332 was rapidly absorbed and exhibited a moderate CL, with a moderate to low Vss, resulting in t½ values of 5 hours in rats and <1 hour in monkeys. Following oral dosing, the overall bioavailability was moderate to high (29 to >100%) in rats but low (<10%) in monkeys. In the repeat dose toxicity studies, mean systemic exposures increased with increasing dose and there were no consistent sex-related differences in rats and monkeys.

Repeated dose PK parameters have been collected in repeated dose toxicity GLP-studies (up to 1-month). There were no consistent sex-related differences in systemic exposure, and mean exposure of PF-07321332 increased with increasing dose in rats and monkeys. In rats following repeat administration, a decrease in PF-07321332 AUC_{24} was observed across dose groups on Day14 or D25 compared with Day 1 (D14/D1: 0.18 to 0.74, D25/D1 0.38 to 0.56). In monkeys, AUC_{24} of PF-07321332 increased on D14 or D25 compared to Day 1 with accumulation ratios up to 1.7 (D14/D1: 0.83-1.7, D25/D1: 1.12-1.55). Systemic exposure increased with increasing doses in pregnant rats and rabbits.

Distribution

PF-07321332 was moderately bound to plasma proteins in rat, monkey and human and similar across these species. Concentration-dependent protein binding was observed in rabbit plasma (2 to 200 µM, 1% to 80%) but not in rat, monkey and human (0.3 to 10 µM, 31-48%) (study 010657). PF-07321332 preferentially distributed into plasma relative to blood cells in rat (0.83), monkey (0.68) and human (0.60) (study 100444). No *in vivo* distribution study (QWBA) was performed at this time.

Metabolism

The metabolism of PF-07321332 was evaluated *in vitro* in liver microsomes (mouse, rat, hamster, rabbit, monkey, and human), hepatocytes (rat, monkey, and human), and *in vivo* in rat and monkey. A total of six metabolites were detected arising from hydroxylation, dehydrogenation, and hydrolysis reactions. The major metabolite was M4 (PF-07329268), an oxidative metabolite arising from hydroxylation at the 5-position of the pyrrolidinone ring, resulting in a pair of interconverting diastereomers. In plasma of rats and monkeys, unchanged parent drug was by far the most prevalent drug-related entity, with M4 as a major metabolite in monkey. All oxidative metabolites were formed by CYP3A4/5, with other CYP enzymes contributing very minor amounts. Unchanged parent drug was the most prevalent drug-related entity in rat and monkey plasma and in rat urine and bile, with M4 as the most prevalent metabolite in monkey plasma (study 084546). CYP3A4 is predicted to be the major contributor (fm = 0.99) to the *in vitro* metabolism of PF-07321332; no significant CYP3A5 contribution is expected to the metabolism of PF-07321332 (study 072016). Besides oxidative biotransformation pathways, a metabolite M5 (PF-07320267) obtained through a hydrolytic cleavage across an amide bond in PF-07321332, was also detected as a minor metabolite in circulation and excreta from animals (study 082057). M7 (PF-07852082), the acyl-glucuronide conjugate of M5 (by UGT2B4 and 2B7), was identified in human urine in trace amounts. The remaining 13.5% of metabolism through the UGT pathway was unassigned (study 021055). Unchanged PF-07321332 was the predominant drug-related

entity in circulation in plasma from healthy adults administered with a single oral dose of 300 mg PF-07321332 in the presence of ritonavir (study 090141).

Excretion

Urinary and/or biliary excretion of PF-07321332 was assessed in single-dose PK studies after intravenous (IV) or oral dosing of PF-07321332 to rats (study 103131) and monkeys (study 111728). The percentage of PF-07321332 dose excreted unchanged was 17% in the urine, 9% in the bile, and up to 11% in the feces in rats, and 7% in the urine and 4% in the feces in monkeys. Based on the results of clinical study 021626 (mass balance study in healthy volunteers), the primary excretion routes of orally administered PF-07321332 with ritonavir were urinary excretion of unchanged drug.

Pharmacokinetic Drug Interactions

Drug-Drug Interactions (DDI) studies are reported in the clinical part of this report (please see below).

2.3.3. Toxicology

The nonclinical toxicology package for PF-07321332 has been designed in line with the requirements of ICH M3 (R2) and taking into consideration the proposed treatment period of 5-days in duration. The species used for the GLP compliant pivotal studies included rats and monkeys and are considered appropriate by CHMP, based on the similar PK profile seen in these species compared to humans (*in vitro* comparison data only at this stage). Furthermore, the pharmacological target of PF-07321332 is an exogenous entity (virus-specific protein) and therefore there are no pharmacologically relevant species. The oral route of administration was selected as it is the route of clinical administration. Rats were administrated once daily and monkeys twice daily (no supportive $T_{1/2}$ in monkey) as it is recommended in humans. Six toxicity studies have been performed: two preliminary studies (4-day) and four pivotal studies (two 2-week and two 1-month repeated-dose studies). Final reports have been submitted except for the 1-month study in rats and in monkeys (unaudited draft). A rat fertility study (unaudited draft submitted), and two EFD studies in rats and rabbits are completed, with a rat PPND study currently ongoing. A standard battery for assessing genotoxicity potential is complete and final reports have been submitted. Margins of exposure were calculated on total Cmax and AUC_{24} (more conservative approach than the one with unbound Cmax and AUC_{24}). The calculation of these margins of exposure are based on predicted human Cmax/AUC_{24} which could not be validated given that the PKPOP available at this stage has particular limitations, notably only based on PK data from healthy volunteers (see clinical PK part of this AR). The margins of exposure are therefore only indicative at this stage and it is expected to be further substantiated at the time of the MAA with the awaited provision of a relevant PKPOP model including PK data collected from the patients enrolled in the EPIC-HR study with relevant covariables to be studied (notably age, weight, formulation,…).

Single dose toxicity studies

No dedicated studies with PF-07321332 have been conducted. This is considered acceptable by CHMP, given the availability of the more relevant repeat dose toxicity studies.

Repeat dose toxicity studies

The toxicity program includes six studies: two 4-d preliminary studies and four pivotal studies in rats and in monkeys up to 1-month duration. Except for the 2-week study in monkeys, all pivotal studies included a 2-week recovery period. As outlined in ICH M3 (R2) for a therapeutic indicated for up to 2-weeks duration of administration, a 1 month study is expected in both rodent and non-rodent species and therefore the duration of the provided studies is in-line with the expectations for the proposed posology of 5-days treatment. PF-07321332 was administered as a methyl tert-butyl ether (MTBE)

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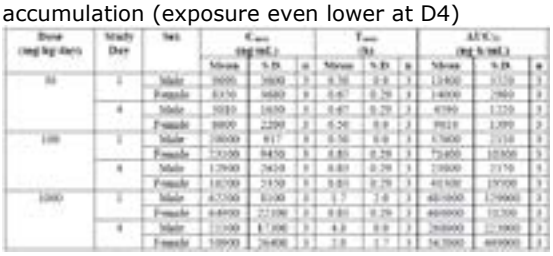
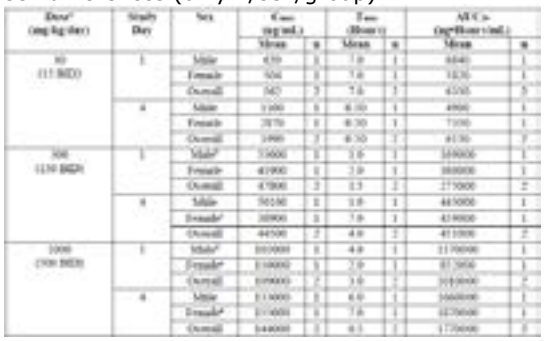
solvate, in the 2-week studies, and as a 50% PF-07321332: 50% HPMCAS-MG (hydroxypropyl methylcellulose acetate succinate-medium granular) spray dried dispersion suspension, in the 4-week studies. The 2-week studies included two control groups, one with administration of vehicle and the other with administration of vehicle spiked with 15% MTBE at an amount equivalent to that associated with the PF-07321332 high dose. Similarly, in the 4-week studies, vehicle control animals were administered an amount of HPMCAS-MF (medium fine) equivalent to the amount of HPMCAS administered to the PF-07321332 high dose group. The company has briefly addressed how the PF-07321332 forms used in the pivotal studies - PF-07321332 as methyl tert-butyl ether (MTBE) solvate or 50% PF-07321332: 50% HPMCAS-MG (hydroxypropyl methylcellulose acetate succinate-medium granular) spray dried dispersion suspension - compare with the PF-07321332 present in the medicine Paxlovid, indicating that the tested forms improved systemic exposures. This issue will be further discussed during the MAA procedure. As applicable, the company is also expected to discuss the impact of any identified differences on safety evaluation.

Regarding data on repeated dose toxicity in the CONDITIONS OF USE, information in section 6. "OTHER INFORMATION" is in accordance with the data provided for PF-07321332 and with the contents of the SmPC for the medicinal product Norvir (with ritonavir), as approved in the EU.

Non pivotal studies

Table 4 - Summary of non-pivotal repeat-dose toxicity studies

Study ID/ GLP	Species/ Sex/Number/ Group	Dose (mg/kg) /Route/	MTD (mg/kg/day)	Noteworthy findings
4 days 20GR250 Non-GLP 19/11/2020	Rat/ Wistar Han 3M+3F/group	Oral gavage, QD, 0, 30, 100, 1000 10 mL/kg (2% [v/v] polysorbate 80 in 0.5% [w/v] methylcellulose in purified water/Suspension) Lot PF-07321332-00-0009	Not reported	None NOAEL: Not determined due to non-reversible tox in testes at 1.5 TK Cmax/AUC: F>M, dose-dependent increase, no accumulation (exposure even lower at D4)  D4 1000 mg/kg/d: Cmax = 21,300 ng/mL (M) 50,900 ng/mL (F) AUC24 = 268,000 ng·h/mL (M) 562,000 ng·h/mL (F)
4 days 20GR271 Non-GLP 20/11/2020	Monkeys/ cynomolgus 1M+1F/group	Oral gavage, BID (6h apart) 0, 30 (15 BID), 300 (150 BID), or 1000 (500 BID) 5 mL/kg (2% [v/v] polysorbate 80 in 0.5% [w/v] methylcellulose in purified water/Suspension) Lot	300<MTD<1000	≥300: emesis resulting in fluid loss, slight body weight loss, and clinical pathology changes indicative of an acute phase/inflammatory response and hemoconcentration/dehydration as the only test article-related effects TK dose-dependent increase, no accumulation, no sex differences (only 1/sex/group)  D4 1000 mg/kg/d: Cmax = 144,000 ng/mL AUC24 = 1,770,000 ng.h/mL

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Pivotal studies

- *2-week toxicity study in rats plus a 2-week recovery period*

Table 5 - 2-week toxicity study in rats plus a 2-week recovery period

Study ID/GLP/ Duration	Species/Sex/ Number/Group	Dose (mg/kg/week)/ Route	NOAEL /MTD (mg/kg/day)
2 wk with 2-wk recovery (+genotox assessment) 20GR276 GLP 15/04/2021 (Amendment 1)	Rat/ Wistar Han 10/sex/group (main) + 5/sex/group (rec)	0, 60, 200, 1000 Administrated as a MTBE solvate (1:1) Once dialy Oral gavage Lot # PF-07321332-00-0018	1000 mg/kg/day D14: Cmax = 51.5 µg/mL AUC24 = 292 µg•h/mL

Mortality: none

Clinical signs: none

Body weight, food consumption: none

Ophthalmic observations: None

Haematology/coagulation:
↑ PT ≥ 60 (M, 1.16x-2.50x), 1000 (F, 1.4x)
↑ APTT ≥ 200 (M, 1.09x-1.19x), 1000 (F, 1.11x), is unclear but
indicates alterations in the coagulation pathway.
↑ PLT 1000 (both sexes, 1.22x-1.25x),
↓ RBC mass parameters (HGB 0.95x, HCT , RBC) and ↑ FIB (F, 1.10x) 1000 mg/kg/day
(completely recovered)

Clinical chemistry:
↑ GLOB 1000 (both sexes 1.07x), ↓ A:G (F, 0.90x), ALP (F, 0.66x) and ↑ CHOL (F, 1.33x)
(completely recovered)

Urinalysis
↓ pH 1000 (M, 0.90x)
(completely recovered)

Organ weights:
↑ liver (both sexes) 1000, correlating microscopic finding of periportal hepatocyte hypertrophy
↓ heart (F) 1000
(completely recovered)

Histopathology:
LIVER: minimal to mild periportal hepatocellular hypertrophy (M 1000 and F ≥ 200) with increased incidence and severity of periportal hepatocyte vacuolation F,
(fully reversible), consistent with microsomal enzyme induction (considered non adverse)

THYROID: minimal to mild follicular cell hypertrophy (M+F 1000
(fully reversible), consistent with microsomal enzyme induction (considered non adverse)

KIDNEY: MTBE-related hyaline droplet in the renal tubule (M all dose or vehicle MTBE) (partially reversible), considered to be male rat specific

TK analysis
No sex differences, dose-dependent increases, no accumulation (systemic exposure lower at D14 in comparison to D1, 0.18 to 0.74)

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Dose (mg/kg/day)[a,b]	Day	Sex	C_{max} (µg/mL)	T_{max} (h)	AUC_{24} (µg•hours/mL)	AUC_{24}/Dose (µg•hours/mL/mg/kg)
60	1	Male	11.0	0.50	25.0	0.417
		Female	14.8	0.50	29.8	0.497
		Overall	12.9	0.50	27.3	0.455
	14	Male	8.31	0.50	12.1	0.202
		Female	18.3	0.50	22.2	0.370
		Overall	13.3	0.50	17.2	0.287
200	1	Male	33.0	0.50	294	1.47
		Female	41.0	0.50	286	1.43
		Overall	37.0	0.50	291	1.46
	14	Male	23.8	0.50	53.2	0.266
		Female	30.4	0.50	108	0.540
		Overall	27.1	0.50	80.5	0.403
1000	1	Male	72.4	4.0	961	0.961
		Female	70.8	1.0	630	0.630
		Overall	62.1	2.0	796	0.796
	14	Male	50.6	2.0	283	0.283
		Female	52.3	2.0	299	0.299
		Overall	51.5	2.0	292	0.292

Interspecies comparison

Key Response(s)	Dose (mg/kg/day)	C_{max}[a] [µg/mL] (Total)	AUC_{24}[a] [µg•h/mL] (Total)	Exposure Margin[b] C_{max} (Total)	Exposure Margin[b] AUC_{24} (Total)
14-Day Oral Gavage GLP Toxicity Study in Rats (15 sex/group) (20GR276)					
↑ PT (M)	60	13.3	17.2	3.2	0.23
All of the above plus: ↑ APTT (M); periportal hepatocyte hypertrophy (F)	200	27.1	80.5	6.5	1.2
All of the above plus: ↑ PT (F); ↑ APTT (F); ↑ PLT; ↓ RBC mass (F); ↓ FIB (F); ↑ GLOB; ↑ CHOL (F); ↓ ALP (F); ↓ A/G (F); ↓ urine pH (M); ↓ heart weight (F); ↑ liver weight; periportal hepatocyte hypertrophy (M); periportal hepatocyte vacuolation (F); thyroid follicular cell hypertrophy	1000 (NOAEL)	51.5	292	12	4.3

- *2-week toxicity study in monkeys*

Table 6 - 2-week toxicity study in monkeys

Study ID/GLP/ Duration	Species/Sex/ Number/Group	Dose (mg/kg/week)/ Route	NOAEL /MTD (mg/kg/day)
2 wk with 2-wk recovery 20GR289 GLP 10/03/2021	Monkey/cynomolgus 3/sex/group	0, 40 (20 BID), 100 (50 BID), or 600 (300 BID) Administrated as a MTBE solvate (1:1) Twice daily (6h apart) Oral gavage Lot # PF-07321332-00-0018	600 mg/kg/day D15: Cmax = 106 µg/mL AUC24 = 1220 µg.h/mL

Mortality: none

Clinical signs: emesis (M 600, F ≥ 100)

Body weight:

↓ bw (1M D15, 0.91x)

Food consumption: none

Ophthalmic observations: None

ECG/heart rate: none

Haematology/coagulation:
↑ fibrinogen (2M+1F, 600, 1.72x-2.09x),
↓ sodium (0.96x) chloride (0.93x) (1M, 600)

Urinalysis
↓ pH 1000 (M+F, 600, 0.73x-0.80x)

Organ weights: none

Histopathology: none

TK analysis
No sex differences, dose-dependent increases, no accumulation (M 0.83 to 1.7x, F 0.56 to 1.6x)

Dose (mg/kg/day)[a,b]	Day	Sex	C_{max} (µg/mL)	AUC_{tau} (µg•h/mL)
40 (20 BID)	1	Male	1.72	6.14
		Female	1.86	14.7
		Overall	1.79	10.4
	15	Male	2.65	8.79
		Female	2.18	10.4
		Overall	2.47	9.61
100 (50 BID)	1	Male	6.80	38.7
		Female	15.8	129
		Overall	11.3	84.2
	15	Male	7.91	33.1
		Female	15.6	72.1
		Overall	11.8	52.6
600 (300 BID)	1	Male	65.6	795
		Female	53.5	651
		Overall	59.6	723
	15	Male	121	1399
		Female	90.4	1060
		Overall	106	1220

a. Animals were dosed orally twice daily for 15 days.
b. 3 animals/sex/dose group

Interspecies comparison

Key Response(s)	Dose (mg/kg/day)	C_{max}[a] [µg/mL] (Total)	AUC_{24}[a] [µg•h/mL] (Total)	Exposure Margin[b] C_{max} (Total)	Exposure Margin[b] AUC_{24} (Total)
15-Day BID Oral Gavage GLP Toxicity Study in Cynomolgus Monkeys (3 sex/group) (20GR289)					
No findings	40 (20 BID)	2.42	9.61	0.58	0.14
† Emesis	100 (50 BID)	11.8	52.6	2.9	0.77
All of the above plus: ↓ BW	600	106	1220	26	18

- *4-week toxicity study in rats plus a 2-week recovery period*

Table 7 - 4-week toxicity study in rats plus a 2-week recovery period

Study ID/GLP/ Duration	Species/Sex/ Number/Group	Dose (mg/kg/week)/ Route	NOAEL /MTD (mg/kg/day)
4 wk with 2-wk recovery 21GR122 GLP 22/11/2021 (unaudited draft)	Rat/ Wistar Han 15/sex/group (main) including 5/sex/group (rec Group vehicle and HD)	0, 60, 200, 1000 Administrated as a 50% spray dried dispersion formulation Once dialy Oral gavage Lot # BREC-2212-122	1000 mg/kg/day D25: Cmax = 44.5 µg/mL AUC_{24} = 548 µg.h/mL

Mortality: no test article related death (1F 60 found in the restrainer after TK blood collection)

Clinical signs: sporadic reports of salivation (all doses), soft feces (200 (single animal) and 1000 mg/kg/day)

Body weight, food consumption: none
Ophthalmic observations: none

Haematology/coagulation:
↑ PLT ≥ 200 (both sexes, 1.12x-1.28x),
↑ PT ≥ 200 M and 1000 F (1.06x-1.15x)
(fully reversible), considered non adverse

Clinical chemistry: none
Urinalysis: none

Organ weights:
↑ liver ≥ 60 (both sexes, 1.07x-1.83x), correlating microscopic finding of minimal to mild periportal hepatocyte hypertrophy ≥ 200 (both sexes) (completely recovered except for M 1000 partially reversible)

Histopathology:
LIVER: ≥ 200 periportal hepatocellular hypertrophy (both sexes) with increased incidence and severity of periportal hepatocyte vacuolation F 1000,
THYROID: ≥ 60 (M) and ≥ 200 (F) thyroid follicular cell hypertrophy
PITUITARY GLAND: ≥ 60 (M) vacuolation of endocrine cells in the pars anterior (distalis)
(fully reversible at 60 and 200, partially at M1000)
consistent with microsomal enzyme induction (considered non adverse)

TK analysis
No sex differences, dose-dependent increases, no accumulation (systemic exposure lower at D25 in comparison to D1, 0.38 to 0.56)

Dose (mg/kg)*	Day	C_{max} (ng/mL)	T_{max} (hours)	AUC_{24} (ng·h/mL)
60	1	16200	0.50	54800
	25	12800	0.50	19200
200	1	55000	1.0	252000
	25	26000	1.0	94900
1000	1	87500	2.0	982000
	25	44500	1.0	548000

Interspecies comparison

Key Response(s)	Dose (mg/kg-day)	C_{max} (ng/mL) (Total)	AUC_{24} (ng·h/mL) (Total)	Exposure Margin C_{max} (Total)	Exposure Margin AUC_{24} (Total)
1-Month Oral Gavage GLP Toxicity Study in Rats (15 sex/group) (21GR122)					
Salivation; ↑ liver weight; thyroid follicular cell hypertrophy; pituitary gland endocrine cells of the pars anterior cytoplasmic vacuolation (M)	60	12.8	19.2	3.1	0.28
All of the above plus: soft feces; ↑ platelets; ↑ PT (M); periportal hepatocellular hypertrophy	200	26.0	94.9	6.3	1.4
All of the above plus: ↑ PT (F);	1000 (NOAEL)	44.5	548	11	8.0

- *4-week toxicity study in monkeys plus a 2-week recovery period*

Table 8 - 4-week toxicity study in monkeys plus a 2-week recovery period

Study ID/GLP/ Duration	Species/Sex/ Number/Group	Dose (mg/kg/week)/ Route	NOAEL /MTD (mg/kg/day)
4 wk with 2-wk recovery 21GR125 GLP 22/11/2021 (unaudited draft)	Monkey/cynomolgus 5/sex/group (main) Including 2/sex/group (rec, Group vehicle and HD)	0, 40 (20 BID), 100 (50 BID), or 600 (300 BID) Administrated as a 50% spray dried dispersion formulation Twice daily (6h apart) Oral gavage Lot # BREC-2212-124	600 mg/kg/day D28: Cmax = 87.5 µg/mL AUC_{24} = 991 µg.h/mL

Mortality: none

Clinical signs: emesis (sporadic occurrence: 600 M/F (9/10), vehicle (2M/5), 440 (1F/3) and 100 (1F/3)

Body weight: none

Food consumption: none

Ophthalmic observations: None

ECG/heart rate: none

Haematology/coagulation:
↑ fibrinogen (M/F, 600, 1.20x - 1.91x) (fully reversible) also observed in control animals but lower magnitude
↑ ALT (1.63-3.53x) and/or AST (2.68x - 7.41x) (2M+1F, 600) (reversible assessment possible only for 1F: fully reversible)

Urinalysis: none

Organ weights: none

Histopathology: none

TK analysis: No sex differences, dose-dependent increases, no accumulation (1.12 to 1.55x)

Dose (mg/kg/day)	Day	Mean C_{max} (ng/mL)	Mean AUC_{24} (ng•h/mL)
40[a]	1	1250±584	4110±1340
	28	1380±700	5620±1420
100[b]	1	5320±3060	29600±12100
	28	7800±3440	45900±16800
600[b]	1	76600±21300	885000±239000
	28	87500±21000	991000±227000

a. 3 animals/sex/group with serial sampling.
b. 5 animals/sex/group with serial sampling.

Interspecies comparison

Key Response(s)	Dose (mg/kg/day)	C_{max}[a] [µg/mL] (Total)	AUC_{24}[a] [µg•h/mL] (Total)	Exposure Margin[b] C_{max} (Total)	Exposure Margin[b] AUC_{24} (Total)
1-Month BID Oral Gavage GLP Toxicity Study in Cynomolgus Monkeys (3 sex/group) (21GR125)					
No findings	40 (20 BID)	1.38	5.62	0.33	0.08
No findings	100 (50 BID)	7.80	45.9	1.9	0.67
↑ Emesis; ↑ ALT (M); ↑ AST; ↑fibrinogen	600 (300 BID) (NOAEL)	87.5	991	21	14

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The toxicity of PF-07321332 was evaluated in two non-pivotal (non-GLP) and 4 pivotal GLP repeat-dose toxicity studies up to 1 month in duration in rats and cynomolgus monkeys. There were no adverse findings in any of the studies. The NOAELs were the highest doses administered. All non-adverse test article related clinical findings observed in rats (salivation and soft feces, increases in aPPT, PT, PLT count) or in monkeys (sporadic occurrence of emesis, increases in ALT, AST, fibrinogen) are monitorable in human. Microscopic findings observed in liver, thyroid gland and pituitary gland in rats are consistent with a rat-specific response to hepatic enzyme induction. This mechanism is usually considered to have little to no relevance to humans.

In terms of toxicokinetics, in rats, systemic exposures increased with dose and decreased with treatment duration. In monkeys, while systemic exposures also increased with dose, there was not a clear decrease in exposure with treatment duration. On the contrary, in the 4 weeks study, at the two highest tested doses, exposures were higher at the end of treatment compared to Day 1. There were no consistent sex-related differences in systemic exposure. There were no quantifiable concentrations of PF-07321332 in plasma samples from control animals from the studies conducted in monkeys (2 and 4 weeks) and the 4 week-study in rats. Regarding the 2-weeks study in rats, there were quantifiable concentrations of PF-07321332 in plasma samples from two control animals, both collected at 2 hours post-treatment. The two concentrations were approximately 5 to 6 times that of the lower limit of quantitation (LLOQ) of the assay (LLOQ = 0.0100 µg/mL) and < 0.5% of the overall mean C_{max} in the lowest dose group (60 mg/kg/day). Furthermore, since these concentrations were only observed at one single time point each, they were considered to not be consistent with inadvertent dose administration and to have no impact on data interpretation.

Genotoxicity

PF-07321332 was assessed in a series of genetic toxicity studies consisting of the microbial bacterial reverse mutation, *in vitro* cytogenetic (micronucleus in human lymphoblastoid TK6 cells), and *in vivo* rat micronucleus assays up to 1000mg/kg/day. All *in vitro* tests were conducted with and without exogenous metabolic activation using concentrations up to applicable guideline limits or those limited by cytotoxicity or insolubility. PF-07321332 was not genotoxic in either *in vitro* or *in vivo* assays. The standard battery performed, and negative results are considered acceptable by CHMP.

Carcinogenicity

No carcinogenicity studies have been completed to date. Considering that the duration of treatment is limited to 5 days then the absence of carcinogenicity studies is in-line with the recommendations of ICH S1A. There are no microscopic findings from the limited duration repeat dose toxicity studies indicative of pre-neoplastic changes.

Reproductive and developmental toxicity

A set of three reproductive and developmental toxicity studies conducted with PF-07321332 administered orally in rats and rabbits were submitted. Fertility and embryo-foetal development studies were completed, while the pre- and postnatal development study is ongoing. For the fertility study, an unaudited draft study report was submitted; final study reports were available for the other completed studies. In all completed studies, PF-07321332 was administered, once daily by oral gavage, as a 50% PF-07321332: 50% HPMCAS-MG (hydroxypropyl methylcellulose acetate succinate-medium granular) spray dried dispersion. Vehicle control animals (0 mg/kg/day) were administered an amount of HPMCAS-MF (medium fine) equivalent to the amount of HPMCAS administered to the PF-07321332 high dose group. The use of medium fine, instead of medium granular, HPMCAS in the control group was justified, by the company, based on the particle size of the 50% PF-07321332: 50% HPMCAS-MG spray dry dispersion.

Table 9 - Overview of completed reproductive toxicity studies with PF-07321332

Study type/ Species Study ID / GLP	**Route, duration, doses**	**Main endpoints**
FEED Rat (Wistar) – 20/sex/group 21GR146 GLP: Yes	Oral (gavage) Males: 14 days premating to sacrifice (total 32 days) Females: 14 days premating to GD6 (C-section GD14) 0, 60, 200, 1000 mg/kg/day	F0 animals: mortality, clinical observations, body weight, food consumption, cohabitation, macroscopic examination, ovarian and uterine examination, placental examination, toxicokinetics (C0.5h on GD10)
EFD Rat (Wistar) – 20 timed-pregnant females/ group 21GR132 GLP: Yes	Oral (gavage) GD 6-17 (C-section GD21) 0, 100, 300, 1000 mg/kg/day	F0 animals: mortality, clinical observations, body weight, food consumption, macroscopic examination, ovarian and uterine examination, gravid uterine weight, placental examination, toxicokinetics (GD17) F1 animals: number, sex, body weight, external/visceral/skeletal examinations
EFD Rabbit (NZW) – 20 timed-pregnant females/ group 21GR126 GLP: Yes	Oral (gavage) GD 7-19 (C-section GD29) 0, 100, 300, 1000 mg/kg/day	F0 animals: mortality, clinical observations, body weight, food consumption, macroscopic examination, ovarian and uterine examination, gravid uterine weight, placental examination, toxicokinetics (GD19) F1 animals: number, sex, body weight, external/visceral/skeletal examinations

FEED: fertility and early embryonic development; EFD: embryo-fetal development; GD: day of gestation

In the fertility study, there was no adverse effect of PF-07321332 on parental endpoints and on the reproductive performance of male and female rats treated at doses up to 1000 mg/kg/day from 14 days premating. C-section data did not highlight any treatment-related adverse effect on early embryonic development in the treated vs. concurrent control group. However, mean control group values for pre- and post-implantation losses seemed rather high, resulting in lower mean number of live embryos. Since a treatment-related effect on post implantation loss was reported neither in rat nor in rabbit embryo-fetal studies at doses up to 1000 mg/kg/day, any treatment-related effect on this endpoint does not seem likely. Regarding preimplantation loss, it is noted that the mean control group value was exceeded in the study control group while the reported values in treated group lied within the historical control range. At the NOAEL of 1000 mg/kg/day for parental toxicity and fertility, the AUC-based exposure ratio reached 4.3.

In the rat embryo-foetal development study, PF-07321332 was not shown to induce maternotoxicity, foetotoxicity or teratogenicity at doses up to 1000 mg/kg/day administered during the whole period of organogenesis. Fetal examination showed increased litter and fetal incidences of 27th presacral vertebrae (skeletal variation) at the high dose level compared to concurrent controls (litter: 6%, 0%, 5%, 21%; fetal: 0.93%, 0.00%, 0.56%, 4.29%) and outside historical control range (litter: 0-10.5%; fetal: 0-2.4%). Since there were no associated skeletal malformations or variations in associated structures, or any other adverse effect on embryo-foetal development, this finding could be considered as non-adverse. Overall, the maternal and developmental NOAEL was 1000 mg/kg/day in rats. At this dose level, the AUC-based exposure ratio was 7.8.

In the rabbit embryo-foetal development study, slight effects on maternal body weight gain and food consumption were noted during the treatment period at the high dose level of 1000 mg/kg/day, but were not considered as adverse based on low magnitude of difference from control and lack of impact on absolute body weights. PF-07321332-related, adverse, lower fetal weight (0.91x control) was observed at 1000 mg/kg/day. At fetal examination, the fetal and/or litter incidences of a skeletal malformation (fused sternebrae) and visceral/skeletal variations (small gallbladder, misaligned sternebrae, bent hyoid arch) were increased compared to those in both concurrent and historical

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controls. It was however noted that the historical control database in the performing facility is quite limited, and the company clarified further that the abovementioned findings were not considered as treatment-related taking into consideration their incidences in larger historical control databases generated from testing facilities involving animals from the same source and strain and using known foetal procedures. Overall, the developmental NOAEL in rabbits was 300 mg/kg/day and corresponds to an AUC-based exposure ration of 2.8.

In the embryo-fetal development study in rabbits, but not in the other two reproductive toxicity studies, there were quantifiable concentrations of PF-07321332 in plasma from control animals (22/25 samples). These concentrations ranged from just above LLOQ (10.0 ng/mL) up to ~16x LLOQ (157 ng/mL). However, since the concentrations in individual animals did not demonstrate the time-dependent change in concentration relative to time post-dose that was generally observed in animals administered the test article, it was considered unlikely that control rabbits were administered the test article. However, the amount of control plasma samples with quantifiable concentrations of PF-07321332 may lead to question the validity of the toxicokinetic data obtained from this study. This issue will have to be discussed by the company at the time of the MAA procedure.

As for the repeated dose toxicity studies, the company briefly addressed how the PF-07321332 form used in the reproductive toxicity studies - 50% PF-07321332: 50% HPMCAS-MG (hydroxypropyl methylcellulose acetate succinate-medium granular) spray dried dispersion suspension - compares with the PF-07321332 present in the medicine Paxlovid. This issue will be further discussed during the MAA procedure. As applicable, the company is also expected to discuss the impact of any identified differences on safety evaluation.

Regarding ritonavir, developmental toxicity was identified in rats and rabbits mainly at maternally toxic dose levels, whereas there was no effect on fertility in rats[1].

Based on the nonclinical data provided and findings to date, use of Paxlovid is not recommended in pregnant women and women of childbearing potential not using contraception.

Local tolerance

No dedicated local tolerance studies with PF-07321332 have not been conducted. No effect of GI tract was observed in pivotal studies in rats and monkeys.

Phototoxicity

PF-07321332 presents no absorption peaks (UV-Vis) with molar extinction coefficient (MEC) exceeding the threshold of 1000 M^{-1} cm^{-1} thus PF-07321332 does not present with phototoxicity potential.

Impurities

Standalone studies with administration of impurities of PF-07321332 have not been conducted at this early stage of development because the drug substance and drug product processes are still in development and should be discussed as part of the MAA.

Combination toxicity

No combination studies with administration of PF-07321332 with ritonavir have been conducted or have been planned. Ritonavir is already marketed as a PK enhancer with well characterized nonclinical and clinical safety profile. No overlapping or additive toxicities between PF-07321332 and ritonavir are expected since no target organs have been identified after PF-07321332 administration rats and monkeys up to 1-month duration. A combination toxicity study, therefore, will not provide any

[1] SmPC adopted for NORVIR, https://www.ema.europa.eu/en/documents/product-information/norvir-epar-product-information_en.pdf

additional information beyond the known individual toxicity profiles of PF-07321332 and ritonavir. This is considered acceptable by CHMP.

Discussion on non-clinical aspects

PF-07321332 is an orally bioavailable selective for coronavirus the SARS-CoV-2 $3CL^{pro}$ inhibitor showing little or no activity against a panel of human proteases, as well as HIV protease. Since the $3CL^{pro}$ from human coronaviruses are structurally similar and share a high degree of conservation at the active site of the enzyme, the ability of PF-07321332 to inhibit the $3CL^{pro}$ of other coronaviruses (SARS-CoV-1, HCoV-229E, MERS-CoV, HCoV-OC43, HCoV-HKU1, and HCoV-NL63) was also confirmed; thereby, indicating a potential for broad spectrum anti-coronavirus activity. PF-07321332 also demonstrated selectivity for coronavirus $3CL^{pro}$.

The antiviral activity of PF-07321332 against SARS-CoV-2 was evaluated in VeroE6 cells, enriched for expression of the cellular ACE-2 receptor, in the absence or presence of an efflux inhibitor. PF-07321332 exhibited antiviral activity against SARS-CoV-2 infection of the physiologically relevant dNHBE cells, a primary human lung alveolar epithelial cell line (EC_{50} value of 61.8 nM and EC_{90} value of 181 nM) after 3 days of drug exposure. The antiviral activity of PF-07321332 was measured against SARS-CoV-1 with EC_{50} value 0.151 µM in the presence of an efflux inhibitor, HCoV-229E with EC_{50} value 0.190 µM, and MERS-CoV with EC_{50} value 0.166 µM in the presence of an efflux inhibitor thus suggesting potential for pan-coronavirus treatment.

Ritonavir, as a P-gp and CYP3A4 inhibitor, is recommended by the company to be applied as a booster of PF-07321332 therapeutic effects. Ritonavir had no effect on viral replication in A549-ACE2 cells up to the highest concentration tested, 3 µM. Cell cytotoxicity was also not observed in the A549-ACE2 cells up to 3 µM for PF-07321332 or ritonavir. The potency of PF-07321332 in combination with fixed doses of ritonavir did not exhibit a monotonic relationship as evidenced by less potent EC50 values with 3 and 2 µM ritonavir and more potent EC50 values with 1.33 and 0.889 µM ritonavir. The company will have to clarify the non-monotonic effect of ritonavir and to correlate the effective concentrations of ritonavir *in vitro* with the unbound concentrations attained *in vivo*. This should be addressed as part of the MAA.

An *in vivo* model to evaluate the anti-viral efficacy of PF-07321332 against SARS-CoV-2 using a mouse-adapted virus, SARS-CoV-2-MA10, was conducted in both BALB/c and the 129-mouse. While some impact on viral replication in the lung was suggested in this model, caution is warranted on the interpretation of the data, derived from this model of particular limitations, in terms of clinical relevance.

The activity was tested against SARS-CoV-2 variants.

PF-07321332 had cell culture antiviral activity (with EC50 values in the low nanomolar range ≤3-fold relative to USA-WA1/2020) against SARS-CoV-2 isolates belonging to the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2) Lambda (C.37) variants. The Beta (B.1.351) variant was the least susceptible tested variant with approximately 4-fold reduced susceptibility relative to the USA-WA1/2020 isolate.

As a critical limitation given the worldwide increasing circulation of the Omicron variant, the company could not provide any *in vitro* data on the antiviral activity against this VOC. This should be provided at the time of the MAA.

Moreover the data on the activity against Delta VOC had limitations, since not tested against a representative strain derived from GISAID to more completely covering pattern of mutations beyond the key mutations.

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Additionally, further investigation is expected to be provided at the time of the MAA on the activity against the Delta sublineage 21J in view of the clinical results by subgroups of patients infected by specific variants.

Finally, at the time of the MAA the company will have to update the data on the *in vitro* activity against SARS-CoV-2 VOC/VOI.

In terms of secondary pharmacology, studies evaluated *in vitro* activity of PF-07321332 against a panel of receptors, transporters, ion channels and enzyme assays, and the results seem to show no significant inhibition of functional or enzyme activity at human relevant concentrations, but this will have to be further investigated at the time of the MAA.

Safety pharmacology studies were conducted in animal to assess potential pharmacodynamic effects on vital organ systems (central nervous, cardiovascular, and respiratory). Translatability of the reported findings to humans is uncertain.

The central nervous system (CNS) and respiratory safety pharmacology studies were conducted in male Wistar Han rats in the same study but in different groups. Relating to the effects on pulmonary system, it was observed test article related higher respiratory rate (up to +44%) and minute volume (up to +38%) compared with vehicle controls from 40 to 160 minutes post dose. Relating to the effects on CNS, test article-related lower number of mean vertical movement counts (-36%) during the first 5 minutes of the assessment period and higher number of mean horizontal (+298%) and vertical (+838%) movement counts during the last 30 minutes of the assessment period compared with vehicle controls. These effects on CNS and respiratory system were observed at exposures 12-fold higher than the anticipated clinical Cmax. A no observed effect level (NOEL) of 60 mg/kg is reported (Cmax 13.3 µg/ml from rat 2-wk study), associated with PF-07321332 exposures 3.2-fold higher than the anticipated clinical Cmax.

One dedicated cardiovascular safety pharmacology study was conducted in conscious telemetered male monkeys in a cross-over design. PF-07321332 administered at 150 (75 BID) mg/kg/day (Cmax = 14.7 µg/ml) . When the QT interval was corrected for HR (QTc), there was a test article-related decrease (down to -7 msec). The cardiovascular effects were observed at exposures 3.5-fold higher than the anticipated clinical Cmax. A no observed effect level (NOEL) of 40 (20 BID) mg/kg is reported, associated with PF-07321332 exposures 0.33-fold higher than the anticipated clinical Cmax.

The toxicity of PF-07321332 was evaluated in repeat-dose toxicity studies up to 1 month in duration in rats and cynomolgus monkeys. There were no adverse findings in any of the studies. The NOAELs were the highest doses administered. All non-adverse test article related clinical findings observed in rats (salivation and soft feces, increases in aPPT, PT, PLT count) or in monkeys (sporadic occurrence of emesis, increases in ALT, AST, fibrinogen) are monitorable in human.

Regarding the developmental and reproductive toxicity (DART) studies, adverse treatment-related effects on fertility and early embryonic development and embryo-foetal development were not identified in rats. In rabbits, an adverse decrease in fetal body weight was observed at 7.8-fold the clinical exposure. The company also justified the use of historical control databases larger than that of the performing laboratory to mitigate the increased occurrence of some skeletal and visceral findings in the high dose group. Some issues should be discussed at the MAA, regarding e.g. the validity of the toxicokinetic data obtained from the rabbit EFD study, or the impact on the formulation of the test-article used in DART studies vs. that in the clinical formulation.

PF-07321332 was not genotoxic in either *in vitro* or *in vivo* assays.

The margins of exposure are only indicative at this stage given that the PKPOP available at this stage has particular limitations, notably only based on PK data from health volunteers (see clinical PK part of

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this report). The margins of exposure are, therefore, expected to be further substantiated at the time of the MAA.

Conclusion on non-clinical aspects

Overall, the nonclinical studies are considered sufficient for supporting the use of Paxlovid in an emergency setting.

2.4. Clinical aspects

2.4.1. Pharmacokinetics

In the current submission, Paxlovid is intended for the treatment of adult patients with symptomatic, confirmed COVID-19 who are at high risk for progressing to severe disease, including hospitalization and/or death.

The proposed recommended oral dose of PF-07321332/ritonavir is 300 mg/100 mg twice daily (two tablets containing PF-07321332 at one strength 150 mg and a tablet containing ritonavir at one strength 100 mg).

The clinical pharmacology program (table 10) consisted of seven Phase 1 studies completed or ongoing, performed in healthy volunteers. The following Phase 1 studies have been conducted:

- One SAD and MAD in Caucasian and Japanese healthy subjects (Study **1001** Part 1 and Part 2)
- rBA/ food effect, mass balance study and QTc analysis (Study **1001** Part 3, Part 4 and Part 5)
- Six PK studies investigating intrinsic (Studies **1010** and **1011**) and extrinsic factors (Studies **1012**, **1013**, **1014**, **1015**)

Phase 1 studies **1012**, **1013** and Phase 2/3 studies **1002** and **1006** are ongoing. An update of PK data from these studies will have to be presented at the time of the MAA.

Additional information is planned to be collected from studies performed in adult patients as presented in table 11 with three pivotal Phase 2/3 studies, with one completed, Study **1005** and two ongoing Studies **1002** and **1006**.

A population PK analysis was performed and comprised PK data from healthy volunteers only. In addition, a simulation exercise was performed to evaluate the predictive performance of the developed PopPK model on the observed PK data in patients from Study **1005**.

Table 10 - Clinical Pharmacology studies

Study ID	Study Title	Study Details/Primary Endpoints		Total Sample Size
Study 1001 (Completed)	A Phase 1, randomized, double-blind, sponsor-open, placebo controlled, single- and multiple-dose escalation study to evaluate the safety, tolerability, and pharmacokinetics of PF-07321332 in healthy adult participants	Pilot study of PF-07321332 in healthy adult participants. Study 1001 is a 5-part study.		
		PART-1 (SAD) PART-2 (MAD) PART-5 (supratherapeutic exposures for QTc assessment)	Frequency, severity, and causal relationship of TEAEs and withdrawals due to TEAEs. Frequency and magnitude of abnormal laboratory findings. Changes from baseline in vital sign measurements and 12-lead ECG parameters	PART-1: 13 participants PART-2: 29 participants PART-5: 10 participants
		PART-3 (relative bioavailability):	Ratio of AUC_{last}, AUC_{inf} and C_{max} of tablet formulation and suspension	PART-3: 12 participants
		PART-4 (metabolism and excretion):	Percent recovery and cumulative recovery of drug-related material in urine and feces	PART-4: 6 participants
Study 1010 (Ongoing) Will be submitted as part of the MAA	A Phase 1, non-randomized, open-label study to assess the pharmacokinetics, safety and tolerability of PF-07321332 boosted with ritonavir in adult participants with moderate hepatic impairment and healthy participants with normal hepatic function	Plasma PF-07321332 PK parameters: C_{max}, AUC_{last}, AUC_{inf} (if data permit)		8 participants without hepatic impairment and 8 participants with moderate hepatic impairment
Study 1011 (Completed)	A Phase 1, non-randomized, open-label study to assess the pharmacokinetics, safety and tolerability of PF-07321332 boosted with ritonavir in adult participants with renal impairment and in healthy participants with normal renal function	Plasma PF-07321332 PK parameters: Cmax, AUC_{inf} (or AUC_{last} if AUC_{inf} cannot be reliably estimated) Urine PF-07321332 PK parameters: A_e, CL_r, if applicable and as data permit		34 participants (8 each in mild, moderate, severe renal impairment, and 10 healthy participants)

Study ID	Study Title	Study Details/Primary Endpoints	Total Sample Size
Study 1012 (Ongoing) Will be submitted as part of the MAA	A Phase 1, open-label, 3-treatment, 6-sequence, 3-period cross-over study to estimate the effect of PF-07321332/ritonavir and ritonavir on the pharmacokinetics of dabigatran in healthy participants	AUC_{inf} and C_{max} of dabigatran with PF-07321332/ritonavir (test) versus dabigatran alone (reference)	~ 24 healthy participants
Study 1013 (Ongoing) Will be submitted as part of the MAA	A Phase 1, open-label, 3-treatment, 6-sequence, 3-period crossover study to estimate the effect of PF-07321332/ritonavir and ritonavir on the pharmacokinetics of midazolam in healthy participants	AUC_{inf} and C_{max} of midazolam with PF-07321332/ritonavir (test) versus midazolam alone (reference)	~12 healthy participants
Study 1014 (Completed)	A Phase 1, open-label, fixed sequence, 2-period crossover study to estimate the effect of carbamazepine on the pharmacokinetics of PF-07321332 boosted with ritonavir in healthy participants	PF-07321332 C_{max} and AUC_{inf} with carbamazepine (test) versus without carbamazepine (reference)	12 healthy participants
Study 1015 (Completed)	A Phase 1, open-label, fixed sequence, 2-period crossover study to estimate the effect of itraconazole on the pharmacokinetics of PF-07321332/ritonavir in healthy participants	PF-07321332 C_{max} and AUC_{inf} with itraconazole (test) versus without itraconazole (reference)	12 healthy participants

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Table 11 - Pivotal clinical studies to support the safety and efficacy assessment for PF-07321332/ritonavir

Study ID	Study Title	Dose and Duration of Study Intervention)	Comparator	Total Planned Sample Size
Study 1002 (Ongoing) Will be submitted as a variation to the future CMA when data are available	An interventional efficacy and safety, phase 2/3, double-blind, 2-arm study to investigate orally administered PF-07321332/Ritonavir compared with placebo in non-hospitalized symptomatic adult participants with COVID-19 who are at low risk of progressing to severe illness.	300/100 mg PF-07321332/ritonavir administered orally q12h for 5 days	PBO	Total ~1140
Study 1005 (Completed)	An interventional efficacy and safety, Phase 2/3, double-blind, 2-arm study to investigate orally administered PF-07321332/Ritonavir compared with placebo in non-hospitalized symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illness	300/100 mg PF-07321332/ritonavir administered orally q12h for 5 days	PBO	Total ~3100
Study 1006 (Ongoing) Will be submitted as a variation to the future CMA when data are available	A Phase 2/3, randomized, double-blind, double-dummy, placebo-controlled study to evaluate the safety and efficacy of 2 regimens of orally administered PF-07321332/Ritonavir in preventing symptomatic SARS-CoV-2 infection in adult household contacts of individuals with symptomatic COVID-19.	300/100 mg PF-07321332/ritonavir administered orally q12h for 5 or 10 days	PBO	Total ~2660 participants

Methods

Throughout the clinical development, two bioanalytical methods were developed to quantify, simultaneously, PF-07321332 and ritonavir, in human K_2EDTA plasma (Report c4679002), and only PF-07321332 in urine (Report c4679003). Both methods were developed and validated by York Bioanalytical Solution (York, YO26 6QR, UK) with satisfactory results.

Absorption

Following single or multiple-dosing of PF-07321332/ritonavir as oral suspension at doses between 75 mg/ 100 mg to 500 mg/100 mg in healthy volunteers, absorption was reasonably rapid with Cmax approximately achieved at Tmax of 0.75-2 h (Study **1001**). At the tested dose of PF07321332/ritonavir 250 mg/100 mg, mean Cmax was 2882 ng/mL and AUCinf was 28220 ng.h/mL (Study **1001**).

Following single dose of PF-07321332/ritonavir as tablet formulation at doses between 100 mg/ 100 mg to 300 mg/100 mg in healthy volunteers, absorption was slightly rapid with Cmax approximately achieved at Tmax of 2-3 h (Study **1011** and **1014**).

At the recommended dose of PF-07321332/ritonavir 300 mg/100 mg as tablet (commercial strength of 150 mg), mean Cmax was 2210 ng/mL and AUCinf was 23010 ng.h/mL (Study **1014**).

Absolute bioavailability

The absolute bioavailability of PF-07321332 has not been investigated. However, based on the mass balance study (Part 4 of Study **1001**), absolute bioavailability could be estimated at least at 55 %.

Relative bioavailability / bioequivalence

Several oral formulations of PF-07321332 were developed and evaluated during the development program:

- An extemporaneously prepared oral suspension used for Study **1001, 1015**
- An uncoated 250 mg immediate release (IR) tablet used for Study **1001** (Part 3)

- A 100 mg IR film-coated tablet used for Study **1011** and in a few patients in the Phase 2/3 Study **1005**
- A 150 mg IR film-coated tablet used for Study **1005** and other Phase 2/3 studies (Studies **1002** and **1006**) as well as in a Phase 1 study **1014.**

The clinical study supplies for the 150 mg tablets used for Study **1005** were manufactured at both the Pfizer Groton (Connecticut, USA) and Freiburg (Germany) sites using identical formulation and manufacturing process.

The proposed commercial formulation dosage form for PF-07321332 is two 150 mg IR film-coated tablets manufactured at Freiburg (Germany) and co-packaged with a 100 mg tablet of ritonavir.

Relative bioavailability Study 1001 (Part 3) [Uncoated tablet 250 mg vs Suspension 250 mg]

The relative bioavailability of PF-07321332 formulated as the 250 mg tablet vs 250 mg oral suspension was evaluated in Study **1001** (**Part 3**) in 12 healthy volunteers without ritonavir combination, as part of an open label, randomized, 3 period, 3 sequence cross over design (food effect also investigated, please refer to the next section) with a wash-out period of 2 days.

PK parameters are summarized descriptively in table 12 below. The estimated ratio of geometric means for Cmax was 56.38% (90% CI of the ratio 43.42%-73.19%) and for AUClast was 81.21% (90% CI of the ratio 69.21%–95.28%). Cmax and AUClast of uncoated tablet was reduced by 44% and 19%, respectively compared to the suspension formulation.

Table 12 - Descriptive summary of plasma PF-07321332 PK parameters- Part 3 rBA/FE (Study 1001)

Parameter (Unit)[a]	PF-07321332 250 mg (Suspension), Fasted (N=12)	PF-07321332 250 mg (Tablet), Fasted (N=12)	PF-07321332 250 mg (Tablet), Fed (N=12)
N1, N2	12, 7	12, 9	12, 9
AUC_{inf} (ng.hr/mL)	3513 (38)	2958 (50)	4256 (24)
AUC_{inf}(dn) (ng.hr/mL/mg)	14.06 (38)	11.82 (50)	17.03 (24)
AUC_{last} (ng.hr/mL)	3318 (35)	2695 (46)	4012 (27)
AUC_{last}(dn) (ng.hr/mL/mg)	13.27 (35)	10.78 (46)	16.03 (27)
CL/F (L/hr)	71.07 (38)	84.56 (50)	58.70 (24)
C_{max} (ng/mL)	883.1 (37)	497.8 (37)	1219 (55)
C_{max}(dn) (ng/mL/mg)	3.533 (37)	1.992 (37)	4.874 (55)
$t_{1/2}$ (hr)	5.626 ± 3.0407	9.086 ± 4.1570	1.854 ± 0.55166
T_{max} (hr)	1.00 (0.500 - 4.00)	1.00 (0.500 - 4.00)	1.75 (0.500 - 4.00)
V_z/F (L)	493.7 (63)	1004 (41)	151.0 (36)

Comparability testing [film coated tablet 100 mg vs 150 mg]

The comparability of PF-07321332 film coated tablets from representative batches of 100 mg and 150 mg was investigated through dissolution profiles comparison at a clinical dose of 300 mg (3X 100 mg vs 2 x 150 mg) at three different pH. An f2 test was calculated to assess similarity of dissolution profiles between the two tablet formulations, and all values were ≥50 suggesting equivalence in dissolution performance of PF-07321332 3x100 mg versus 2x150 mg tablets.

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Comparability testing [Manufacturing sites film coated tablet 150 mg]

The dissolution performance of representative batches of PF-07321332 150 mg film-coated tablets manufactured at Groton, CT, US and Freiburg, Germany sites, was assessed in dissolution media over the physiological pH range. Similarly to the preceding the estimated f2 were ≥50 suggesting equivalence in dissolution performance.

Several oral formulations of PF-07321332 were developed and evaluated during the development program (oral suspension, uncoated tablet at 250 mg, film coated tablet of 100 mg and 150 mg). It is essential to ensure a fair PK comparability between formulations in order to guarantee that the whole PK feature is maintained and allow reliable extrapolation of PK properties with later formulations.

Presently only one relative bioavailability study was performed comparing performance of the oral suspension to the uncoated tablet at 250 mg. Based on the results from Study 1001 Part 3, the biocomparison between formulations clearly indicated that they were different with a 44% decrease in Cmax and 19% decrease in AUClast. Such results should be taken with caution since ritonavir boosted formulations were not compared (for example 250mg/100 mg oral suspension vs 250 mg/100 mg uncoated tablet).

Between uncoated tablet dosed at 250 mg and film coated tablet dosed at 100 (or 150 mg), minor changes are observed in terms of drug loading and presence/absence of coated ingredients. However, no *in vitro* dissolution test was performed between these two formulations and should therefore be provided.

The company has proposed to test the formulation effect as a covariate in the future PopPK model development, this is considered acceptable by CHMP provided the PK dataset will include all the formulations used during the clinical development program (oral suspension, 250 mg uncoated tablet, 100 mg and 150 mg film-coated tablets and 150 mg film-coated tablet by manufacturing process). Such analysis should be provided, at the time of the MAA.

Influence of food

The effect of a high fat meal was investigated at two levels, following the administration of 250 mg PF-07321332 alone (Study **1001 –Part 3,** results in **Table**) or in combination with ritonavir (Study **1001 Part 1**) in a cross-over design. In combination with ritonavir, PF-07321332 plasma exposures were generally similar for AUCs with an increased 15.3% for Cmax for the fed treatment compared to the fasted state. Tmax was delayed by 1.25 h and half-life slightly increased by 1h in the fed state compared to fasted state (6.9 vs 6 h). PF-07321332/ritonavir can therefore be administered with or without food.

Distribution

PF-07321332 was found to be weakly bound to plasma protein (69%). However, it was not mentioned which protein is involved by this binding. The blood/plasma (B/P) ratio was approximately 0.6 indicating limit penetration of PF-07321332 into red blood cells.

Following administration of PF-07321332/ritonavir supplied as tablet formulation at 300 mg/100 mg, the mean apparent volume of distribution (Vz/F) in healthy volunteers was 109.4 L. In patients the Vz/F is unknown.

Elimination

Across clinical studies in healthy volunteers after single or multiple oral doses of PF-07321332/ritonavir as oral suspension half-life ranged from 6.8 to 9.5 h. After single oral dose PF-07321332/ritonavir as tablet formulation half-life ranged from 6.05 to 7.72 h.

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Across clinical studies in healthy volunteers after single or multiple oral doses of PF-07321332/ritonavir as oral suspension CL/F ranged from 5.9 to 12.5 L/h. Based on the PopPK analysis (after correcting by F1 for a 300 m/100 mg dose), CL/F was estimated at 8.17 L/h. After single oral dose PF-07321332/ritonavir as tablet formulation CL/F ranged from 6.9 to 13.0 L/h.

Renal clearance ranged from 2.93 to 3.78 L/h in HV (Caucasian) and was slightly increased in Japanese subjects, estimated at 5.2 L/h.

The main elimination route was renal as unchanged drug, drug metabolism occurs via CYP3A4 enzyme.

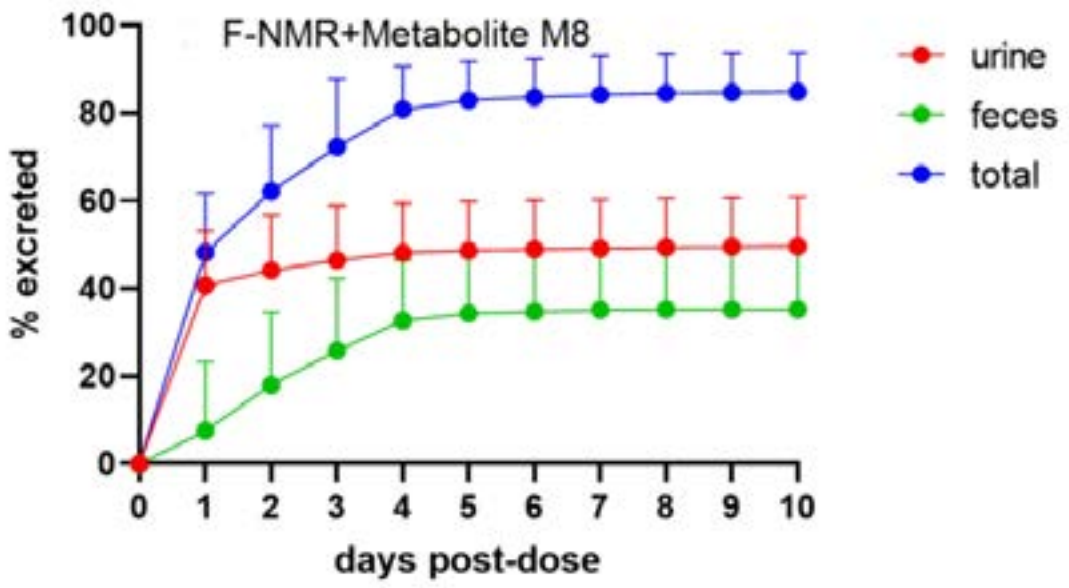
Mass balance

Study **1001 Part 4** was an open label, non-randomized, single period study designed to evaluate the mass balance and metabolism of PF-07321332.

Six male participants with at least 4 completers were enrolled. All participants will receive four doses of 100 mg of ritonavir. Each participant will receive a single dose of 300 mg PF-07321332 on Day 1 along with 100 mg of ritonavir after at least 10h of fasting. Four doses of 100 mg ritonavir were administered at -12h, 0, 12h and 24h. Samples were collected at predetermined time points to determine PF-07321332 concentrations in plasma, urine and feces and metabolite profiling in the three matrix.

By quantitative ^{19}F-NMR, mean ± SD (range) mass recovery was 84.9% ± 8.9% (70.7-95.5%) which consisted of PF-07321332 at 80.7± 8% and M8 metabolite at 4.2%± 1.3% (silent due to loss of trifluoroacetyl group). The excretion into urine and feces was 48.6% and 35.3%, respectively, mainly as unchanged PF-07321332. Most material excreted in urine emerged in the first 24 h while in feces in 5 days (figure 4).

Figure 4 - Cumulative mean (+SD) excretion of PF-07321332 and M8 in urine and feces of HV following administration of oral suspension of PF-07321332/ritonavir using 19F-NMR



Metabolism

In vitro

The *in vitro* metabolism of PF-07321332 (10 µM) was investigated by incubation in liver microsomes and hepatocytes from man and animal various species (Report PF-07321332_09Nov20_084546). In all species including human M4 was considered as the main metabolite. All other metabolites found in

human (M1, M2, M3, m/z 498) were generally found in other species. M5 and M8 were only detected following incubation of PF-07321332 (10 µM and 100 µM) in human gut microbiota.

The CYP isoforms involved in the metabolism of PF-07321332 was investigated using recombinant P450 enzymes at a concentration of 10 µM. CYP3A4 mainly and CYP3A5 are involved (Report PF-07321332_12Oct21_082857) with other CYP enzymes contributing in minor amounts. Particularly CYP3A4 was the major contributor to the oxidative metabolism (Report PF 07321332_21Nov20_072016) and mainly in the formation of M4.

M7 the acylglucuronide of M5 was identified in human urine at trace level. The UGT enzymes responsible of its formation was investigated in human liver microsomes. UGT2B4 and 2B7 contributed to 69.8% and 16.7% of the formation of M5.

In vivo

Metabolite profiling was performed in the three matrix (plasma, urine and feces). In plasma unchanged PF-07321332 was the main circulated compound, M4 and M5 were found at trace levels. In urine and feces after normalization of the data to complete mass balance, unchanged PF-07321332 accounted for 82.5% of the drug material (55% in urine and 27.5% in feces). M5 was present at 12.1% in feces, M8 at 4.2% in plasma (table 13). The proposed metabolic scheme is presented in figure 5.

Table 13 - Summary of metabolites of PF-07321332 in urine and feces of healthy participants following oral administration of PF-07321332/ritonavir suspension

Metabolite	% of Normalized Dose[a]		
	Urine	Feces	Total
PF-07321332	55.0	27.5	82.5
M5 (PF-07320267)	0.4	11.7	12.1
M7 (acyl glucuronide of M5)	0.3	ND	0.3
m/z 519	ND	0.8	0.8
M8 (PF-07331782)	2.6	1.6	4.2
Total	58.4[b]	41.6	100[b]

Source: Appendix 16.2.5.10.5

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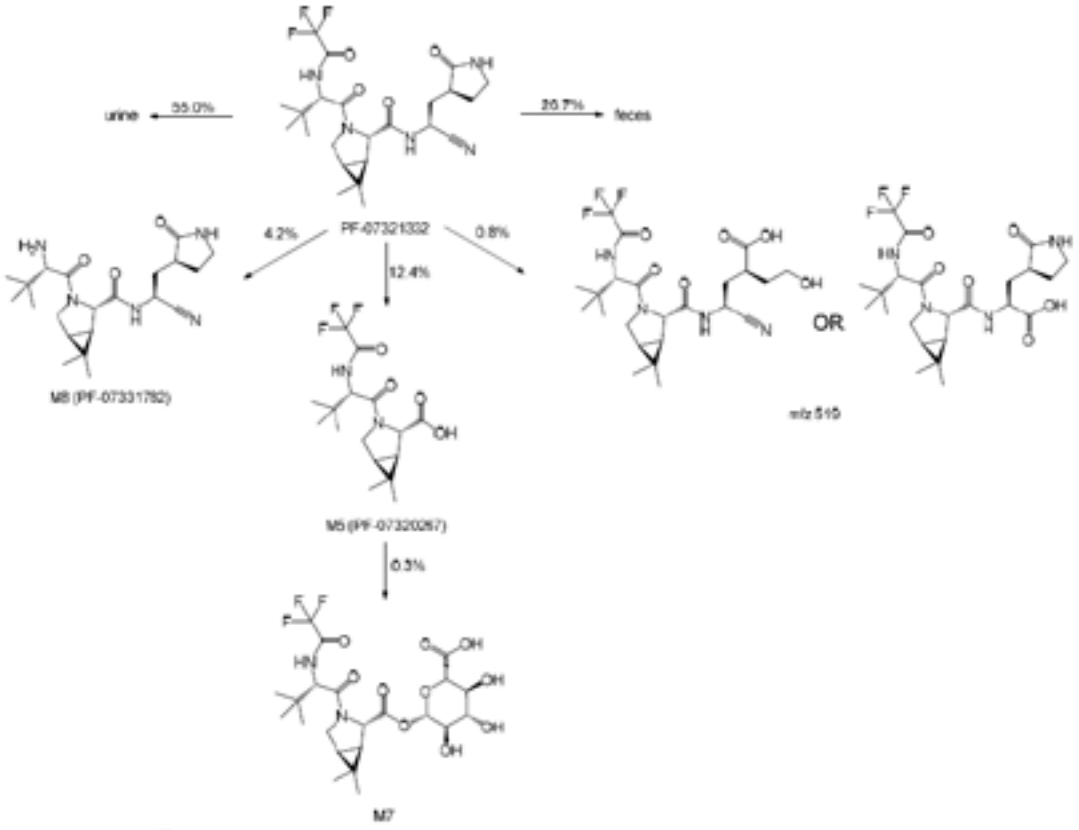
Figure 5 - Summary profile of PF-07321332 metabolism and disposition in healthy participant



Dose proportionality and time dependency

Dose proportionality of PF-07321332 (with or without ritonavir) was mainly investigated following single and multiple escalating oral dose in healthy volunteers during Study **1001**.

- Dose proportionality

Study 1001

Study **1001** was the first-in-human (FIH) study of PF-07321332 in healthy volunteers, which consisted of five parts. **Part 1 (SAD)** and **Part 2 (MAD)** were randomized, double-blind, sponsor open, placebo-controlled triasl to evaluate safety, tolerability and PK.

Part 1 used PF-07321332 (without ritonavir) at a dose range from 150 to 1500 mg, PF-07321332/ritonavir at two dose levels 250 and 750 mg as described in table 14. **Part 2** used PF-07321332/ritonavir from 75 mg/100 mg to 500 mg /100 mg.

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Table 14 - Actual dosing regimen evaluated in Study 1001

Part of the study	Dosing regimen evaluated[a]
PART-1: SAD	PF-07321332 150 mg
	PF-07321332 500 mg
	PF-07321332 1500 mg
	PF-07321332 250 mg at 0h + RTV 100 mg at -12, 0 and 12h
	PF-07321332 750 mg at 0h + RTV 100 mg at -12, 0 and 12h
	PF-07321332 250 mg at 0h (Fed) + RTV 100 mg at -12, 0 and 12h
PART-2: MAD	PF-07321332/RTV 75/100 mg BID for 10 days
	PF-07321332/RTV 250/100 mg BID for 10 days
	PF-07321332/RTV 500/100 mg BID for 10 days
	PF-07321332/RTV 250/100 mg BID for 10 days in Japanese participants
PART-3: RBA/FE	PF-07321332 250 mg Tablet
	PF-07321332 250 mg Tablet (Fed)
	PF-07321332 250 mg suspension
PART-4: M&E	PF-07321332 300 mg at 0h + RTV 100 mg at -12, 0, 12 and 24 h
PART-5: SE	PF-07321332 2250 mg (divided into 3 doses of 750 mg administered at 0, 2 and 4h) + RTV 100 mg at -12, 0 and 12 h

a. Unless specified, dosing of PF-07321332 in all parts were done in fasted state (≥7h in all parts except PART-5 in which PF-07321332 was administered approximately 2h after breakfast).

PK parameters following SAD of PF-07321332 (with or without ritonavir) as oral suspension are presented in table 15 and following MAD in table 16.

Table 15 - Descriptive summary of plasma PF-07321332 PK parameters (Part 1 –SAD, Study 1001)

Parameter (Unit)[a,b]	PF-07321332 150 mg (Suspension), Fasted (N=4)	PF-07321332 500 mg (Suspension), Fasted (N=4)	PF-07321332 1500 mg (Suspension), Fasted (N=4)	PF-07321332 250 mg (Suspension)/ ritonavir 100 mg, Fasted (N=4)	PF-07321332 250 mg (Suspension)/ ritonavir 100 mg, Fed (N=4)	PF-07321332 750 mg (Suspension)/ ritonavir 100 mg, Fasted (N=4)
N1, N2	4, 3	4, 2	4, 0	4, 4	4, 4	4, 4
AUC_{inf} (ng.hr/mL)	2247 (42)	5480, 5450	NR	28220 (14)	28640 (17)	66760 (45)
AUC_{inf}(dn) (ng.hr/mL/mg)	14.97 (42)	11, 10.9	NR	112.8 (14)	114.2 (17)	89.14 (45)
AUC_{last} (ng.hr/mL)	2125 (34)	3753 (29)	10870 (47)	27600 (13)	28020 (16)	64230 (39)
AUC_{last}(dn) (ng.hr/mL/mg)	14.15 (34)	7.507 (29)	7.247 (47)	110.4 (13)	112.0 (16)	85.77 (40)
CL/F (L/hr)	66.83 (43)	91.2, 91.8	NR	8.865 (14)	8.735 (17)	11.22 (45)
C_{max} (ng/mL)	667.7 (28)	674.4 (38)	1538 (32)	2882 (25)	3323 (13)	5086 (25)
C_{max}(dn) (ng/mL/mg)	4.450 (28)	1.349 (38)	1.025 (32)	11.53 (25)	13.32 (13)	6.782 (25)
$t_{1/2}$ (hr)	2.023 ± 0.54556	18.5, 25.6	NR	6.935 ± 1.0794	6.005 ± 1.6502	12.86 ± 8.4196
T_{max} (hr)	0.634 (0.550 - 1.50)	1.00 (0.517 - 1.00)	1.00 (0.533 - 2.00)	2.75 (1.50 - 4.00)	4.00 (4.00 - 4.00)	2.00 (1.50 - 4.00)
V_z/F (L)	190.6 (36)	2440, 3390	NR	87.98 (28)	73.48 (47)	181.9 (35)

Less than dose proportional increases in PF-07321332 exposures was observed following single oral doses of PF-07321332 boosted by 100 mg of ritonavir ranging from 250 mg to 750 mg. Tmax ranged from 2 to 4h, and half-life ranged from 6.93 to 12.8 h.

Less than dose proportional increases in PF-07321332 exposures was observed following multiple oral doses of PF-07321332 boosted by 100 mg of ritonavir ranging from 75 mg to 500 mg during the entire

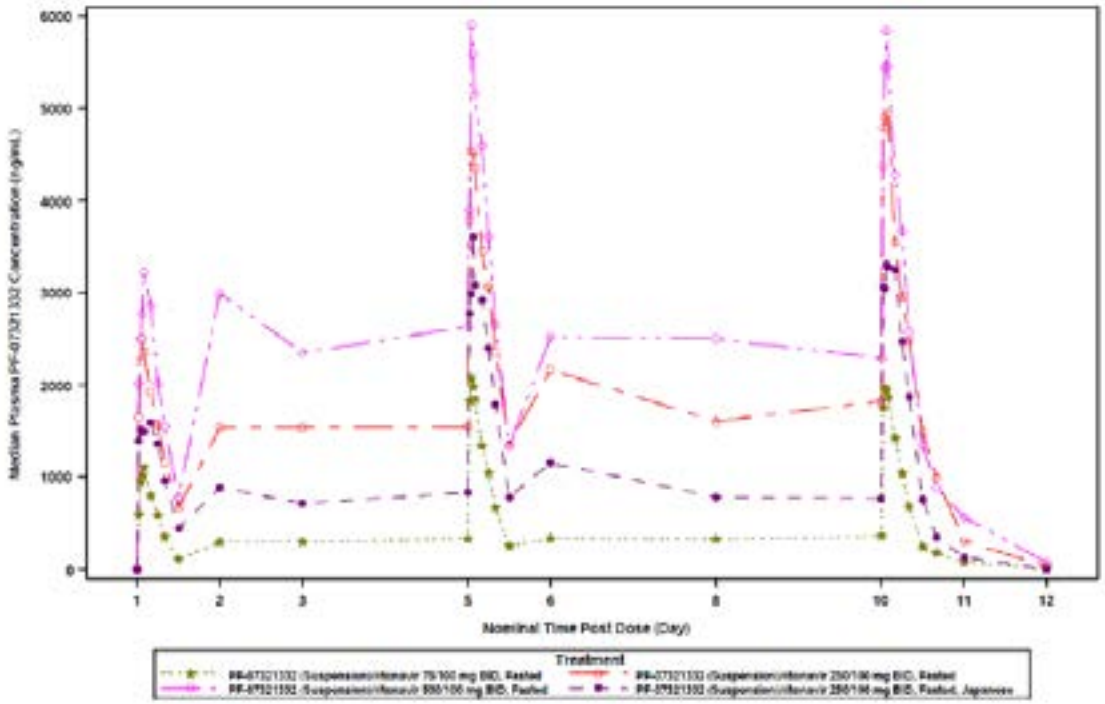
dosing interval (Day 1 to Day 10). Tmax ranged from 0.75 to 2h, and half-life ranged from 6.79 to 8.04 h.

Use of ritonavir as a PK enhancer appeared to considerably increase PF-07321332 exposure. The geometric mean AUCinf, AUClast and Cmax following a single dose of PF-07321332 250 mg in fasted state boosted by ritonavir was 28.22 µg•h/mL, 27.6 µg•h/mL and 2.882 µg/mL, respectively. Comparatively, the geometric mean AUCinf, AUClast and Cmax following a single dose of PF-07321332 250 mg in fasted state (without ritonavir) in PART-3 was 3.51 µg•h/mL, 3.32 µg•h/mL and 0.883 µg/mL, respectively.

- Time dependency

Median plasma PF-07321332 concentration time profiles including Ctrough concentrations are presented in figure 6 and associated PK parameters in table 16.

Figure 6 - Median plasma PF-07321332 concentration -time profiles across all dosing days following MAD of PF-07321332/ritonavir (Part 2, MAD, Study 1001)



Steady-state plasma concentrations appeared to have been achieved by Day 2 for all doses and treatments as shown in figure 6. Plasma PF-07321332 accumulation was approximately 2-fold following multiple dosing and values were similar on Day 5 and Day 10. Geometric mean accumulation ratios ranged from 1.8 to 2.1 for AUCtau (Rac) and Cmax (Rac,Cmax), on Day 10, across all treatments.

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Table 16 - Descriptive summary of plasma PF-07321332 PK parameters (Part 2 –MAD, Study 1001)

Parameter (Unit)[a]	PF-07321332 (Suspension)/ritonavir 75/100 mg BID, Fasted (N=4)	PF-07321332 (Suspension)/ritonavir 250/100 mg BID, Fasted (N=4)	PF-07321332 (Suspension)/ritonavir 500/100 mg BID, Fasted (N=7)	PF-07321332 (Suspension)/ritonavir 250/100 mg BID, Fasted, Japanese (N=4)
Day 1				
N1	4	4	7	4
AUC_{tau} (ng hr/mL)	6017 (33)	18700 (43)	22610 (37)	13130 (26)
AUC_{tau} (dn) (ng hr/mL/mg)	80.19 (33)	74.76 (43)	45.23 (37)	52.60 (26)
C_{max} (ng/mL)	1042 (28)	2435 (36)	3051 (32)	1925 (25)
C_{max}(dn) (ng/mL/mg)	13.89 (28)	9.755 (36)	6.103 (32)	7.698 (25)
T_{max} (hr)	1.75 (1.00 - 2.00)	1.50 (1.00 - 4.00)	2.00 (1.50 - 2.17)	2.75 (1.00 - 4.02)
Day 5				
N1	4	4	7	4
AUC_{tau} (ng hr/mL)	12570 (17)	35560 (26)	38150 (23)	25480 (26)
AUC_{tau} (dn) (ng hr/mL/mg)	167.7 (17)	141.9 (26)	76.32 (23)	102.0 (26)
C_{av} (ng/mL)	1049 (17)	2963 (26)	3181 (23)	2124 (26)
CL/F (L/hr)	5.966 (17)	7.032 (26)	13.11 (23)	9.814 (26)
C_{max} (ng/mL)	2224 (27)	4774 (21)	5296 (21)	3674 (28)
C_{max}(dn) (ng/mL/mg)	29.66 (27)	19.10 (21)	10.59 (21)	14.70 (28)
C_{min} (ng/mL)	251.0 (11)	1315 (37)	1195 (29)	707.3 (35)
PTR	8.857 (27)	3.635 (21)	4.430 (14)	5.194 (19)
R_{ac}	2.091 (24)	1.901 (22)	1.685 (29)	1.937 (18)
$R_{ac,Cmax}$	2.133 (25)	1.959 (16)	1.733 (24)	1.909 (26)
T_{max} (hr)	1.00 (1.00 - 1.50)	0.750 (0.500 - 1.50)	1.50 (1.00 - 2.02)	1.26 (1.00 - 2.02)
Day 10				
N1,N2	4, 4	4, 4	7, 7	4, 4
AUC_{tau} (ng hr/mL)	12650 (16)	37780 (27)	39780 (20)	26930 (15)
AUC_{tau} (dn) (ng hr/mL/mg)	168.3 (16)	151.1 (26)	79.56 (20)	107.7 (15)
C_{av} (ng/mL)	1053 (16)	3147 (27)	3314 (20)	2245 (14)
CL/F (L/hr)	5.933 (16)	6.617 (27)	12.57 (20)	9.278 (15)
C_{max} (ng/mL)	2055 (14)	5123 (24)	5607 (17)	3772 (21)
C_{max}(dn) (ng/mL/mg)	27.40 (14)	20.49 (25)	11.22 (17)	15.08 (21)

C_{max} (ng/mL)	245.3 (27)	1480 (27)	1279 (31)	12.50 (2.0814162E15)
PTR	8.383 (16)	3.462 (5)	4.385 (17)	6.270 (32)
R_{ac}	2.104 (30)	2.022 (16)	1.757 (26)	2.047 (16)
$R_{ac, Cmax}$	1.971 (34)	2.101 (16)	1.840 (29)	1.962 (14)
$t_{1/2}$ (hr)	7.955 ± 2.0401	6.795 ± 1.7072	8.047 ± 1.7871	5.163 ± 2.0915
T_{max} (hr)	1.00 (1.00 - 2.00)	1.00 (1.00 - 2.00)	1.50 (1.00 - 2.00)	1.50 (0.500 - 2.02)
V_2/F (L)	66.45 (24)	63.40 (13)	142.4 (37)	65.04 (31)
Ae_{mu} (mg)	47.83 (12)	129.9 (4)	116.5 (122)	135.4 (5)
Ae_{mu} %	63.79 (12)	51.81 (4)	23.35 (121)	54.20 (5)
CL_r (L/hr)	3.782 (20)	3.433 (23)	2.934 (128)	5.028 (11)

Population PK modelling

A preliminary population PK model of PF-07321332 was developed using plasma concentration data collected in healthy adult data from Study C4671001 (data cut-off date 30 June 2021). The analysis PK dataset included 536 evaluable plasma concentrations from 20 subjects who received 250 and 750 mg single dose and 75, 250 and 500 BID administration of PF-07321332 (suspension formulation) in combination with 100 mg ritonavir (RTV). Modelling used NONMEM, version 7.5. The first-order conditional estimation method with interaction was used during model development.

The final model was a linear 2-compartment model with first-order absorption, a dose-dependent absorption implemented by separate power functions for ka and relative bioavailability (F1) and a linear elimination. Standard allometric scaling of body weight with exponents fixed to 0.75 and 1 was applied on clearance (CL/F) and volumes of distribution, respectively. Residual random effects were described with a combined proportional and additive model in the log domain. IIV were included on all parameters, with a full variance and covariance of the Ω matrix. IOV was included to ka.

Parameter estimates for the final model are presented below.

Table 17 - Parameter estimates for the final population PK model based on preliminary data from Study C4671001

	Final Run (CP1:ST-21050660)			1000 SIR[a] Run Statistics				
Parameter	Estimate	%RSE	Shrinkage (%)	Mean	%RSE	Median	Lower 2.5%	Upper 97.5%
CL (θ_1) [L/h]	1.02	18.9		1.02	10.7	1.02	0.800	1.24
V2 (θ_2) [L]	8.20	20.8		8.21	13.0	8.21	6.03	10.2
Q (θ_3) [L/h]	0.444	8.91		0.446	5.58	0.447	0.395	0.493
V3 (θ_4) [L]	5.65	20.2		5.84	17.5	5.90	3.68	7.64
$k_{a,1mg}$ (θ_5) [1/h]	22.7	4.15		22.6	2.67	22.6	21.5	23.9
$k_{a,power}$ (θ_6)	-0.533	6.25		-0.537	5.30	-0.536	-0.592	-0.481
$F1_{1mg}$ (θ_7)	1.06	30.5		1.05	23.1	1.05	0.591	1.56
$F1_{power}$ (θ_8)	-0.375	16.7		-0.376	10.4	-0.378	-0.455	-0.305
Proportional Error (θ_9) [%]	3.36	111		3.73	57.6	3.50	0.506	7.82
Additive Error (θ_{10}) [ng/mL]	399	11.5		405	30.2	395	250	671
$\omega^2_{1,1}$ IIV$_{CL}$ [%CV]	26.4	29.2	1e-10	26.0	19.6	25.9	20.4	31.0
$\Omega_{2,1}$ COV$_{CL-V2}$	0.0684	36.0		0.0646	22.1	0.0637	0.0377	0.0962
$\omega^2_{2,2}$ IIV$_{V2}$ [%CV]	30.7	41.9	5.73	31.6	29.3	31.4	22.1	39.7
$\Omega_{3,1}$ COV$_{CL-k_a}$	0.0582	73.2		0.0602	51.2	0.0599	0.00709	0.122
$\Omega_{3,2}$ COV$_{V2-k_a}$	0.138	41.4		0.133	33.5	0.129	0.0489	0.227
$\omega^2_{3,3}$ IIV$_{k_a}$ [%CV]	54.3	33.6	15.5	55.3	32.7	54.2	39.3	72.8
$\Omega_{4,1}$ COV$_{CL-V3}$	0.125	58.6		0.104	43.8	0.0987	0.0157	0.229
$\Omega_{4,2}$ COV$_{V2-V3}$	0.0393	152		0.0279	116	0.0262	-0.0589	0.121
$\Omega_{4,3}$ COV$_{k_a-V3}$	0.151	90.5		0.148	62.5	0.149	0.347	0.0269
$\omega^2_{4,4}$ IIV$_{V3}$ [%CV]	69.9	73.0	7.89	69.1	49.1	66.4	38.2	101
$\omega^2_{5,5}$ IOV$_{k_a}$ [%CV]	60.7	15.6	38.1/51.6/5.23[b]	60.8	15.3	61.2	50.7	68.6
$\sigma^2_{1,1}$	1 Fixed		5.58	1 Fixed				

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In general, structural parameters were precisely estimated (low %RSE <20%), except for F1 at 1 mg dose (%RSE = 30.5%). However, proportional error, variance and covariance of the Ω block were poorly estimated (%RSE >30%). This is specifically problematic for the proportional residual error estimated to be low 3.36% but with an RSE% of 111%. These high %RSE and the high condition number (>1000) suggested that the final model is over-parameterized, which is expected given the inclusion of a full variance-covariance block for IIV and the available limited data. Sampling importance resampling were performed and overall were in line the model parameters estimates. All η and ε shrinkage were <20% except for IOV in ka. No major deficiencies were noted GOF plots. The pcVPCs indicated that the final model described the data reasonably well; even clear under-prediction of the low 5th quantile at 250 mg dose with RTV fed and fasted regimens (Please refer to the respective figures) and tendency to over-predict the terminal elimination phase are noted.

The additive error was estimated at 339 ng/L (more than 33 times the LLOQ of 10 ng/mL and even larger than the target IC90% value of 292 ng/mL). Such finding, with the poor precision of the proportional error portion compromise the validity of the model. To handle this point during simulations, the large residual errors was excluded. This approach is not endorsed as it would imply estimation of PK parameters and associated variabilities necessary different from that in the final model and used for simulation. Therefore, model-based PK predictions should be considered with caution.

The parameter estimates after adjustment by F1 at a dose of 300 mg are CL 8.2 L/h, volume of distribution 111 L, and ka 1.1 h-1. This gives a population mean half-live $T_{1/2}$ of 15 hours, which is not consistent with that obtained from NCA calculations (mean $T_{1/2}$ =7 hours). No clear estimate of the bioavailability 300 mg dose is provided / could be found. Importantly, given the observed 44% lower Cmax in tablets compared to the suspension formulation (relative bioavailability part in study 1001), the adequacy of using the current model (based only on tablet formulation data) to simulate PK data for the tablet formulation is not deemed adequate.

The covariate (age, body weight, BMI, ethnicity, renal and hepatic impairment) effects could not be considered adequately explored given the very limited data and the demographic characteristics of subjects included in the dataset (ranges of age, BW and renal clearance were [21-56y], [58-99 kg] and [70 -141 ml/min], respectively and no information on BMI, ethnicity and hepatic impairment could be found).

Using the final population PK model and doses from 100 to 500 mg/100mg RTV BID for 5 days, the predicted PK exposures (table 18) showed that, for a typical 70 kg subject, a dose of PF-07321332/ritonavir 300/100 mg BID would result in median Day 1 and steady state Ctrough (=C12h) concentrations ~3-4 x IC90 and ~6 x IC90, respectively. With this dose, it is projected to have >90% of subjects would achieve Ctrough ≥IC90 even after the first dose and with IIV in CL inflated to 60%.

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Table 18 - Predicted C12h and Percentage of Simulated Subjects Achieving C12h above IC90 of 292 ng/mL (IIV in CL Inflated to 60%)

Dose (mg) + RTV*	Dose Number	C_{12h} (ng/mL) Median	10^{th} percentile	90^{th} percentile	% Subjects Achieved $C_{12h} \geq IC_{90}$
100	1st (Day 1)	458	141	1018	71.5
	2nd (Day 1)	631	175	1546	79.2
	9th (Day 5)	852	238	2276	85.3
200	1st (Day 1)	743	228	1608	85.0
	2nd (Day 1)	1012	281	2443	89.2
	9th (Day 5)	1361	383	3575	93.4
300	1st (Day 1)	987	307	2124	90.7
	2nd (Day 1)	1347	378	3202	93.6
	9th (Day 5)	1800	498	4670	95.7
400	1st (Day 1)	1209	378	2565	94.0
	2nd (Day 1)	1657	468	3879	95.3
	9th (Day 5)	2197	605	5679	97.4
500	1st (Day 1)	1417	449	2979	95.5
	2nd (Day 1)	1952	552	4516	96.5
	9th (Day 5)	2563	704	6640	97.8

The preliminary population PK model and model-based simulations are not considered valid or reliable. Several limitations are highlighted: a) misspecification of the residual error model, b) exclusion of residual errors from the simulation exercise, c) large discrepancy (more than 2-fold) for the estimation of the terminal half-live T1/2 between the population approach (15h) and the NCA calculations (7h) and d) lack of validity of the PK predictions projected with the tablet formulation while the model was developed using only the suspension formulation and especially given that the tablets appear to have a Cmax on average 44% lower than that of the suspension formulation.

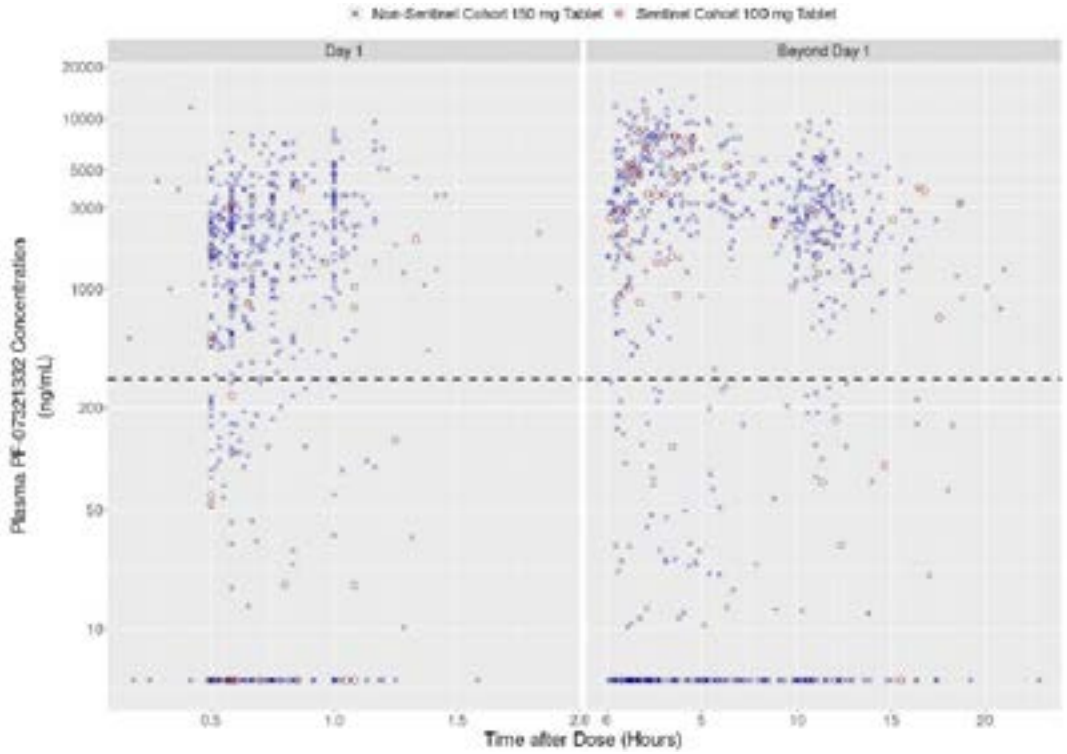
Only very limited data in healthy volunteers (n=20) are part of the analysed dataset. Inclusion of more full data from healthy volunteers and especially from patients in pivotal phase 2/3 studies is deemed essential to better inform the model. Therefore, the company should consider updating the model by inclusion of these data. The covariate effects (age, body weight, BMI, ethnicity, renal and hepatic impairment, pharmaceutical formulation, disease) should be explored as part of the work required to update the model. Clear dosing recommendations (or warning of use if lack of data) for specific subgroups that are not included (elderly, obese and underweighted patients) should be provided. The new relevant population PK analysis should be provided at the time of the MAA.

PK in patients with COVID-19

Preliminary PK data were collected from the ongoing pivotal efficacy and safety Phase 2/3 study (**C4671005**) in patients with confirmed diagnosis of SARS-CoV-2 infection who were at increased risk of progressing to severe illness. Patients received PF-07321332/ritonavir or placebo orally q12h for 5 days (10 doses total). Sparse PK sampling was collected on Day 1 (0.5 to 1.5 hr post dose), on Day 5 (up to 2 hours pre-dose) and optionally on Days 2, 3, or 4. At cut-off date (28 October 2021), a total of 1298 plasma PF-07321332 concentrations, including 1068 evaluable samples and 230 (17.7%) BLQ samples from 601 patients were available for analysis. There were 46 participants who did not have any evaluable samples (all observations were BLQs).

The observed plasma PF-07321332 concentrations in patients are shown in figure 7.

Figure 7 - Observed Plasma PF-07321332 Concentration versus Time after Dose for Participants with COVID-19 on PF-07321332/ritonavir 300 mg/100 mg q12h in Study C4671005 Stratified by Day



PK data at Day 5 (table 19) indicated that 140 out of 173 (>80%) patients achieved a Cmin≥ IC90. When excluding the BLQ samples during Day 5 visit, 140 out of 153 (>90%) patients achieved the target Cmin. Overall, the observed concentrations from patients appears to be consistent with those (dose-normalized to 300 mg) in the healthy participants. However, it is worth noting that a high number of BLQ (17.7% of the dataset) was observed after and beyond the first dose. Such finding requires further investigation. Of these BLQ, 95 samples (41.3%) were collected at Day 1, while no BLQ samples at or beyond 30 min post-dose was observed in healthy volunteers after of PF-07321332/ritonavir dosing.

Table 19 - Summary of Cmin at the Planned Day 5 Visit and Percentage of Participants in Study C4671005 Achieving Cmin ≥EC90

Scenario	Number of Participants	Observed C_{min}[a] (ng/mL)			BLQ[b] Samples		Participants with $C_{min} \geq EC_{90}$	
		Median	10th percentile	90th percentile	Number	Percentage	Number	Percentage
All Participants	173	2180	0	5600	20	11.6	140	80.9
Excluded Participants with only BLQ Samples	167	2290	57.2	5698	14	8.38	140	83.8
Excluded All Participants with BLQ Samples on Day 5	153	2440	701	5808	0	0	140	91.5

A predictive check (simulation) approach was performed to assess the adequacy of the preliminary population PK model in describing the patient data from Study 1005 (PF-07321332/ritonavir 300 mg/100 mg BID).

Overall, a fair agreement was observed. The majority of the PF-07321332 concentrations in COVID-19 patients fall within the 90% prediction interval generated from simulation. The median observed data

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at Day 1 (figure 8) and at steady state (figure 9) appears to be consistent with the model predictions generated population PK model (based on PK data from healthy volunteers). However, as noted above, a high number of unexpected BLQ concentrations after the first dose and at steady was observed.

Figure 8 - Median and 90% Prediction Intervals (5th and 95th percentile) for PF-07321332 concentrations after first dose based on 1000 Simulations (PF-07321332/ritonavir 300 mg/100 mg q12h) overlaid with observed Data from Study C4671005

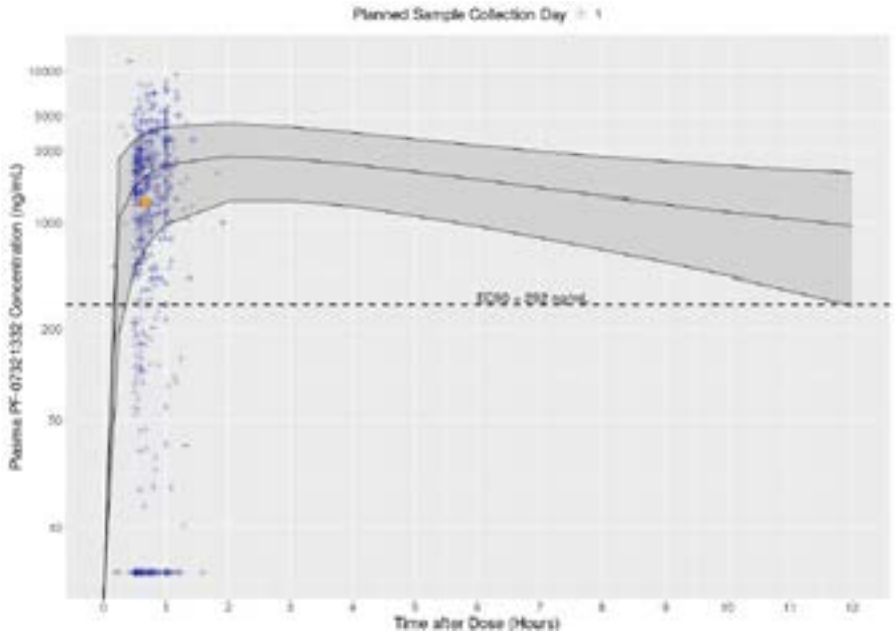
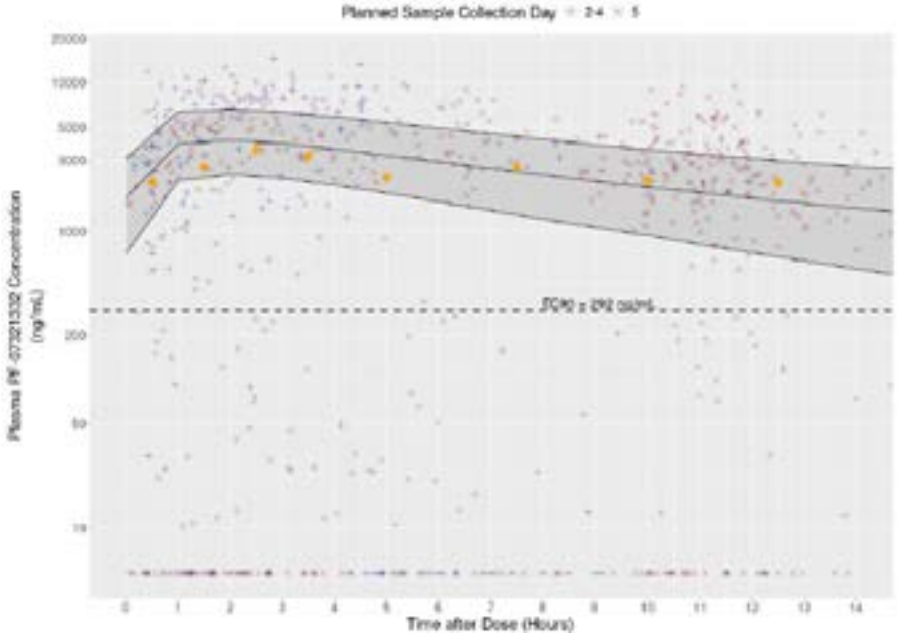


Figure 9 - Median and 90% Prediction Intervals (5th and 95th percentile) for PF-07321332 concentrations at steady-state based on 1000 Simulations (PF-07321332/ritonavir 300 mg/100 mg q12h) overlaid with observed Data from Study C4671005



Special populations

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- Race

Race effect on PF-07321332/ritonavir PK was explored as part of Study 1001 in only 4 Japanese subjects. AUCtau and Cmax values were approximately 30% and 21-26%, respectively, lower in Japanese participants compared to Caucasian subjects. Given the very limited data (n=4), this result should be considered with caution and no valid conclusion regarding PK in Japanese subjects could be drawn from this analysis. In order to propose more reliable dosing recommendation in this subgroup, this preliminary result should be confirmed on a large number of patients (by a dedicated study or using the population approach). This will be further investigated at the time of the MAA.

- Renal impairment

A formal study (**C46711011**) investigated the effect of mild, moderate and severe impairment on the PK of PF-07321332. Subjects were administered a single oral 100 mg dose of PF-07321332 in combination with the PK enhancer ritonavir administered as a 100 mg dose at -12, 0, 12, and 24 hours relative to PF-07321332 dosing. The number of subjects per category of renal impairment was n=8 versus 10 subjects for the normal healthy controls. The estimated eGFR calculated using CKD-EPI equation was used a measure of renal function.

PF-07321332 systemic exposure (AUC and Cmax) increased with increasing severity of renal impairment (figure 10, table 20). Adjusted geometric mean (90% CI) AUCinf, test/reference ratios compared of renal impairment (test) to normal renal function (reference) were 123.84 % (99.64%, 153.91%) for mild renal impairment, 187.40% (148.52%, 236.46%) for moderate renal impairment, and 304.49 % (237.60%, 390.21%) for severe renal impairment. For Cmax, adjusted geometric mean (90% CI) test/reference ratios were 129.78% (101.93%, 165.25%), 138.12% (113.18%, 168.55%) and 148.02% (111.40%, 196.68%) for mild, moderate and severe renal impairment subjects, respectively.

Apparent CL/F and CLr decreased with increased renal impairment severity. Mean CL/F in the moderate and severe group decreased 47% and 67% and mean CLr decreased 47% and 80% respectively compared to the normal renal functional group.

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Figure 10 - Median Plasma PF-07321332 Concentration-Time Plot, Following a Single Oral Dose of PF-07321332/Ritonavir, Protocol C4671011

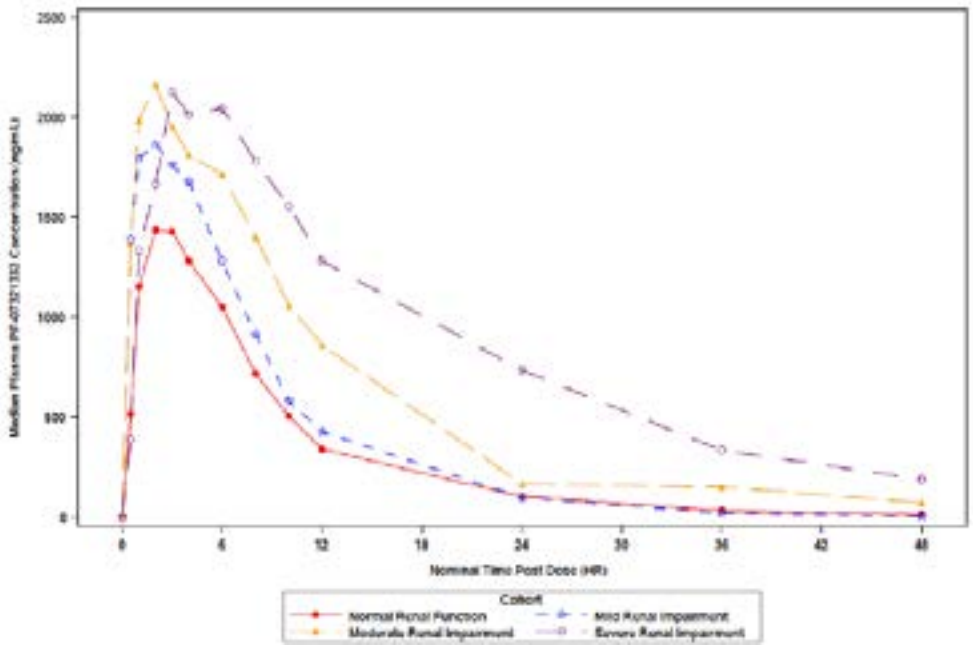

Table 20 - Descriptive Summary of Plasma and Urine PF-07321332 PK Parameters. Protocol C4671011.

Parameter (Unit)[a]	Normal Renal Function (N=10)	Mild Renal Impairment (N=8)	Moderate Renal Impairment (N=8)	Severe Renal Impairment (N=8)
N1, n	10, 10	8, 8	8, 6	8, 7
AUC_{inf} (ng.hr/mL)	14460 (20)	17910 (30)	27110 (27)	44040 (33)
AUC_{last} (ng.hr/mL)	14270 (20)	17770 (30)	26660 (21)	39420 (28)
C_{12} (ng/mL)	341.9 (35)	438.0 (30)	785.6 (33)	1213 (33)
C_{24} (ng/mL)	99.10 (35)	112.8 (55)	179.1 (108)	694.2 (42)
CL/F (L/hr)	6.913 (20)	5.581 (30)	3.689 (27)	2.270 (33)
C_{max} (ng/mL)	1600 (31)	2077 (29)	2210 (17)	2369 (38)
$t_{1/2}$ (hr)	7.725 ± 1.8234	6.606 ± 1.5844	9.948 ± 3.4171	13.37 ± 3.3225
T_{max} (hr)	2.000 (1.00 - 4.00)	2.000 (1.00 - 3.00)	2.500 (1.00 - 6.00)	3.000 (1.00 - 6.05)
V_2/F (L)	74.95 (35)	51.95 (32)	50.34 (27)	42.73 (26)
Ae (mg)	31.20 (45)	42.65 (23)	30.83 (56)	18.46 (50)
Ae %	31.20 (45)	42.65 (23)	30.83 (56)	18.46 (50)
CL_r (L/hr)	2.180 (50)	2.395 (33)	1.154 (71)	0.4398 (73)

No dose adjustment of PF-07321332 is needed in mild renal impairment, while the dose should be reduced by one-half in moderate renal impairment: PF-07321332/ritonavir 150 mg/100 mg BID.

In severe renal impaired subjects, an increase of AUC by 204% was observed compared to the normal renal group. Appropriate dose for patients with severe renal impairment has not yet been determined. Based on the significant exposure increase, a contraindication regarding use in subjects with severe renal impairment has been included in the Conditions of Use.

- Hepatic impairment

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A formal study (**C46711010**) investigated the effect of moderate hepatic impairment on the PK of PF-07321332, in comparison to matched healthy subjects with normal hepatic function. Subjects were administered a single oral 100 mg dose of PF-07321332 in combination with the PK enhancer ritonavir administered as a 100 mg dose at -12, 0, 12, and 24 hours relative to PF-07321332 dosing. The number of subjects was n=8 in each cohort. Categorization of participants into normal hepatic function or hepatic impairment group was based on Child-Pugh scores.

The study is still ongoing and only a preliminary PK report (22 November 2021) is provided.

Preliminary median PK profiles and PK data by hepatic function are shown in figure 11 and summarized in table 21.

Figure 11 - Median Plasma PF-07321332 Concentration-Time Profiles Following a Single Oral Dose of PF-07321332 Enhanced with Ritonavir

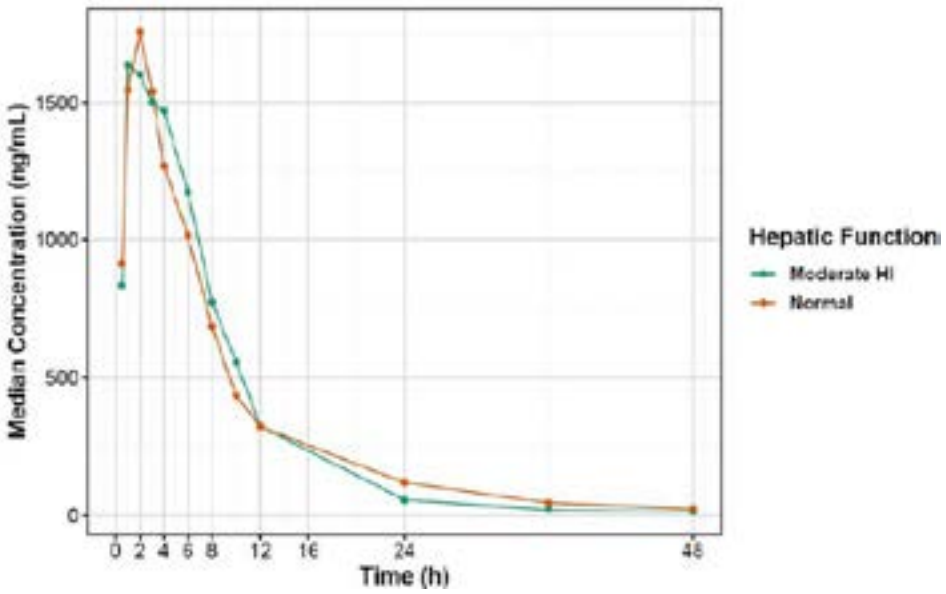


Table 21 - Descriptive Summary of Preliminary (Unaudited) Plasma PK Parameters of PF-07321332 by Hepatic Function in Study C4671010

Hepatic Function	PK Parameters[a]				
	N, n[b]	T_{max} (hr)	C_{max} (µg/mL)	AUC_{inf} (µg.hr/mL)	$t_{½}$ (hr)
Normal Hepatic Function	8,8	2 (0.5-2)	1.89 (20)	15.28 (36)	7 (29)
Moderate Hepatic Impairment	8,8	1.5 (1-2)	1.92 (48)	15.07 (43)	5.5 (32)

Abbreviations: %CV = percent coefficient of variation; AUC_{inf}= Area under the concentration-time curve from time zero to last measurable concentration; C_{max} = Peak plasma concentration; T_{max}=Time to achieve C_{max}; $t_{½}$=Half-life

Currently, the preliminary PK data in the moderate hepatic impaired group do not suggest a significant clinical PK change compared to subjects with normal hepatic function. However, these data could not be considered definitive. No data are provided for the severe hepatic impaired group. Pending availability of appropriate dosing recommendations with PF-07321332, a cautionary statement regarding use in subjects with mild and moderate hepatic impairment and a contraindication in subjects with severe hepatic impairment has been added to the Conditions for Use.

- Elderly

Preliminary PK data was provided in patients (study C4671005) between 18 and 86 years. However, the PK data from elderly patients included in the following subgroups of age: [65 to 74 years], [75 to 84 years] and >85 years could not be interpreted in the absence of full descriptive information (including detailed number by subgroup). Given that chronic renal disease is very common in elderly (especially with increasing age) together with the clinically significant increase of PK exposures (AUC and Cmax) for both moderate and severe renal impaired subjects, dosing recommendations in elderly should be further investigated at the time of the MA, notably with updated relevant PKPOP integrating PK data in patients and assessing age in covariate

The PK of PF-07321332 in elderly patients could not be considered elucidated yet.

Overall, among the 608 patients included in the PK dataset of patients, the applicant will be asked to further substantiate the PK profile in the relevant following subgroups of elderly: [65 to 74 years] and [75 to 84 years] and >85 years (including number of patients per category, the number of PK observations per each group of age), the mean and 90% observed interval [5-95th] Cmax at Day 1 and Ctrough at steady state after repeated administration of the recommended dose with comparison to a reference group (adults <65 years old). This is expected to enable providing dosing recommendation for each subgroup. If no or limited clinical / PK data are available in a given subgroup of age and also referring to the clinical data available by age category, restriction and/or warnings would have to be considered.

2.4.2. Pharmacodynamics

PF-07321332 has been shown to be active against SARS-CoV-2 $3CL^{pro}$ (Ki = 0.00311 µM, IC50 = 0.0192 µM) in a biochemical enzymatic assay and against other alpha and betacoronaviruses (SARS-CoV-1, HCoV-229E, MERS-CoV, HCoV-OC43, HCoV-HKU1, and HCoV-NL63).

PF-07321332 binds to the active site SARS-CoV-2 3CL protease and forms a covalent interaction via mainly 13 contact residues in the active site of $3CL^{pro}$. The conservation of these contact residues was assessed across different SARS-COV-2 isolates. These residues were highly conserved, with frequency of mutation <0.024%. The analysis indicates that 9 of 13 contact residues are identical among all alpha/beta CoV strains examined. This could explain the pan-coronavirus $3CL^{pro}$ inhibition by PF-07321332.

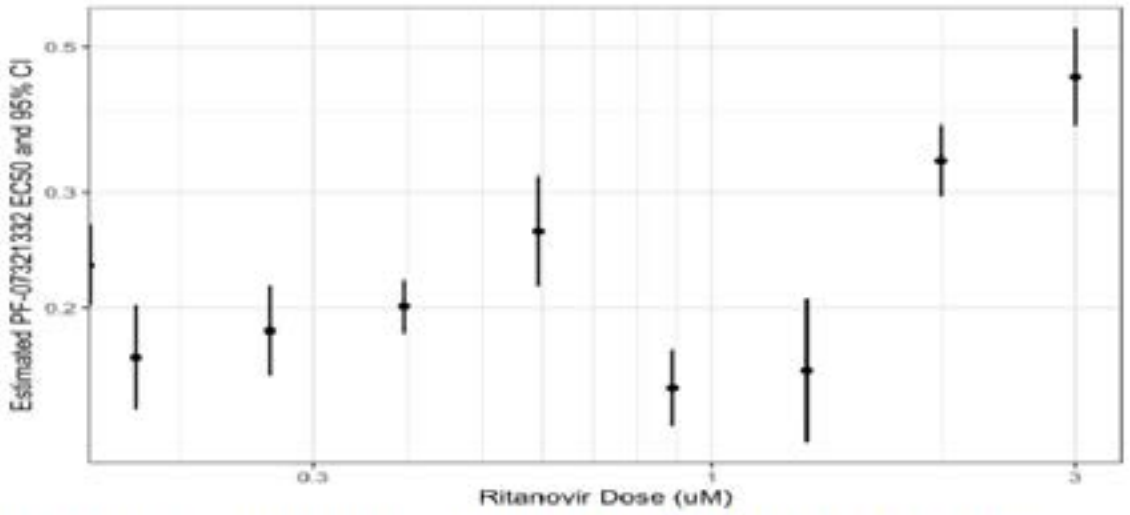
PF-07321332 also demonstrated >521-fold selectivity for coronavirus $3CL^{pro}$, compared with human cellular proteases, showing little or no activity against this panel of mammalian proteases as well as viral HIV protease (IC50>10 µM at human chymotrypsin and >100 µM at all other proteases tested). PF-07321332 did not inhibit enterovirus 71 (EV71) and human rhinovirus 1B (HRV1B) viral-induced CPE in human RD or HeLa cells, respectively (EC50 >100 µM), nor did it demonstrate cytotoxicity (CC50 of >100 µM). The activity of PF-07321332 seems selective to the coronavirus family.

The *in vitro* antiviral activity of PF-07321332 was demonstrated in VeroE6 ACE-2 cells with an EC50 of 0.0745 µM in the presence of P-gp inhibitor to better represent physiological cells which is acceptable, A549-ACE2 cells with EC50/EC90 values of 0.0779 µM / 0.215 µM, and physiologically relevant **dNHBE** (differentiated normal human bronchial epithelial) cells with EC50 of 0.0618 µM and 0.0326 µM, at Day 3 and Day 5 post-infection respectively. The metabolite, PF-07329268 inhibited SARS-CoV-2 CPE in VeroE6 ACE-2 cells with an EC50 value of 0.690 µM, in the presence of P-gp inhibitor (9-fold less potent than PF-07321332).

The antiviral activity of PF-07321332 was specific and not due to cellular toxicity (no cytotoxicity was observed up to >100 µM in VeroE6 ACE-2 cells) resulting in a TI of >21.5 in the absence of P-gp inhibitor.

Ritonavir had no antiviral effect up to 3 µM in an A549 cell line. Ritonavir does not demonstrate antiviral SARS-CoV-2 activity either alone or in combination with PF-07321332 (figure 12 below). Cell cytotoxicity was not observed up to 3 µM for PF-07321332 or ritonavir in an A549 cell line.

Figure 12 - PF-07321332 in Combination with Fixed Doses of Ritonavir (PF-00346560) Against SARS-CoV-2 nLuc Reporter Virus in A549-ACE2 Cells



Graph made using GeneData EC50 values and 95% CIs (Appendix 12.3) within the R programming environment to represent PF-07321332 potency estimates as a function of ritanovir concentration. The ritanovir dose is plotted on the log-scale, with the PF-07321332 potency with no ritanovir represented by the estimate and confidence interval on the far left of the plot.

Table 22 - EC50 for PF-07321332 and Remdesivir in dNHBE Cells at 3 and 5 Days Post Inoculum

Virus Collection Day	PF-07321332							
	[a] EC50 (µM)			GeoMean (95% CI)	[a] EC90 (µM)			GeoMean (95% CI)
	N=1	N=2	N=3		N=1	N=2	N=3	
3	0.0757	0.0678	0.0461	0.0618 (0.0324 to 0.118)	0.157	0.141	0.2676	0.181 (0.0769 to 0.425)
5	0.0555	0.0231	0.0271	0.0326 (0.0102 to 0.104)	0.0924	0.0436	0.0440	0.0561 (0.0192 to 0.164)
Virus Collection Day	Remdesivir							
	[a] EC50 (µM)			GeoMean (95% CI)	[a] EC90 (µM)			GeoMean (95% CI)
	N=1	N=2	N=3		N=1	N=2	N=3	
3	0.0019	0.0053	0.0026	0.00297 (0.000805 to 0.0109)	0.0043	0.0099	0.0322	0.0111 (0.000901 to 0.137)
5	0.0024	0.0069	0.0098	0.00545 (0.000885 to 0.0336)	0.008	0.0136	0.0349	0.0156 (0.0024 to 0.0993)

a. EC_{50} curves were fit to a Hill slope of 3 when >3 and defined by top dose only which was ≥50%.
b. Data generated at Utah State University: (2020). SARS-CoV-2 (USA_WA1/2020; Washington strain). Study Report PF-07321332_23Oct20_010204.

Of note, PF-07321332 is shown to exhibit pan-coronavirus antiviral activity against SARS-CoV-1 (EC50 12.3µM), MERS-CoV (EC50 5.41µM), both in the absence of an efflux inhibitor, that shifted to 0.151µM and 0.166 µM respectively, in the presence of P-gp inhibitor. The EC50 value against HCoV-229E, was of 0.190 µM in MRC-5 cells. The translability of these data in favour of this pan-coronavirus antiviral activity in clinic in uncertain.

The antiviral activity of PF-07321332 against SARS-CoV-2 variants B.1.1.7 (Alpha), B.1351 (Beta), P.1 (Gamma) and B.1.1.1.37 (Lambda, λ) was demonstrated using a cytopathic effect protection assay in

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Vero E6 P-gp Knockout cells, with reported EC50 values of 75.3 nM, 171 nM, 87.7 nM and 59.5nM respectively, compared with 96.3 nM for WA1 (USA-WA1/2020).

Due to the inability of the SARS-CoV-2 delta variant to exhibit CPE in the Vero E6 P-gp knockout cell line, the variants were also evaluated in Vero E6 TMPRSS2 with P-gp inhibitor. Mean EC50 values were 71.2 nM, 170 nM, 217 nM, 204 nM, 93 nM and 82.2 nM in the USA-WA1/2020 SARS-CoV-2 strain and alpha, beta, gamma, lamda, and delta variants, respectively.

PF-07321332 activity using a qPCR assay, showed inhibition with mean EC50 values of 32.2 nM, 41.0 nM, 127.2 nM, 24.9 nM, 21.2 nM, 15.9 nM in the USA-WA1/2020 SARS-CoV-2 strain and the Alpha, Beta, Gamma, Delta and Lambda variants, respectively. PF-07321332 is overall active *in vitro* against currently circulating SARS-CoV-2 strains with moderate decrease in PF-07321332 susceptibility against the beta variant (4-fold increase in EC50). The Delta variant represents the most prevalent VOC circulating notably in Europe. Recently, sub lineages of the Delta (B.1.617.2) variant carrying non-silent mutations in different areas of the genome, have emerged. A discussion on the potential impact of $3CL^{pro}$ mutations on the activity of PF-07321332 is considered important and, *in vitro* study in a substantial number of representative sequences will have to be provided at the time of the MA. Further investigation on Delta variant and its sublineages should be provided at the time of the MA. Antiviral activity of PF-07321332 against a fully representative Delta variant and its sublineages taking into account GISAID database remains to be provided. Moreover, investigations of the antiviral activity against the Delta 21J sublineage will have to be provided at the time of the MA, in view of the clinical data by the subgroups of patients with VOC (patients infected with this sublineage tend to show lower efficacy but the enrolled population was almost exclusively infected by the Delta variant (98%), notably including a vast majority of the patients infected with the 21J sublineage.

Table 23 - Activity of PF-07321332 Against Major SARS-CoV-2 Variants

SARS-CoV-2	Drug	Vero E6 P-gp knockout		Vero E6 TMPRSS2	
		Geomean EC_{50} (nM) Range	Geomean EC_{90} (nM) Range	Geomean EC_{50} (nM) Range	Geomean EC_{90} (nM) Range
USA-WA1	PF-07321332	96.3 (86.7 – 110)	195 (174 – 225)	71.2 (51.7 – 92.1)	147 (105 – 191)
	Remdesivir	57.9 (51.8 – 65.0)	122 (109 – 137)	91.4 (61.3 – 150)	196 (134 – 322)
α Variant	PF-07321332	75.3 (58.7 – 90.5)	186 (172 – 199)	170 (145 – 182)	364 (309 – 399)
	Remdesivir	41.7 (36.8 – 53.2)	132 (99.7 – 172)	113 (64.4 – 223)	240 (136 – 465)
β Variant	PF-07321332	171 (138 – 207)	363 (288 – 441)	217 (175 – 243)	460 (378 – 517)
	Remdesivir	50.5 (44.0 – 58.7)	106 (91.4 – 134)	105 (60.2 – 162)	221 (129 – 345)
γ Variant	PF-07321332	87.7 (68.2 – 121)	222 (187 – 251)	204 (137 – 250)	430 (287 – 533)
	Remdesivir	21.1 (17.6 – 26.9	53.6 (41.7– 66.6)	79.8 (52.4 – 116)	171 (111 – 253)
λ Variant	PF-07321332	59.5 (51.2 – 66.6)	171 (129 – 297)	93.0 (87.3 – 97.7)	193 (181 – 203)
	Remdesivir	26.5 (19.6 – 33.2)	64.4 (59.3 – 69.0)	80.3 (38.8 – 119)	171 (80.6 – 254)
Δ Variant	PF-07321332	N.A.	N.A.	82.2 (71.0 – 98.2)	168 (147 – 205)
	Remdesivir	N.A.	N.A.	122 (63.4 – 236)	261 (134 – 511)

N.A. = Not applicable as the Δ-Variant did not kill Vero E6 P-gp Knockout cells efficiently, therefore an EC_{50} could not be generated on this variant using this cell line. Vero-E6 TMPRSS2 cell assay was conducted in the presence of 2 μM P-gp inhibitor drug. Geomeans calculated from N=3, data presented as 3 significant figures

As a critical caveat no *in vitro* data on PF-07321332 against the new-emerging omicron variant were yet available. In view of the very rapidly increasing circulation of omicron, results of these *in vitro* data should be provided at the time of the MAA.

PF-07321332 was only evaluated in resistance selection assay against murine hepatitis virus (MHV) infected L929 cells (10 passages). Antiviral analysis of four mutant viruses harbouring the 5 treatment-emergent mutations in the MHV 3CL protease, shows a decrease in PF-07321332 susceptibility with 4.4 to 5 fold increase in mean EC50 values (ranging from 2.65-2.93 µM compared to 0.6 µM for parent MHV in murine L929 cells). These preliminary results indicate a possible likelihood of resistance development to PF-07321332 (the mutation S144A is near a catalytic site of the protease). *In vitro* selection of PF-07321332 resistant SARS-CoV-2 is currently underway and should be provided at the time of MA, to notably further substantiate the genetic barrier, which appears limited at this stage. Mutants that can replicate at each passage should be monitored for reduction viral fitness or decrease in susceptibility to the treatment. A resistance selection assay against delta variant and omicron should be provided at the time of the MAA.

Table 24 - Antiviral Activity of PF-07321332 against Mutant MHV

MHV Virus and mutants	Mutations	Titer at 48h post-infection (PFU/mL)	Log reduction at 48h post-infection (PFU/mL)	EC_{50} Geomean µM (Range)	EC_{50} Fold-change
Parent Virus	N/A	1.5e+06	N/A	0.60 (0.4-1.0)	1
30XEC50-13	Pro55Leu, Ser144 Ala Thr129Met, Thr50Lys	12500	2 logs	2.93 (2.0-4.5)	4.9
40XEC50-11	Pro55Leu, Ser144 Ala Pro15Ala	25000	2 logs	2.80 (1.6-4.4)	4.7
30XEC50-1	Pro55Leu, Ser144 Ala	125000	1 log	2.63 (1.4-3.9)	4.4
40XEC50-1	Pro55Leu, Ser144 Ala	72500	2 logs	2.65 (1.6-3.8)	4.4

N/A = not applicable

A total of 38 mutant SARS-CoV-2 $3CL^{pro}$ enzymes were tested for PF-07321332 inhibition of enzymatic activity (mutants with single point mutations in the PF-07321332 contact residues and highest prevalent mutations circulating in the population). Four mutations (H41Y, C145I, C145F, H163A) of the 13 mutations identified as key contact residues, showed lack of self-cleavage activity and would most likely yield an inactive enzyme. PF-07321332 showed a statistically significant drop in potency for inhibiting five of the 13 mutant enzymes (E166A, F140A, H164N, Q189K, and Y54A) with geomean Ki values of 31.2, 36.4, <5.98, 61.0, and 22.0 nM, respectively, versus wild type SARS-CoV-2 $3CL^{pro}$ (Ki of 1.68 nM). These mutants are being reverse engineered into SARS-Cov-2 and will be evaluated for changes in viral fitness and SARS-CoV-2 activity.

In addition to in-vitro PD data, some PD endpoints were measured amongst the efficacy endpoints in Study 1005, namely Viral Load over Time, allowing for a preliminary analysis on the effect of PF-07321332 in PD biomarkers. An update of those data should be provided at the time of the MAA.

Viral titers measured via RT-PCR in nasal swabs over time

A quantitative SARS-CoV-2 RT-PCR assay was used to measure viral load (copies/mL). Participants with samples collected using unvalidated (local) swabs or collected at non-NP sites were excluded from this POC assessment, as were participants with no virus detected at baseline (0 copies/mL). Viral load below the detection limit of 100 copies/mL was imputed as approximately 50 copies/mL, ie, using 1.69 Log10 (copies/mL) for Log10 (viral load) values below 2 Log10 (copies/mL).

Results in the mITT1 analysis set were also examined by serology status and baseline viral load. As expected, the additional viral load reduction from PF-07321332/ritonavir treatment relative to placebo were more apparent in participants who were seronegative than participants who were seropositive (-

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1.15 versus -0.77 Log10 copies/mL on a log-10 scale), and more apparent in participants with higher versus lower (≥107 copies/mL versus <107 copies/mL) viral load at baseline (-1.40 versus -0.79 Log10 copies/mL on a log-10 scale). An update of those data should be provided at the time of the MA.

Descriptive statistics in change in viral load from baseline to Day 5 in the three analysis population are presented below. This should be interpreted with particular caution in terms of magnitude given the descriptive analysis and the limited information.

Table 25 - Statistical analysis of change from baseline in Log10 transformed viral load (copies/mL) data – mITT, mIIT1 and mITT2 (protocol C4671005)

Analysis Population	Analysis Visit		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
mITT	Day 5	n	144	159
		LS mean (SE)	-2.99 (0.12)	-1.96 (0.12)
		Versus placebo		
		LS mean difference (SE)	-1.03 (0.16)	
		1-sided 80% CI for LS mean difference	(-Infty, -0.89)	
mITT1	Day 5	n	211	240
		LS mean (SE)	-2.69 (0.10)	-1.75 (0.09)
		Versus placebo		
		LS mean difference (SE)	-0.93 (0.13)	
		1-sided 80% CI for LS mean difference	(-Infty, -0.83)	
mITT2	Day 5	n	233	266
		LS mean (SE)	-2.81 (0.14)	-1.85 (0.13)
		Versus placebo		
		LS mean difference (SE)	-0.96 (0.12)	
		1-sided 80% CI for LS mean difference	(-Infty, -0.86)	

n=Number of participants with non-missing data in the analysis population and the covariates in the statistical model.
Infty=Infinity. Only Upper Limit for 80% CI is presented.
Participants are excluded from the analysis for reasons of Not Detected or Missing baseline viral load result, and local swabs use. Results from samples collected at non-nasopharyngeal site are also excluded.
Change from baseline modeled using ANCOVA
For mITT analysis set Model = Treatment + Baseline viral load + geographic region + serology status.
For mITT1 analysis set Model = Treatment + Baseline viral load + geographic region + serology status + symptom onset.
For mITT2 analysis set Model = Treatment + Baseline viral load + COVID-19 mAb treatment + geographic region + serology status + symptom onset.

Variants

The evaluation of the Mu VOC is ongoing. Data on PF-07321332 in the cell-based assay and qPCR assay is expected to be submitted during the MAA.

Antiviral activity data against omicron variant are thus currently unavailable (this has been reflected in the Conditions of Use). Given the epidemiological situation with highly increasing circulation of omicron worldwide, the company should provide this crucial information at the time of the MAA.

In line with prior discussion on the Delta variant and its sublineage, phenotypic antiviral assays will be performed on the subvariant Delta 21J and data will be expected at the time of the MAA.

2.4.3. Interactions

Pharmacodynamic Drug Interactions

In vivo pharmacodynamic drug interaction studies with PF-07321332 have not been conducted. In vitro and *in vivo* antiviral activity of PF-07321332 is described above in the non-clinical section.

Pharmacokinetic Drug Interactions

Interactions potential for Paxlovid (PF-07321332 / ritonavir) were only documented for PF-07321332 as, ritonavir interactions are already documented from the already approved ritonavir, NORVIR and have been integrated in the CoU, since it is currently difficult to estimate the net effect of the combination with PF-07321332 and ritonavir. This will be further investigated at the time of the MAA notably with additional expected ddI studies.

Paxlovid as perpetrator

The Appraisal of PF-07321332 interaction profile was based on *in vitro* studies. Its induction potential, inhibition of UGTs, inhibition of CYPs isoforms, as well as inhibition of transporters were performed in line with EMA drug-drug interaction guideline (CPMP/EWP/560/95/Rev. 1).

PF-07321332 was found to be an inducer of CYP3A4, CYP2B6, CYP2C8 and CYP2C9. It was identified as time-dependent inhibitor of CYP3A4 with estimated KI of 15.5 µM and 13.9 µM, and estimated Kinact estimated to 0.0142 min-1, and 0.0165 min-1, using respectively midazolam and testosterone as substrate. PF-07321332 was also an inhibitor of P-gp (IC50 70.6 µM), OATP1B1 (IC50 44.4 µM), OATP1B3 (IC50 283.2 µM), OCT1 (IC50 138.1 µM) and MATE1 (IC50 111 µM).

Ritonavir (RTV) interaction profile was based on Norvir SmPC. RTV is an inducer of CYP1A2, CYP2C8, CYP29, and CYP2C19, as well as inducer of UGTs. Ritonavir has also shown to be a time-dependent inhibitor of CYP3A4, an inhibitor of CYP2D6, and a P-gp inhibitor.

Overall, based on *in vitro* studies, Paxlovid seems to be an inhibitor of CYP2D6, P-gp, OATP1B1, OATP1B3, and OCT1 and MATE1. It induces UGTs, CYP3A4, CY2B6, CYP2C8, CYP2C9, CYP1A2, and CYP2C19. This will be further substantiated at the time of the MAA.

Paxlovid net effect on CYP3A4 and P-gp substrates *in vivo* is not established given Paxlovid is substrate, inhibitor, and inducer of CYP3A4, and also substrate and inhibitor of P-gp. This is currently being assessed in the following on-going studies, DDI study 1013 with midazolam, and DDI study 1012 with dabigatran. The results are expected to be submitted as part of the MAA.

Given the large drug-drug interaction spectrum of Paxlovid, clinical interaction study to assess the magnitude of interaction with MATE1, OATP1B1, OATP1B3, and OCT1 will have to be provided as part of the subsequent MAA.

The recommendations related to co-medications will then have to be updated in the light of the results of these clinical studies expected as part of MAA.

Paxlovid as victim

PF-07321332 is mainly excreted unchanged. Notably, 55.0% and 27.5% of the dose is excreted as parent compound in urine and feces, respectively. Regarding the fraction of PF-07321332 metabolized, CYP3A4 was identified as the major contributor (fm = 0.99) of the oxidative metabolism, based on *in vitro* studies. M5 and M8 metabolites, respectively arising via loss of amide and trifluoro acetyl group from PF-07321332, were the two main metabolites found *in vivo* representing 12.5% (12.1% in feces), and 4.2% (2.6% in urine and 1.6% in feces) of the total drug related material based on the ADME

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study. Furthermore, M7 the acyl-glucuronide conjugate of M5, was identified in human urine in trace amounts. In vitro results indicated that UGT2B4 and 2B7 contributed to 69.8% and 16.7% of the total metabolism of M5, respectively.

PF-07321332-transporter interaction profile was studied based on *in vitro* inhibition studies. PF-07321332 was found to be a substrate of the human MDR1 P-gp.

In vivo PF-07321332 interaction profile was assessed in clinical studies with a potent inhibitor and an inducer of CYP3A4 enzyme.

After co-administration of PF-07321332/ritonavir (300/100 mg SD) and carbamazepine (dose escalation design: 100mg BID from day 1 to 3, 200mg BID from day 4 to 7, 300 mg BID from day 8 to 15), the $AUC_{0-\infty}$ and C_{max} of PF-07321332 were decreased by 55% and 43%, respectively, as compared to administration of PF-07321332/ritonavir alone.

Based on these results, a recommendation in case of concomitant use of anti-convulsivant and Paxlovid should take into consideration a risk of efficacy loss caused by carbamazepine induction, and an urgent medical need to treat patients with epilepsy at high risk for progression to severe COVID-19. Because anti-convulsivant treatment in this population cannot be easily interrupted, even for a short period of time, further discussion is needed on the expected efficacy at the proposed therapeutic dose (i.e. 300 mg / 100 mg PF-07321332 / ritonavir) and the therapeutic margin in this particular population. The consequences in terms of efficacy and safety on concentrations 12h after dosing below 3-4 times EC90 on day 1 and below 5 to 6 times EC90 at steady state but above the EC90 (i.e. 292 ng/mL) are unclear. Thus, based on these preliminary data, presently the clinical impact in terms of efficacy at 300/100 mg of Paxlovid is uncertain. Given the available tablet strength of PF-07321332, and given that it is difficult to predict that the PK resulting from a dose increase would enable to strictly avoid a sub-optimal concentration with a critical risk of resistance, a dose increase cannot be proposed. Therefore, a conservative contra-indication with anti-convulsant is agreed and reflected in the Conditions of Use. This needs be further substantiated by the company as part of the MAA, potentially with the help of the ongoing investigation on a more adequate PK/POP model (see PK part) to avoid depriving epileptic patients (impossibility to stop treatment during the COVID treatment course).

After co-administration of PF-07321332/ritonavir (5 oral doses 300/100 mg q12h) and itraconazole (200 mg orally q24h for 8 days), the AUC_{tau} and C_{max} of PF-07321332 were increased by 38% and 19%, respectively, as compared to administration of PF-07321332/ritonavir alone. Such increases are not expected to be clinically relevant. Therefore, no dosing adjustment of PF-07321332/ritonavir is necessary when a CYP3A4 inhibitor is co-administrated with Paxlovid.

2.4.4. Data on Efficacy

The main clinical study in support of this Article 5(3) review is study C4671005 for which the design and results are presented below.

Other ongoing studies include:

-C4671002 is a ph2/3 pivotal study in non-hospitalised patients who are at low risk of progressing to severe illness (EPIC-SR for standard risk as opposed to High risk for EPIC-HR).

-C4671006 is a Ph2/3 Pivotal study in preventing symptomatic COVID-19 in adults who are household contacts of an individual infected with SARS CoV-2 (EPIC PEP).

No dedicated phase 2 dose-finding study in the intended population was conducted.

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Dose selection for the pivotal phase 2/3 study C4671005 (EPIC HR) was based on available preclinical and clinical safety data, from the Phase 1 study (C4671001), and *in vitro* pharmacology studies with PF-07321332.

The rationale for dose selection for the pivotal phase 2/3 study C4671005, based on reaching unbound Ctrough values above EC90 of 90.4 ng/mL determined in dNHBE cells (equivalent to 181 nM, fu, human=0.310) was agreed in principle by the CHMP during a Scientific Advice procedure. At the proposed dose of PF-07321332/ritonavir 300/100 mg BID, more than 95% of the participants are predicted to maintain free PF-07321332 concentrations above the *in vitro* EC90 over the 12-hour dosing interval (for a hypothetical intersubject variability of 60%). The proposed dose results in median Day 1 and steady state trough concentrations 3-4x EC90 and ~5-6 x EC90, respectively.

The use of ritonavir as a PK enhancer is also supported by literature and experimental data. Ritonavir did not demonstrate *in vitro* anti-viral activity toward SARS-CoV-2. The 100 mg dose is deemed appropriate.

The selected duration of treatment (5 days) for the C4671005 clinical study (and consequently for the CoU) is similar to what has been used with other antiviral agents for the treatment of acute respiratory infections. Rationale for treatment duration was based on the viral dynamics of SARS-CoV-2 in humans. To that end, a QSP model capable of describing viral dynamics with time (5d and 10d dosing regimens) was used to confirm the selection of a 5-day dosing duration of oral PF-07321332/ritonavir 300 mg /100 mg BID. The model predicted that a 5-day regimen would be sufficient for the treatment of symptomatic confirmed SARS-CoV-2 participants, with no benefit predicted for longer dosing.

A dosing regimen of 300 mg PF-07321332 coadministered with 100 mg ritonavir q12h administered orally for 5 days was then evaluated in the pivotal study.

Study C4671005

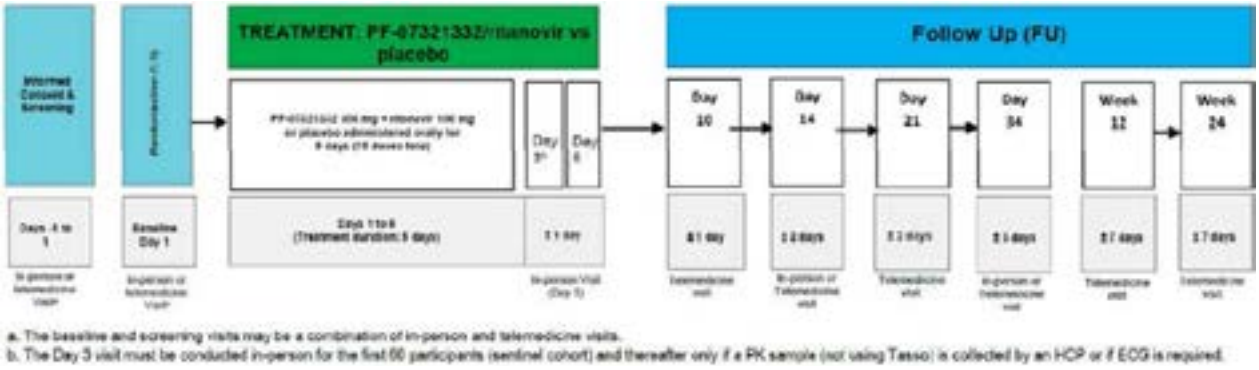
The clinical development for the treatment of non-hospitalized, symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illness is supported by one Phase 2/3 trial: Study C4671005 (abbreviated Study 1005).

Method

This Phase 2/3, randomized, double-blind, placebo-controlled study in non-hospitalized, symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illness will determine the efficacy, safety, and tolerability of PF-07321332/ritonavir compared with placebo in a 1:1 ratio.

Participants were to be screened within 48 hours of randomization. Eligible participants received PF-07321332 plus ritonavir or placebo orally q12h for 5 days (10 doses total). The total study duration was up to 24 weeks, study intervention through Day 5 or Day 6, efficacy assessments through Day 28, a safety follow-up period through Day 34, and long-term follow-up at Weeks 12 and 24.

Figure 13 - Schema of the study



a. The baseline and screening visits may be a combination of in-person and telemedicine visits.
b. The Day 3 visit must be conducted in-person for the first 60 participants (sentinel cohort) and thereafter only if a PK sample (not using Tasso) is collected by an HCP or if ECG is required.

- **Study participants**

Inclusion Criteria

Participants eligible to be included in the study were male and female aged ≥18 years with:

Type of Participant and Disease Characteristics

- Confirmed SARS-CoV-2 infection as determined by RT-PCR in any specimen collected within 5 days prior to randomization. RT-PCR was the preferred method; however, with evolving approaches to confirmation of SARS-CoV-2 infection, other molecular or antigen tests that detect viral RNA or protein were allowed. Participants may be enrolled based on positive results of a rapid SARSCoV-2 antigen test performed at screening.
- Initial onset of signs/symptoms attributable to COVID-19 within 5 days prior to the day of randomization and at least 1 of the specified signs/symptoms attributable to COVID-19 present on the day of randomization:

  Cough, Shortness of breath or difficulty breathing, Fever (>38°C), Chills or shivering, Fatigue, Muscle or body aches, Diarrhea, Nausea, Vomiting, Headache, Sore throat, Stuffy or runny nose.
- Has at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19 including:
  - ≥60 years of age;
  - BMI >25;
  - Current smoker (cigarette smoking within the past 30 days) and history of at least 100 lifetime cigarettes;
  - Immunosuppressive disease (eg, bone marrow or organ transplantation or primary immune deficiencies) OR prolonged use of immune-weakening medications:
    - Has received corticosteroids equivalent to prednisone ≥20 mg daily forat least 14 consecutive days within 30 days prior to study entry.
    - Has received treatment with biologics (eg, infliximab, ustekinumab), immunomodulators (eg, methotrexate, 6MP, azathioprine) or cancerchemotherapy within 90 days prior to study entry.
    - HIV infection with CD4 cell count <200 mm3 and a viral load less than400 copies/mL

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- Chronic lung disease (if asthma, requires daily prescribed therapy);
- Known diagnosis of hypertension;
- CVD, defined as history of any of the following: myocardial infarction, stroke, TIA, HF, angina with prescribed nitroglycerin, CABG, PCI, carotid endarterectomy, and aortic bypass;
- Type 1 or Type 2 diabetes mellitus;
- CKD provided the participant does not meet Exclusion Criterion 5;
- Sickle cell disease;
- Neurodevelopmental disorders (eg, cerebral palsy, Down's syndrome) or other conditions that confer medical complexity (eg, genetic or metabolic syndromes and severe congenital anomalies);
- Active cancer, other than localized skin cancer, including those requiring treatment as long as the treatment is not among the prohibited medications that must be administered/continued during the trial period;
- Medical-related technological dependence (eg, CPAP [not related to COVID-19]).

Exclusion Criteria

Main exclusion criteria were:

Medical Conditions

- History of hospitalization for the medical treatment of COVID-19.
- Current need for hospitalization or anticipated need for hospitalization within 48 hours after randomization in the clinical opinion of the site investigator.
- Prior to current disease episode, any confirmed SARS-CoV-2 infection, as determined by a molecular test (antigen or nucleic acid) from any specimen collection.
- Known medical history of active liver disease (other than nonalcoholic hepatic steatosis), including chronic or active hepatitis B or C infection, primary biliary cirrhosis, Child-Pugh Class B or C, or acute liver failure.
- Receiving dialysis or have known moderate to severe renal impairment.
- Known HIV infection with a viral load greater than 400 copies/mL or taking prohibited medications for HIV treatment (from known medical history within past 6 months of the screening visit).
- Suspected or confirmed concurrent active systemic infection other than COVID-19 that may interfere with the evaluation of response to the study intervention.
- Any comorbidity requiring hospitalization and/or surgery within 7 days prior to study entry, or that is considered life threatening within 30 days prior to study entry, as determined by the investigator.

Diagnostic Assessments

- Oxygen saturation of <92% on room air obtained at rest within 24 hours prior to randomization.

Prior/Concomitant Therapy

- Current or expected use of any medications or substances that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations may be associated with serious and/or

life-threatening events during treatment and for 4 days after the last dose of PF-07321332/ritonavir.

- Concomitant use of any medications or substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to first dose of PF-07321332/ritonavir and during study treatment.
- Has received or is expected to receive convalescent COVID-19 plasma.
- Has received or is expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit.

As a note, throughout the study period, provision was made to allow study visits to be conducted at a participant's home or at another non-clinic location approved by the investigator where possible when participants are unwilling or unable to attend a clinic visit.

- **Treatments**

The dosing instruction were:

- 2 tablets of PF-07321332 150 mg (or 3 tablets of 100 mg for some participants in the sentinel cohort) or placebo for PF-07321332 q12h
- 1 capsule of ritonavir 100 mg or placebo for ritonavir q12h.

The treatment was administered for 5 days (10 doses in total).

PF-07321332/ritonavir

A dosing regimen of 300 mg PF-07321332 co-administered with 100 mg ritonavir q12h administered orally for 5 days was evaluated in this study. Dose selection for this study included consideration of all relevant available preclinical and clinical data, including repeat-dose toxicology studies, clinical safety, and PK data from the Phase 1 study (C4671001), and *in vitro* pharmacology studies with PF-07321332 (please see PK and pharmacology sections).

Comparator

The company selected placebo as the comparator since there were no-globally approved Standard of Care (SoC) treatment for this patient population as of June 2021.

Concomitant therapies

Participants in either treatment group could receive SoC therapy so long as it is not prohibited (please see Exclusion criteria).

Eligibility for mAbs was limited to persons meeting EUA-defined (Emergency Use Authorization) criteria of being at high risk for progression to severe COVID-19 or hospitalization, may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction and require patients be monitored during administration and for at least 1 hour after infusion is complete.

Additionally, the company clarified that the case report form was designed to collect supplemental oxygen administered due to COVID-19 illness; therefore, the number of participants on chronic supplementary oxygen for an underlying condition at baseline cannot be characterized.

- **Objectives and outcomes/endpoints**

The primary objective and endpoint were:

Objectives	Endpoints
Primary:	**Primary:**
• To compare the efficacy of PF-07321332/ritonavir to placebo for the treatment of COVID-19 in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28.

The secondary objectives and endpoints were:

Objectives	Endpoints
Secondary:	**Secondary:**
• To describe the safety and tolerability of PF-07321332/ritonavir relative to placebo in the treatment of nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Incidence of TEAEs. • Incidence of SAEs and AEs leading to discontinuations.
• To compare the efficacy of PF-07321332/ritonavir to placebo for the treatment of COVID-19 in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28
• To describe the viral load in nasal samples over time in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Viral titers measured via RT-PCR in nasal swabs over time.

Additional secondary/endpoints were planned, but not for the interim analysis.

Hospitalization was defined as >24 hours of acute care, in a hospital or similar acute care facility, including Emergency Rooms or temporary facilities instituted to address medical needs of those with severe COVID-19 during the COVID-19 pandemic. This included specialized acute medical care unit within an assisted living facility or nursing home. This did not include hospitalization for the purposes of public health and/or clinical trial execution.

While the primary endpoint used the mITT analysis set (all participants treated ≤3 days after COVID-19 symptom onset), the second secondary endpoint used the mITT-1 analysis set (all participants treated ≤3 days and > 3 days after COVID-19 symptom onset) (please see Statistical method section).

- **Sample size**

This study was designed to have 90% statistical power to show a difference of 3.5% in the proportion of participants hospitalised/dying that did not receive COVID-19 therapeutic mAb between the treatment arms (PF07321332/ritonavir versus placebo) and were treated ≤ 3 days after COVID-19 symptom onset, using a 2-sided Type I error rate of 5%. Based on the BLAZE study, the proportion of hospitalization/death in the placebo arm was assumed to be 7%.

Using EAST (Version 6.5) for a 2 sample proportion test, the sample size needed to detect a 3.5% difference with 90% power at a 2-sided significance level of 5% was determined to be 1717 randomised participants. Enrolment of participants who at baseline had received or were expected to receive COVID-19 therapeutic mAb treatment was estimated to be approximately 20% of participants and limited/capped to 25% enrolment.

Enrolment of participants that had COVID-19 symptom onset >3 days prior to randomisation was expected to be approximately 25% and was to be limited to approximately 1000 participants. Assuming a 5% dropout rate, the total sample size for this study was to be approximately 3100 participants.

To allow for a 5% dropout rate, enrolment was to be stopped after approximately 1870 participants had been enrolled to ensure at least 1779 participants were available for the primary analysis.

Interim analysis

This report presents the results of the planned interim (IA) analysis of Study 1005. As specified in the protocol, this IA for efficacy and futility with a sample size-re-estimation was conducted and reviewed by an independent E-DMC after approximately 45% overall participants had completed the Day 28 assessments in the mITT analysis set (ie, 28 days after randomisation).

A second IA for efficacy and futility was to be performed after approximately 70% of participants in the mITT analysis set completed the Day 28 assessments (ie, 28 days after randomisation).

At the time of planning the Phase 2/3 study, there was uncertainty about the rate of COVID-19-related hospitalisation or death in the primary analysis population, and about the treatment effect of PF-07321332. Hence, a sample size re-estimation was to be conducted during the first IA based on conditional power.

Subsequent to the planned interim analyses, there were 2 analyses planned for reporting the results of this study. The primary analysis was to be performed after all participants had completed the Day 34 visit. The follow-up analysis was to be performed after all participants had completed the Week 24 visit.

The nominal significance level for the 2 planned interim and final proportion of hospitalisation/death analyses was determined by means of the Lan-DeMets procedure with an O'Brien-Fleming stopping

boundary. Further details are provided in the statistical methods section under multiplicity adjustment procedures.

- **Randomisation**

Eligible participants with a confirmed diagnosis of SARS-CoV-2 infection were randomized (1:1) to receive PF-07321332 and ritonavir or placebo orally q12h for 5 days (10 doses total).

Randomisation was stratified by geographic region and by whether participants had received/were expected to receive treatment with COVID-19 therapeutic mAbs (yes/no) based on the site investigator's assessment at time of randomisation.

Randomisation for the strata where participants had received or were expected to receive COVID-19 therapeutic mAb treatment was to be capped at a maximum of 25% enrolment.

Geographical region was defined as follows:

- US region: country of the United States, including Puerto Rico.
- Europe region: countries of Bulgaria, Czech Republic, Hungary, Netherlands, Poland, Spain, and Ukraine.
- Brazil region: country of Brazil.
- India region: country of India.
- Rest of the World region: countries of Argentina, Colombia, Japan, Malaysia, Mexico, Peru, Russian Federation, South Africa, Republic of Korea, Taiwan, Thailand, and Turkey.

- **Blinding (masking)**

This is a double-blind study.

The majority of sponsor staff were blinded to study intervention allocation. There was an unblinded team supporting the interactions with, and the analyses for, the E-DMC while the study was ongoing. The team consisted of medical monitor/clinicians, reporting statistician and reporting programmer(s) and was separate from the direct members of the study team. After all participants completed the Day 34 visit (or Early Termination (ET) prior to Day 34 visit), the study was to be unblinded and analyses through Day 34, including the primary efficacy endpoint analyses, was to be conducted. However, a blinded study team was to manage the completion of the study until all participants had completed the Week 24 visit (or ET prior to the Week 24 visit). The blinded team was to be separate from the unblinded team.

The independent E-DMC was to review unblinded data to ensure the safety of participants on an ongoing basis throughout the duration of the study, as specified in the E-DMC Charter. In addition, the E-DMC was to review the following:

- Sentinel cohort safety review: The E-DMC reviewed unblinded safety data after approximately the first 60 participants have completed Day 10 of the study, at which point enrolment was paused pending E-DMC review of the safety data.
- Proof-of-concept assessment: The E-DMC reviewed load data when approximately 200 participants in the primary analysis set with evaluable data complete the Day 5 assessments. Enrolment was not be paused during review of these data but could be paused or stopped following E-DMC review.

- Interim analyses (as described above)

- **Statistical methods**

This report includes the results from the planned interim analysis (IA) including the participants randomised through 29 September 2021. A selection of analyses were performed for the IA, in accordance with the company's statistical analysis plan.

Analysis populations

The following efficacy analysis sets were defined for the interim analysis.

Analysis set	Description	Endpoints
Modified Intent-To-Treat (mITT)	All participants randomly assigned to study intervention, who take at least 1 dose of study intervention, with at least 1 post-baseline visit through Day 28 visit, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were treated ≤3 days of COVID-19 onset. Participants will be analysed according to the study intervention to which they were randomised.	Primary endpoint Sensitivity analysis of primary endpoint Supplemental analysis of primary endpoint Subgroup analysis of primary endpoint Secondary analysis of POC Secondary endpoints
Modified Intent-To-Treat 1 (mITT1)	All participants randomly assigned to study intervention, who take at least 1 dose of study intervention, with at least 1 post-baseline visit through Day 28 visit and who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment. Participants will be analysed according to the study intervention to which they were randomised.	First key secondary analysis of the primary endpoint Subgroup analysis of first key secondary endpoint Secondary analysis of POC Secondary endpoints
Modified Intent-To-Treat 2 (mITT2)	All participants randomly assigned to study intervention, who take at least 1 dose of study intervention, and with at least 1 post-baseline visit through Day 28. Participants will be analysed according to the study intervention to which they were randomised.	Sensitivity analysis of primary endpoint Secondary analysis of POC Secondary endpoints

Other analysis sets were used for disposition, baseline or safety summaries.

Full Analysis Set (FAS): All participants randomly assigned to study intervention regardless of whether or not study intervention was administered.

Safety Analysis Set (SAS): All participants who receive at least 1 dose of study intervention. Participants were analysed according to the intervention they actually received.

Hypothesis testing and multiplicity adjustment

The primary hypothesis to be tested was whether or not there is a difference in proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28 between PF-7321332/ ritonavir and placebo. The statistical hypothesis was as follows:

$$H_o: \pi_{PF\text{-}7321332} - \pi_{placebo} = 0$$

versus

$$H_a: \pi_{PF\text{-}7321332} - \pi_{placebo} \neq 0$$

Where $p_{PF\text{-}7321332}$ and $p_{placebo}$ are the proportions of participants with hospitalization or death through Day 28. The hypotheses will be tested at an overall significant level of 5% (2-sided).

Following the positive test of the primary endpoint, sequential testing was to be performed for the following 2 secondary endpoints:

- Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28 who did not receive COVID-19 therapeutic mAb treatment, regardless of their onset of COVID-19 related signs and symptoms.
- Time (days) to sustained alleviation of all targeted signs/symptoms through Day 28.

Some inconsistencies were found in the company's documentation regarding the sequential testing of the first two secondary endpoints. Indeed, the "proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28 who did not receive COVID-19 therapeutic mAb treatment, regardless of their onset of COVID-19 related signs and symptoms" is described as the "first key secondary endpoint". However, the SAP also includes the following text: "The time to sustained alleviation of all targeted signs/symptoms through Day 28 is to be tested first. If this test is positive, then will continue with second endpoint. The hypotheses were to be tested at an overall level of 5% (2-sided)." Given the focus on the primary analysis (mITT) and mITT1 population (part of the key secondary endpoints) at the time of the interim analysis in support of the Art5(3) and the consistency shown in the results as described further, this does not impact the Art5(3) but will have to be clarified at the time of MA.

Other secondary endpoints listed below were to be subsequently tested following the Hochberg procedure1:

1. Time (days) to sustained resolution of all targeted signs/symptoms through Day 28.

2. Proportion of participants with a resting peripheral oxygen saturation ≥95% at Days 1 and 5.

3. Number of COVID-19 related medical visits through Day 28.

The nominal significance level for the 2 planned interim and final proportion of hospitalisation/death analyses was determined by means of the Lan-DeMets procedure with an O'Brien-Fleming stopping boundary, with an overall 2-sided type I error rate of 5%. For the first IA (45%), O'Brien-Fleming approach was used for decision making, ie, reject H0 with 2-sided p-value ≤0.002, or reject H1 with 2-sided p-value >0.9184. The actual stopping boundaries depended on the exact timing of the IA.

For the second IA (70%), O'Brien-Fleming approach was to be used for decision making, ie, reject H0 with 2-sided p-value ≤0.014, or reject H1 with 2-sided p-value >0.337. The actual stopping boundaries were to depend on the available percentage of information.

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A sample size re-estimation was to be conducted during the first interim analysis based on conditional power. The sample size could have been adjusted one time and the increase was to be capped at 30%. The Cui, Hung, and Wang (1999) method would be used to control the Type I error probability.

Another discrepancy is noted regarding the stopping boundaries which would have resulted from the potential sample size re-estimation. Although the CHW method would be expected to adequately preserve the type I error and would require fixed stopping boundaries, the SAP also includes the following text: "The actual stopping boundaries will depend on the available percentage of information". In fact there was no sample size re-estimation. The DSMB recommended to stop enrolment in view of efficacy level at the pre-specified interim analysis.

Primary analysis

The cumulative proportion of participants who experienced a COVID-19-related hospitalization or death due to any cause during the first 28 days of the study was estimated for each treatment group of the mITT analysis set using the Kaplan-Meier method to consider losses to follow-up and patients who discontinued early.

The estimand was the difference of the proportions in the 2 treatment groups and its 95% confidence interval was presented, as well as the associated two-sample proportion test. For the 95% CI, the corresponding estimate of the standard error was computed using Greenwood's formula (Kalbfleisch and Prentice; 1980). The Greenwood's formula to estimate the variance of the difference of proportions at Day 28 is sqrt[Var(S_{PF}(28))+Var($S_{Placebo}$(28))]. Instead of dealing with S(t_i) the log-log approach to CI was used. The 95% CI was computed for the estimate of L(t)= log(-log(S(t))), the hazard function.

$$Var\left(\hat{L}(t)\right) = Var\left[log\left(-log\left(\hat{S}(t)\right)\right)\right]$$

The CI will be in right range when transforming back to S(t) = exp (-exp (L(t)). Antilogging this confidence interval gives a 95% confidence interval for the difference itself.

The above primary analysis was to be conducted for the 2 planned interim analyses as well. Two-sided 95% CI (adjusted for the 2 planned interim analyses) and associated p-value (two-sample proportion test) for the null hypothesis of no difference between treatment groups were to be presented. Significance level was to be determined using the O'Brien-Fleming approach at the interim analysis and the final analysis. The overall significance level was set at 5% (2 sided).

For participants who completed Day 28 efficacy assessment (Day 34 visit), they were censored at their last visits. For participants who discontinued before Day 28 assessment or are lost to follow-up, they were censored at the last known date in the study.

Participants were analysed under the mAb stratum assigned at randomisation/baseline.

The proportion of participants with COVID-19 related hospitalisation or death from any cause through Day 28 were summarised graphically using Kaplan-Meier plots.

Key secondary analysis

The analysis of the proportion of participants with COVID-19 related hospitalization or death due to any cause through Day 28 in the mITT1 analysis set was similar to the primary endpoint analysis.

Sensitivity analyses of the primary endpoint

A sensitivity analysis of the primary endpoint was performed using the mITT2 analysis set.

A post-hoc sensitivity analysis was performed using the mITT analysis set whereby participants that did not have follow-up data through Day 21 were hypothetically assumed to experience both COVID-19-related hospitalization and death in a worst-case scenario.

Supplemental analyses of the primary endpoint

Supplemental analyses were performed on the primary endpoint using the mITT analysis set where:

- Participants who received a therapeutic COVID-19 mAb treatment post-baseline were considered as an event for the endpoint (in addition to COVID-19 related hospitalisation and death due to any cause) with mAb treatment date as the time of event.
- A logistic regression model was fitted to the primary endpoint of hospitalisation/death and included treatment and region effect as independent variables

Subgroup analyses

Pre-specified subgroup analyses of the primary and first key secondary endpoints using the mITT and mITT1 analysis sets, respectively, were conducted by age (<65, ≥65 years), gender, race, BMI (<25, 25-29, ≥30 kg/m2), baseline serology status (antibody negative, antibody positive), baseline viral load ([<104, ≥104 copies/mL] and [<107, ≥107 copies/mL]), baseline comorbidities and number of baseline comorbidities present (0-1, 2-3, ≥4).

Viral Load Measured via RT-PCR Over Time

The viral load data measured in Day 1 and Day 5 are nasopharyngeal samples. These are the samples to be used on the Proof of Concept (POC) analysis. POC analysis of viral load data was to occur when approximately 200 participants in the mITT population with evaluable data completed the Day 5 assessments.

Descriptive statistics by treatment group for the change from baseline to Day 5 was provided for each treatment group and included the difference between the PF-07321332/ritonavir arm and placebo. An ANCOVA model was used to analyse the change from baseline in Log10 transformed viral load (copies/mL) data which included treatment group, baseline viral load and baseline serology status for the mITT, mITT1 and mITT2 analysis sets. The mAb treatment status and symptom onset to first dose date status (≤3 days, >3 days) was used in the model dependent of population.

Participants were excluded from the analysis due to missing or baseline viral load below the limit of detection (<550 Log10 copies/mL), or collection with an unvalidated (local) swab. Preliminary data suggests swab type is critical and viral load determined with different swab types cannot be combined, therefore, only samples collected with the validated I-Swab-plus were used for formal viral load analysis. Data reported as less than 2.0 Log10 copies/mL was recorded as 1.69 Log10 copies/mL and data reported as "not detected' was recorded as 0 Log10 copies/mL. Results from samples collected at non-NP sites (like nasal, other or missing) were also excluded.

Changes to planned analyses

Several important changes were made to the planned analyses as part of protocol amendments 2 and 3. Most relevant modifications are briefly described in the table below.

Protocol amendment	Change in planned analyses
Amendment 2	The primary analysis set (mITT) has been refined to include just those participants who were treated ≤3 days after COVID-19 symptom onset

	(.symptom onset window reduced from <5 days to ≤3 days). Other impacts include: - Key secondary endpoint added as a consequence on mITT1 population, i.e. regardless of COVID-19 symptom onset - Sample size increased from 2260 to approximately 3000 (adjusted for updated primary efficacy analysis) - Enrolment of participants that had COVID-19 symptom onset > 3 days prior to randomisation expected to be approximately 25% and limited to 1000 participants
Amendment 3	Additional planned interim analysis for efficacy and futility to be done after approximately 70% of participants in the mITT analysis set complete the Day 28 assessments (i.e., 28 days after randomization). Other impacts include: - Modification of first interim analysis to be planned for efficacy and futility (rather than efficacy and safety) - Sample size increased from 3000 to 3100 participants due to addition of second interim analysis

Several changes were also implemented by SAP amendments. Key changes were:

- A sensitivity analysis of the primary endpoint based on mITT2 in the SAP (v1.1; 12 October 2021) was initially described as a secondary analysis of the primary endpoint (in protocol amendment 2, 2 August 2021)
- The POC analysis of viral load (described previously) was specified in the SAP.

Results

The trial began on 16 July 2021 and the data cut-off for the 45% interim analysis was 26 October 2021.

- **Participant flow**

As of the data cut-off (26 October 2021), all 1361 participants in the interim analysis had entered the treatment phase.

This interim CSR presents the results of a planned interim analysis of participants randomized through 29 September 2021 who completed Day 28 assessments.

Table 26 - Disposition Events Summary - Full Analysis Set (Protocol C4671005_45IA)

Number (%) of Participants	PF-07321332 300 mg + Ritonavir 100 mg (N=678) n (%)	Placebo (N=683) n (%)	Total (N=1361) n (%)
Disposition phase: Treatment			
Participants Entered:	678 (100.0)	683 (100.0)	1361 (100.0)
Discontinued	48 (7.1)	61 (8.9)	109 (8.0)
Reason for discontinuation			
Adverse event	16 (2.4)	29 (4.2)	45 (3.3)
Death	0	0	0
Lack of efficacy	0	0	0
Lost to follow-Up	1 (0.1)	1 (0.1)	2 (0.1)
Noncompliance with study drug	0	0	0
Pregnancy	0	0	0
Protocol deviation	0	0	0
Study terminated by sponsor	0	0	0
Withdrawal by subject	24 (3.5)	23 (3.4)	47 (3.5)
Medication error without associated adverse event	0	1 (0.1)	1 (<0.1)
No longer meets eligibility criteria	1 (0.1)	1 (0.1)	2 (0.1)
Other	6 (0.9)	6 (0.9)	12 (0.9)
Completed	630 (92.9)	622 (91.1)	1252 (92.0)

Number (%) of Participants	PF-07321332 300 mg + Ritonavir 100 mg (N=678) n (%)	Placebo (N=683) n (%)	Total (N=1361) n (%)
Ongoing	0	0	0
Disposition phase: Follow-up			
Participants Entered:	678 (100.0)	683 (100.0)	1361 (100.0)
Discontinued	50 (7.4)	57 (8.3)	107 (7.9)
Reason for discontinuation			
Death	0	10 (1.5)	10 (0.7)
Lost to follow-Up	9 (1.3)	7 (1.0)	16 (1.2)
Study terminated by sponsor	0	0	0
Withdrawal by subject	31 (4.6)	32 (4.7)	63 (4.6)
Other	10 (1.5)	8 (1.2)	18 (1.3)
Completed	545 (80.4)	541 (79.2)	1086 (79.8)
Ongoing	83 (12.2)	85 (12.4)	168 (12.3)
Disposition phase: Long-term follow-up			
Participants Entered:	594 (87.6)	597 (87.4)	1191 (87.5)
Discontinued	47 (6.9)	56 (8.2)	103 (7.6)
Reason for discontinuation			
Adverse event	0	0	0
Death	0	10 (1.5)	10 (0.7)
Lost to follow-Up	8 (1.2)	7 (1.0)	15 (1.1)
Study terminated by sponsor	0	0	0
Withdrawal by subject	31 (4.6)	32 (4.7)	63 (4.6)
Other	8 (1.2)	7 (1.0)	15 (1.1)
Completed	0	0	0
Ongoing	547 (80.7)	541 (79.2)	1088 (79.9)

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(Data cutoff date : 26OCT2021 Database snapshot date : 29OCT2021) Output File: /nda_unblinded/C4671005_45IA/adds_s001
Table 14.1.1 PF-07321332 is for Pfizer internal use.

Further enrolment in the study was stopped on 05 November 2021, and at the time of this decision, 2426 of the intended sample size (3100) had been randomized.

- **Recruitment**

1361 participants enrolled in the study through 29 September 2021 are included in this interim analysis.

As a note, as of 09 November 2021, a total of 2426 participants have been randomized into Study 1005, and the final primary analysis has been performed when all participants have completed follow-up through Day. 34. Only preliminary data from the final analysis were provided for this Art5(3) which seem to show consistent effect size with the following described results of the interim analysis.

Results of the final analysis should be provided at the time of the MAA

Halt center's recruitment

The company made a data driven decision to halt recruitment (22 September 2021, total of 193 participants randomized) in India due to observations in a blinded data review of a >90% rate of serology positive participants at baseline (92% versus 45% in patients from India versus ROW, respectively), with corresponding low levels of viral load measured at baseline from a blinded assessment (mean baseline viral load [Log10 copies/mL] = 2.36 versus 5.25 copies/mL in patients from India versus ROW, respectively), and the high frequency of participants experiencing mild COVID-19 symptoms at baseline (73% versus 15% of participants with only mild symptoms at baseline, India versus ROW, respectively).

- **Conduct of the study**

Protocol Amendments

The permitted window in the inclusion criteria for a positive RT-PCR test prior to randomization was updated from 3 days to 5 days (Protocol Amendment 1, 02 July 2021) (For other mains protocol amendment, please see Statistical methods' section).

Deviation

The most frequently reported important protocol deviations occurred within the procedures/tests (20.6%), investigational product dosing or administration error (16.5%), randomization (2.9%), and inclusion/exclusion criteria (2.4%) categories. All other categories occurred in ≤1.7% of participants.

Protocol deviations were comparable between both treatment groups.

GCP noncompliance

Site 1470, terminated for GCP noncompliance, reported a total of 12 important protocol deviations in 12 of 37 enrolled participants at the site: 8 participants in PF-07321332/ritonavir arm and 4 participants in placebo arm. Important protocol deviations by category include:

- Inclusion/Exclusion criteria (PF-07321332/ritonavir: 3 participants; placebo: 0 participants)
- Investigational Product (PF-07321332/ritonavir: 3 participants; placebo: 1 participant)
- Procedures/Tests (PF-07321332/ritonavir: 2 participants; placebo: 3 participants).

Stop of the study

On 03 November 2021, the E-DMC reviewed data from the 45% interim analysis and determined that the pre-specified criteria for stopping the trial due to overwhelming efficacy had been achieved (PF-07321332/ritonavir is superior to placebo in the mITT analysis set for reduction in hospitalization/death; p<0.0001, the pre-specified p-value per protocol to stop the trial for efficacy was p<0.002). Further enrolment in the study was stopped.

- **Baseline data**

Demographic and baseline characteristics are presented below.

Table 27 - Demographic and Baseline Characteristics - Full Analysis Set

	PF-07321332 300 mg + Ritonavir 100 mg (N=678)	Placebo (N=683)	Total (N=1361)
Age (Years), n (%)			
< 18	0	0	0
18 - 44	361 (53.2)	336 (49.2)	697 (51.2)
45 - 59	208 (30.7)	201 (29.4)	409 (30.1)
60 - 64	38 (5.6)	61 (8.9)	99 (7.3)
65 - 74	54 (8.0)	62 (9.1)	116 (8.5)
≥ 75	17 (2.5)	23 (3.4)	40 (2.9)
Mean (SD)	43.86 (14.93)	45.47 (15.69)	44.67 (15.33)
Median (range)	42.00 (18.00, 86.00)	45.00 (18.00, 84.00)	44.00 (18.00, 86.00)
Gender, n (%)			
Male	344 (50.7)	369 (54.0)	713 (52.4)
Female	334 (49.3)	314 (46.0)	648 (47.6)
Race, n (%)			
White	424 (62.5)	435 (63.7)	859 (63.1)

	PF-07321332 300 mg + Ritonavir 100 mg (N=678)	Placebo (N=683)	Total (N=1361)
Black or African American	37 (5.5)	25 (3.7)	62 (4.6)
Asian	134 (19.8)	140 (20.5)	274 (20.1)
American Indian or Alaska Native	76 (11.2)	77 (11.3)	153 (11.2)
Native Hawaiian or other Pacific Islander	0	0	0
Multiracial	1 (0.1)	0	1 (<0.1)
Other	0	0	0
Not reported	5 (0.7)	4 (0.6)	9 (0.7)
Unknown	1 (0.1)	2 (0.3)	3 (0.2)
Ethnicity, n (%)			
Hispanic or Latino	324 (47.8)	330 (48.3)	654 (48.1)
Not Hispanic or Latino	352 (51.9)	349 (51.1)	701 (51.5)
Not reported	2 (0.3)	4 (0.6)	6 (0.4)
Unknown	0	0	0
Weight (kg)			
Mean (SD)	80.44 (17.59)	81.26 (18.85)	80.85 (18.23)
Median (range)	78.90 (42.00, 158.3)	78.50 (42.00, 166.0)	78.80 (42.00, 166.0)
Height (cm)			
Mean (SD)	166.2 (9.74)	166.4 (10.27)	166.3 (10.00)
Median (range)	166.0 (136.9, 195.6)	166.0 (125.2, 207.3)	166.0 (125.2, 207.3)
BMI (kg/m^2), n (%)			
< 25	142 (20.9)	139 (20.4)	281 (20.6)
25 - < 30	290 (42.8)	291 (42.6)	581 (42.7)
30 - < 35	163 (24.0)	164 (24.0)	327 (24.0)
35 - < 40	45 (6.6)	53 (7.8)	98 (7.2)
≥ 40	38 (5.6)	36 (5.3)	74 (5.4)
Mean (SD)	29.08 (5.65)	29.21 (5.61)	29.14 (5.63)
Median (range)	28.30 (16.58, 58.07)	28.35 (16.05, 59.07)	28.32 (16.05, 59.07)
Duration since first diagnosis (Days), n (%)			
≤ 3	623 (91.9)	642 (94.0)	1265 (92.9)
> 3	55 (8.1)	41 (6.0)	96 (7.1)
Mean (SD)	1.44 (1.33)	1.38 (1.28)	1.41 (1.30)
Median (range)	1.00 (0.00, 5.00)	1.00 (0.00, 9.00)	1.00 (0.00, 9.00)
Duration since first symptom (Days), n (%)			
≤ 3	433 (63.9)	426 (62.4)	859 (63.1)
> 3	245 (36.1)	257 (37.6)	502 (36.9)
Mean (SD)	3.02 (1.14)	3.09 (1.10)	3.06 (1.12)
Median (range)	3.00 (0.00, 7.00)	3.00 (0.00, 9.00)	3.00 (0.00, 9.00)
Number of risk factors of interest, n (%)			
0	2 (0.3)	0	2 (0.1)

	PF-07321332 300 mg + Ritonavir 100 mg (N=678)	Placebo (N=683)	Total (N=1361)
1	293 (43.2)	267 (39.1)	560 (41.1)
2	240 (35.4)	254 (37.2)	494 (36.3)
3	91 (13.4)	101 (14.8)	192 (14.1)
4	44 (6.5)	49 (7.2)	93 (6.8)
>4	8 (1.2)	12 (1.8)	20 (1.5)
Comorbidities, n (%)			
Cardiovascular disorder	24 (3.5)	26 (3.8)	50 (3.7)
Chronic kidney disease	3 (0.4)	5 (0.7)	8 (0.6)
Chronic lung disease	40 (5.9)	27 (4.0)	67 (4.9)
Cigarette smoker	244 (36.0)	257 (37.6)	501 (36.8)
Diabetes mellitus	87 (12.8)	88 (12.9)	175 (12.9)
Hypertension	207 (30.5)	234 (34.3)	441 (32.4)
Immunosuppression	6 (0.9)	6 (0.9)	12 (0.9)
Cancer	2 (0.3)	2 (0.3)	4 (0.3)
Neurodevelopmental disorder	2 (0.3)	0	2 (0.1)
HIV infection	0	1 (0.1)	1 (<0.1)
Device dependence	4 (0.6)	1 (0.1)	5 (0.4)
COVID-19 mAb treatment, n (%)			
Received/expected to receive	55 (8.1)	57 (8.3)	112 (8.2)
Not received/not expected to receive	623 (91.9)	626 (91.7)	1249 (91.8)
Geographic region, n (%)			
United States	304 (44.8)	304 (44.5)	608 (44.7)
Europe	122 (18.0)	121 (17.7)	243 (17.9)
Brazil	0	1 (0.1)	1 (<0.1)
India	95 (14.0)	98 (14.3)	193 (14.2)
Rest of World	157 (23.2)	159 (23.3)	316 (23.2)
Serology status, n (%)			
Negative	291 (43.9)	301 (45.0)	592 (44.4)
Positive	372 (56.1)	368 (55.0)	740 (55.6)
Viral load (Log_{10} copies/mL), n (%)			
<4	237 (37.6)	238 (37.8)	475 (37.7)
≥4	393 (62.4)	392 (62.2)	785 (62.3)
≥5	331 (52.5)	333 (52.9)	664 (52.7)
≥6	259 (41.1)	247 (39.2)	506 (40.2)
<7	459 (72.9)	464 (73.7)	923 (73.3)
≥7	171 (27.1)	166 (26.3)	337 (26.7)
≥8	73 (11.6)	69 (11.0)	142 (11.3)
≥9	3 (0.5)	1 (0.2)	4 (0.3)
≥10	0	0	0
Mean (SD)	4.69 (2.82)	4.72 (2.74)	4.71 (2.78)
Median (range)	5.25 (0.00, 9.13)	5.26 (0.00, 9.06)	5.26 (0.00, 9.13)

All participants had a laboratory confirmed SARS-CoV-2 diagnosis, with 92.9% of participants having a qualifying SARS CoV-2 positive test collected within 3 days of first dose of study intervention.

Across treatment groups, the following could be underlined:

- 91.8% participants did not receive or were not planning to receive mAbs for the disease under study at the time of randomization.
- 55.6% of participants were serological positive at baseline.
- 62.3% participants had baseline viral load ≥4.0 Log10 copies/mL.

The most common risks factor at baseline were across treatment groups:

- BMI >25 kg/m^2: 79.4% (BMI >30 kg/m2: 36.7%)
- Cigarettes smokers: 35.8%
- Hypertension: 32.4%

Across treatment groups, 41.1% and 36.3% had respectively 1 and 2 risk factors.

Variants of concern (VOC)

An analysis was conducted from the first 490 participants with sequencing data. Two participants available for sequencing did not receive either placebo or PF-07321332/ritonavir and are not included in the assessment. The preliminary analysis is described in an interim virology sequencing report.

The primary variant across both treatment arms was Delta (98.0%) and was distributed in high prevalence as subvariants Delta (21J) (72.1%), Delta (21A) (12.5%) and Delta (21I) (13.3%).

Table 28 - Distribution of Variant of Concern by Treatment

CLADE	PF-07321332 300 mg + Ritonavir 100 mg (N=239)	Placebo (N=249)	All (N=488)
20A	0 (0%)	1 (0.4%)	1 (0.2%)
20C	1 (0.4%)	2 (0.8%)	3 (0.6%)
20I (alpha, V1)	1 (0.4%)	0 (0%)	1 (0.2%)
20J (Gamma, V3)	1 (0.4%)	0 (0%)	1 (0.2%)
All Delta (21A, 21I, 21J)	234 (97.9%)	244 (98.0%)	478 (98.0%)
21A (Delta)	35 (14.6%)	26 (10.4%)	61 (12.5%)
21I (Delta)	31 (13.0%)	34 (13.7%)	65 (13.3%)
21J (Delta)	168 (70.3%)	184 (73.9%)	352 (72.1%)
21H (Mu)	1 (0.4%)	0 (0%)	1 (0.2%)
Not Available	1 (0.4%)	2 (0.8%)	3 (0.6%)

Note: 490 participants had Day 1 and/or Day 5 sequencing data available, out of those participants, only 488 received either placebo or PF-07321332/Ritonavir Percentage in parentheses were calculated using a total of 488 participants. For each participant, CLADE is determined from Day 1 Sample, if day 1 sample is not available,

- **Number analysed**

The analysis of efficacy was performed using the mITT, mITT1, and mITT2 sets as follow.

Table 29 - Participant Evaluation Groups - All Screened Participants

	PF-07321332 300 mg + Ritonavir 100 mg (N=678) n (%)	Placebo (N=683) n (%)	Total (N=1361) n (%)
Screened: 1361 Screened Failure: 0 Not Screen Failure but not Randomized: 0			
Assigned to Treatment	678 (100.0)	683 (100.0)	1361 (100.0)
Treated	672 (99.1)	677 (99.1)	1349 (99.1)
Not Treated	6 (0.9)	6 (0.9)	12 (0.9)
Safety Analysis Set	672 (99.1)	677 (99.1)	1349 (99.1)
Full Analysis Set	678 (100.0)	683 (100.0)	1361 (100.0)
mITT Analysis Set	389 (57.4)	385 (56.4)	774 (56.9)
mITT1 Analysis Set	607 (89.5)	612 (89.6)	1219 (89.6)
mITT2 Analysis Set	661 (97.5)	669 (98.0)	1330 (97.7)

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Table 14.1.1.1 PF-07321332 is for Pfizer internal use.

Of note, screened failure and not randomized participants are not reported in this interim analysis. This will have to be provided at the time of the MAA (notably screening failure in relation to ddI).

Table 30 - Duration of Treatment (Actual Dosing Day) - Safety Analysis Set

	PF-07321332 300 mg + Ritonavir 100 mg (N=672)	Placebo (N=677)	Total (N=1349)
Duration of treatment (Days)[a]			
n	672	677	1349
Mean (SD)	5.04 (0.82)	5.01 (0.89)	5.03 (0.85)
Median (range)	5.00 (1.00, 6.00)	5.00 (1.00, 7.00)	5.00 (1.00, 7.00)
Category (Days)[a]			
1	15 (2.2)	10 (1.5)	25 (1.9)
2	5 (0.7)	18 (2.7)	23 (1.7)
3	9 (1.3)	15 (2.2)	24 (1.8)
4	7 (1.0)	5 (0.7)	12 (0.9)
5	508 (75.6)	492 (72.7)	1000 (74.1)
> 5	128 (19.0)	137 (20.2)	265 (19.6)

a. The Total Number of Dosing Days on which study drug was actually administered
PFIZER CONFIDENTIAL SDTM Creation: 29OCT2021 (15:07) Source Data: adex Table Generation: 16NOV2021 (12:52)
(Data cutoff date : 26OCT2021 Database snapshot date : 29OCT2021) Output File: /nda_unblinded/C4671005_45IA_Secondary/adex_s001
Table 14.4.1.1 PF-07321332 is for Pfizer internal use.

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- **Outcome and estimations**

Primary Efficacy Analysis

COVID-19-Related Hospitalization or Death from Any Cause (mITT)

This analysis was conducted in patients who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were treated ≤3 days of COVID-19 onset.

Table 31 - Primary Analysis of Proportion of Participants with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28 - mITT, Kaplan-Meier Method

	PF-07321332 300 mg + Ritonavir 100 mg	Placebo
N	389	385
Participants with event, n (%)	3 (0.8)	27 (7.0)
Participants with COVID-19 hospitalization	3 (0.8)	27 (7.0)
Participants with death	0	7 (1.8)
Average time at risk for event (Days)[a]	27.2	25.9
Average study follow-up (Days)[b]	27.3	26.9
Estimated proportion (95% CI), %	0.776 (0.251, 2.386)	7.093 (4.919, 10.174)
Difference from Placebo (SE)	-6.317 (1.390)	
95% CI of difference	-9.041, -3.593	
p-value	<.0001	

N – number of participants in the analysis set.
The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.
a. Average time at risk for event is computed as time to first event, or time to last day of participation, or Day 28, whichever is earlier.
b. Average study follow-up is computed as time to last day of participation, or Day 28, whichever is earlier.
PFIZER CONFIDENTIAL SDTM Creation: 29OCT2021 (15:04) Source Data: adrte Table Generation: 09NOV2021 (09:18)
(Data cutoff date : 26OCT2021 Database snapshot date : 29OCT2021) Output File: ./nda_unblinded/C4671005_45IA_adhoc/adtteh_s001_mitt
Table 14.2.1.1 PF-07321332 is for Pfizer internal use.

Sensitivity Analyses

At the request of FDA, a post-hoc sensitivity analysis of the mITT analysis set was performed whereby participants who did not have follow-up data through Day 21 were hypothetically assumed to have experience both COVID-19-related hospitalization and death in a worst-case scenario.

- 2 participants in the PF-07321332/ritonavir group and 1 participant in the placebo group were assumed to have had a primary endpoint event.
- A 6.05% (95% CI: -8.90% to -3.19%; p<0.0001) absolute reduction, reducing the primary endpoint event rate from 7.35% to 1.30%, with PF-07321332/ritonavir in comparison with placebo treatment.

Additionally, to evaluate whether the results in the primary analysis were affected by data from India and Site 1470, the analysis was repeated while excluding data from these sites.

- 3 participants in the PF-07321332/ritonavir group and 27 participants in the placebo group were assumed to have had a primary endpoint event.
- A 7.51% (95% CI: 10.73% to -4.28%; p<0.0001) absolute reduction, reducing the primary endpoint event rate from 8.44% to 0.94%, with PF-07321332/ritonavir in comparison with placebo treatment.
- It is to note that, of 193 participants from India randomized, none progressed to hospitalization or death.

Supplemental Analyses

Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28 (mITT-2)

This supportive analysis was to assess the treatment effect in a population including participants who received mAb treatment or planned to receive mAb treatment. The population includes patients regardless they received treatment within 3 days and after 3 days since onset of symptom.

Table 32 - Proportion of Participants with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28 - mITT2, Kaplan-Meier Method

	PF-07321332 300 mg + Ritonavir 100 mg	Placebo
N	661	669
Participants with event, n (%)	7 (1.1)	43 (6.4)
Participants with COVID-19 hospitalization	7 (1.1)	43 (6.4)
Participants with death	0	10 (1.5)
Average time at risk for event (Days) *	27.0	25.9
Average study follow-up (Days) *	27.2	26.9
Estimated proportion (95% CI), %	1.067 (0.510, 2.226)	6.492 (4.856, 8.655)
Difference from Placebo (SE)	-5.425 (1.038)	
95% CI of difference	-7.460, -3.390	
p-value	<.0001	

First Secondary Efficacy Analysis

Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28 (mITT-1)

This secondary analysis was to assess the treatment effect in a population including participants who have received treatment within 3 days of symptom onset and those who have received treatment after

3 days. This population analysis is the clinically relevant population in terms of generalizability to clinical practice.

Table 33 - Proportion of Participants with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28 – mITT1, Kaplan-Meier Method

	PF-07321332 300 mg + Ritonavir 100 mg	Placebo
N	607	612
Participants with event, n (%)	6 (1.0)	41 (6.7)
Participants with COVID-19 hospitalization	6 (1.0)	41 (6.7)
Participants with death	0	10 (1.6)
Average time at risk for event (Days)[a]	27.0	25.9
Average study follow-up (Days)[b]	27.2	26.8
Estimated proportion (95% CI), %	0.999 (0.450, 2.209)	6.764 (5.025, 9.074)
Difference from Placebo (SE)	-5.765 (1.098)	
95% CI of difference	-7.917, -3.613	
p-value	<.0001	

N – number of participants in the analysis set.
The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.
a. Average time at risk for event is computed as time to first event, or time to last day of participation, or Day 28, whichever is earlier.
b. Average study follow-up is computed as time to last day of participation, or Day 28, whichever is earlier.
PFIZER CONFIDENTIAL SDTM Creation: 29OCT2021 (15:04) Source Data: adtte Table Generation: 09NOV2021 (09:18)
(Data cutoff date : 26OCT2021 Database snapshot date : 29OCT2021) Output File: ./nda_unblinded/C4671005_45IA_adhoc/adtteh_s001_mitt1
Table 14.2.1.2 PF-07321332 is for Pfizer internal use.

Secondary analysis

Viral titers measured via RT-PCR in nasal swabs over time

Please refer to the section on Pharmacodynamics.

- **Ancillary analysis**

Subgroup analysis

Serological status

Subgroup analysis by serology status performed in mITT-1 are presented below.

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Table 34 - Proportion of Participants with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28, by Subgroup of Serology Status - mITT1, Kaplan-Meier Method

Subgroup		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
Negative	N	256	272
	Participants with event, n (%)	5 (2.0)	36 (13.2)
	Participants with COVID-19 hospitalization	5 (2.0)	36 (13.2)
	Participants with death	0	9 (3.3)
	Average time at risk for event (Days) *	26.7	24.2
	Average study follow-up (Days) *	27.1	26.0
	Estimated proportion (95% CI), %	1.980 (0.829, 4.691)	13.433 (9.877, 18.134)
	Difference from Placebo (SE)	-11.453 (2.262)	
	95% CI of difference	-15.886, -7.021	
	p-value	<.0001	
Positive	N	344	332
	Participants with event, n (%)	1 (0.3)	5 (1.5)
	Participants with COVID-19 hospitalization	1 (0.3)	5 (1.5)
	Participants with death	0	1 (0.3)
	Average time at risk for event (Days) *	27.2	27.2
	Average study follow-up (Days) *	27.2	27.5
	Estimated proportion (95% CI), %	0.291 (0.041, 2.045)	1.513 (0.633, 3.598)
	Difference from Placebo (SE)	-1.223 (0.732)	
	95% CI of difference	-2.657, 0.211	
	p-value	0.0947	

Number of baseline comorbidities

Subgroup analysis by number of baseline comorbidities performed in mITT-1 are presented below.

Table 35 - Proportion of Participants with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28, by Subgroup of number of baseline comorbidities - mITT1, Kaplan-Meier Method

Subgroup		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
0-1	N	486	486
	Participants with event, n (%)	3 (0.6)	26 (5.3)
	Participants with COVID-19 hospitalization	3 (0.6)	26 (5.3)
	Participants with death	0	4 (0.8)
	Average time at risk for event (Days) *	27.1	26.0
	Average study follow-up (Days) *	27.2	26.9
	Estimated proportion (95% CI), %	0.623 (0.201, 1.919)	5.379 (3.694, 7.801)
	Difference from Placebo (SE)	-4.756 (1.087)	
	95% CI of difference	-6.887, -2.625	
	p-value	<.0001	
2-3	N	115	122
	Participants with event, n (%)	3 (2.6)	15 (12.3)
	Participants with COVID-19 hospitalization	3 (2.6)	15 (12.3)
	Participants with death	0	6 (4.9)
	Average time at risk for event (Days) *	25.6	25.1
	Average study follow-up (Days) *	27.3	26.6
	Estimated proportion (95% CI), %	2.632 (0.857, 7.940)	12.359 (7.642, 19.662)
	Difference from Placebo (SE)	-9.727 (3.343)	
	95% CI of difference	-16.279, -3.174	
	p-value	0.0036	
≥ 4	N	4	2
	Participants with event, n (%)	0	0
	Participants with COVID-19 hospitalization	0	0
	Participants with death	0	0
	Average time at risk for event (Days) *	28.0	28.0
	Average study follow-up (Days) *	28.0	28.0
	Estimated proportion (95% CI), %	-	-
	Difference from Placebo (SE)	-	
	95% CI of difference	-	
	p-value	-	

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Age

Subgroup analysis by age performed in mITT-1 are presented below.

Table 36 - Proportion of Participants with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28, by Subgroup of Age - mITT1, Kaplan-Meier Method

Subgroup		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
Age < 65 years	N	544	537
	Participants with event, n (%)	5 (0.9)	29 (5.4)
	Participants with COVID-19 hospitalization	5 (0.9)	29 (5.4)
	Participants with death	0	3 (0.6)
	Average time at risk for event (Days) *	27.0	26.1
	Average study follow-up (Days) *	27.2	27.0
	Estimated proportion (95% CI), %	0.930 (0.388, 2.220)	5.460 (3.826, 7.763)
	Difference from Placebo (SE)	-4.531 (1.009)	
	95% CI of difference	-6.627, -2.434	
	p-value	<.0001	
Age ≥ 65 years	N	63	75
	Participants with event, n (%)	1 (1.6)	12 (16.0)
	Participants with COVID-19 hospitalization	1 (1.6)	12 (16.0)
	Participants with death	0	7 (9.3)
	Average time at risk for event (Days) *	26.9	24.4
	Average study follow-up (Days) *	27.3	25.9
	Estimated proportion (95% CI), %	1.587 (0.225, 10.738)	16.000 (9.421, 26.452)
	Difference from Placebo (SE)	-14.413 (4.517)	
	95% CI of difference	-23.265, -5.560	
	p-value	0.0014	

Gender

Subgroup analysis by gender performed in mITT-1 are presented below.

Table 37 - Proportion of Participants with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28, by Subgroup of Gender - mITT1, Kaplan-Meier Method

Subgroup		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
Male	N	306	332
	Participants with event, n (%)	3 (1.0)	24 (7.2)
	Participants with COVID-19 hospitalization	3 (1.0)	24 (7.2)
	Participants with death	0	6 (1.8)
	Average time at risk for event (Days) *	27.2	25.7
	Average study follow-up (Days) *	27.4	26.8
	Estimated proportion (95% CI), %	0.991 (0.321, 3.042)	7.306 (4.957, 10.734)
	Difference from Placebo (SE)	-6.314 (1.545)	
	95% CI of difference	-9.343, -3.286	
	p-value	<.0001	
Female	N	301	280
	Participants with event, n (%)	3 (1.0)	17 (6.1)
	Participants with COVID-19 hospitalization	3 (1.0)	17 (6.1)
	Participants with death	0	4 (1.4)
	Average time at risk for event (Days) *	26.8	26.1
	Average study follow-up (Days) *	27.0	26.9
	Estimated proportion (95% CI), %	1.005 (0.325, 3.083)	6.128 (3.854, 9.673)
	Difference from Placebo (SE)	-5.123 (1.552)	
	95% CI of difference	-8.164, -2.082	
	p-value	0.0010	

BMI

Subgroup analysis by BMI performed in mITT-1 are presented below.

Table 38 - Proportion of Participants with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28, by Subgroup of BMI - mITT1, Kaplan-Meier Method

Subgroup		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
< 25 kg/m²	N	131	130
	Participants with event, n (%)	0	5 (3.8)
	Participants with COVID-19 hospitalization	0	5 (3.8)
	Participants with death	0	1 (0.8)
	Average time at risk for event (Days) *	27.1	27.2
	Average study follow-up (Days) *	27.1	27.4
	Estimated proportion (95% CI), %	0.000 (0.000, 0.000)	3.858 (1.624, 9.021)
	Difference from Placebo (SE)	-3.858 (1.692)	
	95% CI of difference	-7.175, -0.542	
	p-value	0.0226	
25 - < 30 kg/m²	N	265	272
	Participants with event, n (%)	3 (1.1)	16 (5.9)
	Participants with COVID-19 hospitalization	3 (1.1)	16 (5.9)
	Participants with death	0	3 (1.1)
	Average time at risk for event (Days) *	27.0	26.0
	Average study follow-up (Days) *	27.3	27.0
	Estimated proportion (95% CI), %	1.136 (0.368, 3.482)	5.908 (3.661, 9.463)
	Difference from Placebo (SE)	-4.771 (1.574)	
	95% CI of difference	-7.857, -1.686	
	p-value	0.0024	
≥ 30 kg/m²	N	211	210
	Participants with event, n (%)	3 (1.4)	20 (9.5)
	Participants with COVID-19 hospitalization	3 (1.4)	20 (9.5)
	Participants with death	0	6 (2.9)
	Average time at risk for event (Days) *	26.9	24.8
	Average study follow-up (Days) *	27.1	26.3
	Estimated proportion (95% CI), %	1.438 (0.466, 4.392)	9.722 (6.383, 14.667)
	Difference from Placebo (SE)	-8.284 (2.225)	
	95% CI of difference	-12.645, -3.923	
	p-value	0.0002	

Hypertension

Subgroup analysis by hypertension status performed in mITT-1 are presented below.

Table 39 - Proportion of Participants with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28, by Subgroup of hypertension status - mITT1, Kaplan-Meier Method

Subgroup		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
Hypertension = Yes	N	192	210
	Participants with event, n (%)	4 (2.1)	27 (12.9)
	Participants with COVID-19 hospitalization	4 (2.1)	27 (12.9)
	Participants with death	0	9 (4.3)
	Average time at risk for event (Days) *	26.6	24.9
	Average study follow-up (Days) *	27.1	26.6
	Estimated proportion (95% CI), %	2.114 (0.799, 5.536)	12.891 (9.028, 18.234)
	Difference from Placebo (SE)	-10.777 (2.541)	
	95% CI of difference	-15.757, -5.796	
	p-value	<.0001	
Hypertension = No	N	415	402
	Participants with event, n (%)	2 (0.5)	14 (3.5)
	Participants with COVID-19 hospitalization	2 (0.5)	14 (3.5)
	Participants with death	0	1 (0.2)
	Average time at risk for event (Days) *	27.2	26.4
	Average study follow-up (Days) *	27.2	27.0
	Estimated proportion (95% CI), %	0.485 (0.121, 1.925)	3.521 (2.101, 5.874)
	Difference from Placebo (SE)	-3.037 (0.986)	
	95% CI of difference	-4.969, -1.104	
	p-value	0.0021	

Diabetes mellitus

Subgroup analysis by diabetes mellitus status performed in mITT-1 are presented below.

Table 40 - Proportion of Participants with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28, by Subgroup of diabetes mellitus status - mITT1, Kaplan-Meier Method

Subgroup		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
Diabetes mellitus = Yes	Average study follow-up (Days) *	27.5	26.7
	Estimated proportion (95% CI), %	2.597 (0.656, 9.988)	8.928 (4.359, 17.819)
	Difference from Placebo (SE)	-6.331 (3.696)	
	95% CI of difference	-13.575, 0.913	
	p-value	0.0867	
Diabetes mellitus = No	N	530	533
	Participants with event, n (%)	4 (0.8)	34 (6.4)
	Participants with COVID-19 hospitalization	4 (0.8)	34 (6.4)
	Participants with death	0	6 (1.1)
	Average time at risk for event (Days) *	27.0	25.9
	Average study follow-up (Days) *	27.1	26.9
	Estimated proportion (95% CI), %	0.764 (0.287, 2.022)	6.443 (4.647, 8.901)
	Difference from Placebo (SE)	-5.680 (1.135)	
	95% CI of difference	-7.904, -3.456	
	p-value	<.0001	

Cigarette smoker

Subgroup analysis by cigarette smoker performed in mITT-1 are presented below.

Table 41 - Proportion of Participants with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28, by Subgroup of cigarette smoker - mITT1, Kaplan-Meier Method

Subgroup		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
Cigarette smoker = Yes	N	221	230
	Participants with event, n (%)	3 (1.4)	8 (3.3)
	Participants with COVID-19 hospitalization	3 (1.4)	8 (3.3)
	Participants with death	0	1 (0.4)
	Average time at risk for event (Days) *	27.1	26.7
	Average study follow-up (Days) *	27.4	27.1
	Estimated proportion (95% CI), %	1.366 (0.443, 4.175)	3.381 (1.705, 6.647)
	Difference from Placebo (SE)	-2.015 (1.412)	
	95% CI of difference	-4.783, 0.753	
	p-value	0.1537	
Cigarette smoker = No	N	385	373
	Participants with event, n (%)	3 (0.8)	33 (8.8)
	Participants with COVID-19 hospitalization	3 (0.8)	33 (8.8)
	Participants with death	0	9 (2.4)
	Average time at risk for event (Days) *	27.0	25.3
	Average study follow-up (Days) *	27.1	26.7
	Estimated proportion (95% CI), %	0.792 (0.256, 2.437)	8.944 (6.443, 12.350)
	Difference from Placebo (SE)	-8.151 (1.554)	
	95% CI of difference	-11.196, -5.105	
	p-value	<.0001	

Supplemental analysis

Analysis to compare efficacy of PF-07321332/ritonavir treatment versus placebo when initiated 4-5 days from symptom onset

This analysis represents participants with onset of symptoms >3 days from treatment initiation who at baseline did not receive nor were expected to receive mAb therapy for COVID-19.

Table 42 - Primary Analysis of Proportion of Participants With COVID-19-Related- Hospitalization or Death From any Cause Through Day 28 by Subgroup of Symptom Onset of > 3 Days - mITT1, Kaplan-Meier Method (Protocol C4671005)

	PF-07321332 300 mg + Ritonavir 100 mg	Placebo
N	218	227
Participants with event, n (%)	3 (1.4)	14 (6.2)
Participants with COVID-19 hospitalization	3 (1.4)	14 (6.2)
Participants with death	0	3 (1.3)
Average time at risk for event (Days)[a]	26.7	25.8
Average study follow-up (Days)[b]	26.9	26.7
Estimated proportion (95% CI), %	1.402 (0.454, 4.285)	6.194 (3.716, 10.236)
Difference from Placebo (SE)	-4.792 (1.794)	
95% CI of difference	-8.308, -1.276	
p-value	0.0076	

N = number of participants in the subgroup of the analysis set. Participants 12255001, 14705011 and 14705012 had duration of symptom onset greater than 5 days, and are count in sub-group of symptom onset of > 3 days.

The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.

a. Average time at risk for event is computed as time to first event, or time to last day of participation, or Day 28, whichever is earlier.

b. Average study follow-up is computed as time to last day of participation, or Day 28, whichever is earlier.

Source: Table 004.1.1 PF-07321332

PFIZER CONFIDENTIAL SDTM Creation: 29OCT2021 (15:04) Source Data: adtte Table Generation: 07DEC2021 (01:14)

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Concomitant medication

Overall, 111 (8.3%) participants received corticosteroids with ATC2 classification of "Corticosteroids for systemic use" during the study period (through Day 34). A total of 13 (1.0%) participants received remdesivir.

Table 43 - Concomitant Medications by ATC2 (Corticosteroids for Systemic use) and Preferred Term (Remdesivir) - mITT2 Analysis Set (Protocol C4671005)

ATC2 Preferred Name	PF-07321332 300 mg + Ritonavir 100 mg (N=661) n (%)	Placebo (N=669) n (%)	Total (N=1330) n (%)
Participants with any concomitant medications	40 (6.1)	72 (10.8)	112 (8.4)
ANTIVIRALS FOR SYSTEMIC USE	1 (0.2)	12 (1.8)	13 (1.0)
REMDESIVIR	1 (0.2)	12 (1.8)	13 (1.0)
CORTICOSTEROIDS FOR SYSTEMIC USE	40 (6.1)	71 (10.6)	111 (8.3)
BETAMETHASONE	0	1 (0.1)	1 (0.1)
BETAMETHASONE DIPROPIONATE	0	1 (0.1)	1 (0.1)
BETAMETHASONE;LORATADINE	3 (0.5)	4 (0.6)	7 (0.5)
CORTICOSTEROIDS	0	1 (0.1)	1 (0.1)
DEFLAZACORT	0	1 (0.1)	1 (0.1)
DEXAMETHASONE	13 (2.0)	37 (5.5)	50 (3.8)
DEXAMETHASONE SODIUM PHOSPHATE	0	1 (0.1)	1 (0.1)
HYDROCORTISONE	2 (0.3)	1 (0.1)	3 (0.2)
METHYLPREDNISOLONE	10 (1.5)	12 (1.8)	22 (1.7)
METHYLPREDNISOLONE SODIUM SUCCINATE	0	1 (0.1)	1 (0.1)
PREDNISOLONE	1 (0.2)	6 (0.9)	7 (0.5)
PREDNISONE	13 (2.0)	16 (2.4)	29 (2.2)
STEROIDS	0	1 (0.1)	1 (0.1)
TRIAMCINOLONE	0	1 (0.1)	1 (0.1)
TRIAMCINOLONE ACETONIDE	0	1 (0.1)	1 (0.1)

WHODDG B3 v202103 coding dictionary applied.
a. Medication was pre-specified on CRF.
Source: Table 004.2.1 PF-07321332
PFIZER CONFIDENTIAL SDTM Creation: 29OCT2021 (15:07) Source Data: adcm Table Generation: 06DEC2021 (20:20)
(Data cutoff date : 26OCT2021 Database snapshot date : 29OCT2021) Output File: /nda_unblinded/SCSC4670004/adcm_s003

Variants of concern

For the subset of 488 participants in the interim analysis with sequencing data available, there were 5 events in the PF-07321332/ritonavir treatment group (out of a total of 6 events in the interim analysis) and 17 events in the placebo (out of a total of 41 events in the interim analysis). All 5 events in the PF-07321332/ritonavir participants were infected with the Delta (21J) subvariant. For placebo, 16 events occurred in participants infected with the Delta variant (subvariant:10 in 21J, 5 in 21I, and 1 in 21A) and one event in a participant infected with 20A variant.

Overview of key efficacy data submitted

Table 44 - Overview of key efficacy data submitted

Study id and design / reference	Key objectives / endpoints	Population	Inclusion/ exclusion criteria	Treatment	Main efficacy results
Therapeutic indication 1					
Study 1005	Primary objective: • To compare the efficacy of PF-07321332/ritonavir to placebo for the treatment of COVID-19 in non-hospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease. Primary endpoint: • Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28.	Non-hospitalized, symptomatic adult participants with COVID-19, who were at increased risk of progressing to severe illness (including n = 1361)	Main inclusion criteria: • Confirmed SARS-CoV-2 infection as determined by RT-PCR (other molecular or antigen tests) within 5 days prior randomization • Initial onset of signs/symptoms attributable to COVID-19 within 5 days prior randomization • Has at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19 : diabetes, overweight (BMI > 25), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease, hypertension, sickle	• 300/100 mg PF-07321332/ritonavir administered orally q12h for 5 days • placebo administered orally q12h for 5 days	• mITT: A 6.32% (95% CI: -9.041% to -3.593%; p<0.0001) absolute reduction, reducing the primary endpoint event rate from 7.093% to 0.776%, with PF-07321332/ritonavir in comparison with placebo treatment. • mITT-1: A 5.765% (95% CI: -7.917% to -3.613%; p<0.0001) absolute reduction, reducing the primary endpoint event rate from 6.764% to 0.999%, with PF-07321332/ritonavir in comparison with placebo treatment.

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			cell disease, neurodevelopmental disorders, active cancer, medically related technological dependence, or were 60 years of age and older regardless of comorbidities Main exclusion criteria: • History of hospitalization for the medical treatment of COVID-19 • Current need for hospitalization or anticipated need for hospitalization within 48 hours hours after randomization • Prior to current disease episode, any confirmed SARS-CoV-2 infection • Has received or is expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit. • Oxygen saturation of <92%		

Discussion on Efficacy

Demonstrated benefits

Method

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The main clinical study in support of this procedure was a Phase 2/3, randomized, double-blind, placebo-controlled study (C4671005 or EPIC-HR study) to compare the efficacy, the safety, and the tolerability of PF-07321332/ritonavir, versus placebo, in non-hospitalized, symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illness. The total study duration was up to 24 weeks, study intervention through Day 5 or Day 6, efficacy assessments through Day 28, a safety follow-up period through Day 34, and long-term follow-up at Weeks 12 and 24.

The general design of this Phase 2/3 clinical trial appears appropriate.

The selection criteria are globally consistent with the target population. To be enrolled, positive RT-PCR, or other molecular or antigen tests, and initial onset signs/symptoms attributable to COVID-19 were needed, both within 5 days prior randomization. This seems reasonable to define symptomatic patients with COVID-19, as well as the list of the specified signs/symptoms.

Risk factors of progressing to severe illness were predefined. It has to be noted that patients were to be enrolled on the basis of an overweight (BMI >25 kg/$m^{2,}$), likely referring to CDC, and not necessarily requiring obesity (BMI >30 kg/m^2) based on WHO's criteria and ECDC. Additionally, the lower bound for age regardless of comorbidities was >60 y/o, and not > 65 y/o to enrich population with very old patients.

Additionally, the selection criteria allowed to enrol patients with oxygen saturation of ≥92% on room air, while SpO2 <94% is one of the criteria to define severe illness. Nonetheless, current need for hospitalization or anticipated need for hospitalization within 48 hours after randomization was an exclusion criterion, as such it might be unlikely that patients with severe illness were recruited at screening. However, SpO2 <94% population could have been likely more clinically at risk of progressing. It has to be underlined that the company did not provide a definition of the population of mild to moderate patients as claimed in the indication of Condition of Use. Nevertheless it is currently acknowledged that non severe patients are rather to be defined as not requiring O2 for COVID19 in clinical practice. Moreover, obviously this study targets non severe patients insofar that requirement of hospitalisation for COVID-19 is part of the exclusion criteria. In this perspective, a rewording of the indication is proposed in the Condition of Use, removing, the statements "mild to moderate" and focusing on the non-requirement of O2.

Regarding prior and concomitant medication, drug-drug interactions related to CYP3A4, due to the administration of ritonavir, was taken into account.

It should also be highlighted that subjects were not vaccinated (allowed only from Day 34, while primary timepoint is at Day 28) but could receive mAb (in fact almost exclusively intended to receive).

Regarding the study treatment, patients were instructed to take 2 tablets of PF-07321332 150 mg (or 3 tablets of 100 mg for some participants in the sentinel cohort) plus 1 capsule of ritonavir 100 mg q12h. Taking into consideration assessment of pharmacodynamics and Scientific Advice provided by CHMP, the rationale for dose selection, based on reaching unbound Ctrough values above EC90 and assuming an inflated intrasubject variability, can be agreed, all the more in view of the results with this selected dose. Further scrutiny will apply at the time of the MA with PK data some subgroups of patients (notably with BMI>30).

The treatment duration, 5 days (10 doses), was defined by the company based on other antiviral agents used in the treatment of acute respiratory infections, such as remdesivir for SARS-CoV-2 and oseltamivir for influenza. While this should be further explored, notably for immunodeficient patients based on kinetic of viral load decrease, this is agreed in the context of an emergency use situation, based on the results of the clinical study with this tested treatment duration However further

discussion might be requested at the time of the MAA (notably if available viral load is available after D5).

The choice of placebo as comparator is considered appropriate.

Overall, the primary objective and the primary endpoints appear acceptable. However, given that this is an interim analysis report, only few secondary endpoints were planned.

The sample size calculations appear to be in line with corresponding protocol assumptions. The assumed proportion of hospitalization/death in the placebo arm (7%) is consistent with the observed rate in these interim results.

The primary analysis population, mITT, was defined as participants randomly assigned to study intervention, who take at least 1 dose of study intervention, with at least 1 post-baseline visit through Day 28 visit, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were treated ≤3 days of COVID-19 onset. The mITT1 included in addition subjects treated >3 days of COVID-19 onset and therefore is the population of analysis of clinical relevance, better supporting the generalizability to clinical practice. Finally, the mITT2 included on top of all that participants who received or were expected to receive COVID-19 therapeutic mAb treatment.

The primary analysis method (proportions derived from Kaplan-Meier method with 95% CIs based on Greenwood's formula of the variance estimate) appears overall acceptable. The Lan-DeMets procedure with O'Brien-Fleming boundaries for the testing of the primary endpoint across interim and final analyses is expected to provide an appropriate control of the study type I error.

It should be highlighted that 2 interim analyses were pre-specified in the protocol for decision making (i.e. based on 45% and based on 70% of the overall population).

Results

This study was initiated the 16 July 2021. On 03 November 2021, the E-DMC reviewed data from the 45% interim analysis and determined that the pre-specified criteria for stopping the trial due to efficacy had been achieved (primary endpoint met in the mITT population); further enrolment in the study was stopped.

This report includes thus the results from the planned 45% IA, corresponding to 1361 participants (n=678 for PF-07321332/ritonavir, n=683 for placebo), randomised through 29 September (with data cut-off 26 October 2021).

It is highlighted that 1065 additional patients have been enrolled between the date of randomization of the last patients included in the interim analysis (i.e. 29 September 2021) and the time of the stop of the study (i.e. 05 November 2021). The final analysis that should be provided at the time of the MAA will be thus based on 2426 participants.

Overall, demographic and baseline characteristics are balanced across the treatment groups. It should be noted that a high percentage of patients with positive serology status at baseline was observed (55.6% vs 43.4%) while any confirmed SARS-CoV-2 infection prior the study and vaccination prior to Visit at day 34 (+/ -3d) were part of the exclusion. This will be further scrutinized at the time of the MA A(notably with discriminant IgG/IgM serology), given the potential impact for generalizability to vaccinated subjects.

8.2% of participants received or were expected to receive COVID-19 therapeutic monoclonal antibody at baseline, which remains a limited proportion.

Across treatment groups, 41.1% and 36.3% had respectively 1 and 2 risk factors. Main risk factors observed in the participants were overweight (79.4% with a BMI >25 kg/m^2, 36.7% with a BMI >30

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kg/m2), cigarettes smokers (35.8%), hypertension (32.4%) and diabetes mellitus (12.9%). However, 18.7% were older than 60 years of ages (and 11.4% older than 65). Furthermore, other risks factors are less represented.

62.3% participants had baseline viral load ≥4.0 Log10 copies/mL.

The population enrolled was mainly from US (app. 45%), 17.9% of the subjects were recruited in Europe. The generalizability will be further explored at the time of the MAA.

The Delta variant was largely predominant (i.e. 98.0%) in the subset population with sequencing data (n=490). This is reassuring given this variant is currently predominantly circulating in Europe. However, concerns are raised as regards the Delta (21J) subvariant, since represented in the 5/6 events in the interim analysis, but nevertheless having in mind that it was also the most common (app70%) among the 98 % of patients with delta variant. This will be further scrutinized at the time of the MAA.

Regarding concomitant medication, during the study period (through Day 34), 8.4% of the participants received systemic corticosteroids or remdesivir which remains limited. The administration was numerically higher in the placebo group (10.8%) compared to the PF-07321332/ritonavir group (6.1%), which seems consistent with the observed efficacy of the study treatment. However, the estimation of the effect size across these subgroups is not interpretable, given the very limited number of patients having those comedications.

The number of important protocol deviations through the data cut-off date (26 October 2021) was comparable between the treatment groups as was the number by subcategory of protocol deviations.

The primary endpoint was met with a 6.317% (95% CI: -9.041% to -3.593%; p<0.0001) absolute reduction, reducing the primary endpoint event rate from 7.093% to 0.776% at Day-28, with PF-07321332/ritonavir in comparison with placebo treatment. No patient died in the Paxlovid treatment group whereas 7 deaths occurred in the placebo group. The results are consistent with the analysis conducted in mITT1 and mITT2 populations (respectively -5.765% [95% CI: -7.917% to -3.613%; p<0.0001] and -5.425% [95% CI: -7.460% to -3.390%; p<0.0001]). Additionally, when performing the analysis only in participants with onset of symptoms >3 days from treatment initiation (and who at baseline did not receive nor were expected to receive mAb therapy for COVID-19), the size effect is consistent with above results (-4.792% [95% CI: -8.308% to -1.276%; p=0.0076]).

CHMP discussed the clinical relevance of the analysis in the mITT and mITT1 population. Almost 43% of the patients were not treated ≤3 days of COVID-19 onset and are excluded of the mITT. Moreover, if such proportion of patients failed to start the treatment within 3 days while clinical trials offer generally optimal conditions and follow-up, it is unlikely that the proportion will be better in clinical practice. Results in mITT1 may thus appear more appropriate for generalization and more representative of the population of interest (notably encompassing patients treated within 5 days since symptoms onset). To this purpose, a time limit for treatment initiation was added in the Condition of Use (i.e. start treatment within 5 days of onset of symptoms).

Sensitivity analysis were generally consistent with primary results; removed data from Indian participants and the GLC non-compliant site would likely not change the conclusions.

Given above considerations regarding the population of interest, together with the much larger number of subjects available in mITT1 than in mITT, subgroup analysis are assessed with mITT1 outcomes.

Overall, results seem consistent in subgroup analysis for the risk factors mainly represented. It can observed an absolute reduction of: -8.28% (95% CI: -12.65% to -3.92%; p=0.0002) in patients with a BMI >30 kg/m2, 10.77% (95% CI: -15.75% to -5.80%; p<0.0001) in patients with hypertension,

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-14.41% (95% CI: -13.58% to -5.56%; p=0.0014) in patients older than 65, and -6.33% (95% CI: -23.26% to -0.91%; p=0.0867) in patients with diabetes mellitus.

However, the absolute reduction, -2.01% (95% CI: -4.78% to -0.75%; p=0.1537) in patients who are cigarettes smoker (majority among patients with comorbidities), was more limited.

Likewise, in patients with positive serology status at baseline (55.6%), results make difficult to conclude on the efficacy, with an absolute reduction of -1.22% (95% CI: -2.66% to -0.21%; p=0.0947). However, it is to note that the number of events was low in the placebo group (3 hospitalisation and 0 death).

Finally, a slightly larger reduction of the viral load from baseline to day 5 seems to be observed in the active group versus the placebo group. However, the limited data available at this stage and the descriptive nature of the analysis warrant caution in the interpretation. This will be further substantiated at the time of the MAA.

Overall, the efficacy data submitted are considered sufficient for supporting the use of Paxlovid in an emergency setting. Some uncertainties are however highlighted below that will need complementary data/clarifications from the company at the time of the MAA.

Uncertainty about benefits

In absence or further stratification factors, as commented below, it is not fully clear in which extent both subpopulations, patients with mild-illness and patients with moderate illness, are sufficiently represented and well balanced across the treatment groups. Likewise, there are concerns that participants with SpO_2 ≥92 % but < 94%, thus likely at risk to progress, are in similar proportion in each treatment groups. More broadly, further discussion in the balance of the severity illness at baseline across arms will be needed at the time of the MAA.

A number of risk factors are poorly represented (chronic lung disease, CVD, immunosuppressive disease etc…) making difficult to conclude on the relevance of the results in these subpopulations.

Regarding variants, all five participants with an event in the PF-07321332/ritonavir group were infected with the Delta (21J) subvariant. This is of concern, as this variant, in contrast to the 21A subvariant, harbours mutations in the ORF1a that encodes for nsp5 (the 3CL-protease). This data may point to a potential loss of efficacy in VOCs harbouring mutations in ORF1a. Mutations in ORF1a were also identified in the Omicron variant. These data and the lack of information on the resistance profile of Paxlovid, neither *in vitro* nor *in vivo*. Those limitations will have to be resolved at the time of the MAA.

Finally, the current lack of *in vitro* data of antiviral activity of PF-07321332 on Omicron VOC has become a critical caveat for the early access in view of the evolving epidemiological situation with rapidly increasing circulation of omicron.

Those data will have to be provided at the time of the MAA

Moreover, the reduce effect size in patients with positive serology status and in cigarettes smokers raise concern whether efficacy results to administrate PF-07321332/ritonavir can be translated in a significant benefit in these patients.

Considering that viral loads are not available in all patients, together with the concerns on the methods to handle missing data as commented below, and the logistic issues to perform measurement (kit delays), it seems premature, at this stage, to consider any analysis on this parameter. Additionally, discussion on the clinical relevance of the observed reduction is lacking.

Follow-up data (including Day-34 data) were not yet available in the proposed interim report. In order to ensure that no later events could impact the benefice observed at the primary timepoint, these longer-term data will be needed at the time of the MAA.

More broadly, the analysis based on the total number of the patients enrolled (i.e. n=2426) are awaited to confirm the interim results. The company has provided the top line results from final analysis. However, only few outcomes are available: the primary endpoint (mIIT), the key secondary endpoint (mITT1) and the subgroup analysis by viral load at baseline. The information provided in the preliminary presentation of the interim analysis are too high level and partial to draw a reliable interpretation to draw conclusion on the reliability of the preliminary presentation. While the first final results from this preliminary presentation seem consistent with the interim outcomes, it is preferred to remain cautious awaiting the completed final analysis (notably including sensitivity and subgroup analyses by risk factor, serologic status and variants (including sublineage especially 21J for the almost exclusively reported variant) to be provided at the time of the MAA.

The extent of efficacy in vaccinated patients with breakthrough infection has not been characterised, as such patients were excluded from the pivotal trial. Data in patients with positive SARS-CoV-2 serology status might inform on the potential generalizability to those patients.

The number of participants on chronic supplementary oxygen for an underlying condition at baseline cannot be provided. Uncertainties on the efficacy results thus remains. If such individuals had an oxygen saturation of at least 92% at rest within 24 hours prior to randomisation they were not to be excluded according to the study protocol if this criterion was fulfilled while on their standard home oxygen supplementation. This will be further scrutinized at the time of the MAA.

Statistical methods

Randomisation was stratified by geographic region and by whether participants had received/were expected to receive treatment with COVID-19 therapeutic mAbs (yes/no) based on the site investigator's assessment at time of randomisation. First, it is unclear in which extend this factor is appropriate to defined patients the most of progressing to severe illness. Secondly, as the study primary analysis is restricted to patients who were treated ≤ 3 days after COVID-19 symptom onset, time since COVID-19 symptom onset at randomisation (≤ 3 vs >3 days) would be expected as an additional stratification factor of the randomisation. The lack of stratification for the time since symptom onset could raise a concern on the preservation of the randomisation in the primary analysis population (mITT). Nevertheless, given the observed balance of treatment arms and other stratification factors in the primary analysis set, this issue is not thought to have affected the results.

All efficacy populations [mITT, mITT1 (clinically relevant in terms of generalizability to the clinical practice) and mITT2] excluded subjects who were not treated or without at least 1 post-baseline visit through Day 28. This is not in line with the defined estimands that should estimate the treatment effect irrespective of adherence to randomized treatment. Efficacy analysis sets would be generally expected to include all randomised subjects regardless of treatment with study drug and regardless of post-baseline visit attendance. Such analysis sets would be more closely aligned with the ITT principle. The difference between mITT2 and FAS (all randomised) consists of subjects either not treated or without at least one post-baseline visit through day 28. It is acknowledged that this appears to represent a relatively small proportion of subjects (2.3% of subjects in the FAS are not included in mITT2).

A discrepancy is also noted in the definition of mITT1 and mITT2 between the SAP/study report and the clinical overview/conditions for use (annex I). The SAP/study report do not specify any criteria regarding COVID-19 symptom onset for mITT1/mITT2 (subjects are included regardless of symptom onset date), whereas the clinical overview/conditions for use specify a ≤ 5 days criterion. The 5 days

onset criteria is understood to be the study inclusion criteria but is not actually used for defining mITT1 and mITT2 populations. In fact, based on demographic summary tables, there appears to be a few subjects with symptom onset > 5 days from treatment that are included in mITT1/mITT2, so the SAP definition seems to be the one actually followed for analyses.

The presentation of missing data is unclear, in particular regarding how many untreated patients and treated patients without post-baseline values were excluded from the different analysis populations. The number of drop-outs and the time to discontinuation was also not presented for the different analysis populations. These uncertainties will be further explored during the assessment of the marketing authorization procedure.

There is some inconsistency in the company's SAP regarding the sequential testing of the first two secondary endpoints. It is not entirely clear which one is meant to be tested first. Again this will be further explored during the assessment of the marketing authorization procedure.

Although the primary analysis method seems acceptable, the censoring of subjects who discontinued before their Day 28 assessment or were lost to follow up could be questioned. Indeed, data from subjects who withdrew early are likely missing not at random, which could lead to biased estimates. It is acknowledged that a post-hoc sensitivity analysis has been performed with subjects not providing follow-up data through Day 21 hypothetically assumed to experience both COVID-19-related hospitalisation and death. This may provide an alternative treatment effect estimate under more conservative assumptions.

Several factors leading to exclusion of participants from the POC viral load analysis were described. Data may be missing not at random (MNAR) which would likely result in biased estimates. These are exploratory analyses and results should be interpreted with caution.

There were several important changes to the planned analyses that were implemented while the study was ongoing. A change in the primary analysis population and the addition of a key secondary endpoint are two key updates to the study design which could potentially raise concerns about the trial integrity. Nevertheless, these modifications were performed before unblinding the study. More importantly, the primary analysis has been repeated on all mITT, mITT1 and mITT2 populations. These alternative populations may be used to assess the robustness and consistency of the primary analysis results on wider analysis sets

2.4.5. Data on Safety

The safety data provided is based on the pivotal Study 1005. Safety results are from the 45% interim analysis which includes 1349 participants (safety analysis set) enrolled through 29 Sep 2021 with the database cut-off on 26 Oct 2021. The safety analysis set is defined as all participants who receive at least 1 dose of study intervention.

Updated safety data from the current data base of 1881 participants for Study 1005 interim analysis was provided during the procedure; the data cut-off date was however not provided.

The safety follow-up period was planned through Day 34.

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Visit Identifier Abbreviations used in this table may be found in Appendix 12.	Screening	Baseline (Day 1)	Day 3	Day 8	Day 10	Day 14	Day 21	Day 34	LT F/U		ET (prior to Day 34)	Notes
									Week 12	Week 24		
Visit Window	Day -1 to Day 1	0 days	±1 day	±1 day	±1 day	±2 days	±2 days	±3 days	±7 days	±7 days	±5 days	
												• 30 days before study entry (considered prior treatment) will be recorded. • Concomitant therapies will be collected through the Day 34 visit. • Refer to Section 6.8.
Adjunctive therapeutic procedures	X	X		X	X	X	X	X			X	• Will be collected through the Day 34 visit.
SERIOUS AND NONSERIOUS AE MONITORING	X	X	[X]	X	X	X	X	X			X	• AEs should be assessed by means of a telemedicine visit if not feasible via an in-person visit. • Refer to Section 8.3.

Safety data from supportive Phase 1 studies 1001, 1011, 1014 and 1015 were also submitted.

Clinical safety data

The intended posology is PF- 07321332 300mg and ritonavir 100mg Q12h for 5 days. The extent of exposure was not provided in the submitted data.

Demographic and Baseline Characteristics – Safety analysis set

Overall demographic and baseline characteristics were similar between the two arms of Study 1005. The median age is 44.71 yrs (range 18.00 – 86.00) with a greater proportion of 18-44 (51.1%); subjects ≥60 years of age represented 18.9% of total safety database. The repartition of male and female is comparable (52.3% of male, 47.7% female) and the majority of subjects were White (63.4%). There was 36.6% of subjects with obesity (BMI ≥30) and 42.8% of subjects with overweight (BMI 25≤30). The most reported comorbidities were cigarettes smokers (36.8%), hypertension (32.5%), diabetes mellitus (12.9%), chronic lung disease (4.9%) and cardiovascular disease (3.7%). The other comorbidities defining the high risk of developing severe illness from COVID-19 were reported in <1% of the SAS.

Overview of Adverse Events

Overall, the occurrence of TEAEs in PF1332/ritonavir and placebo arms was comparable, i.e. 19.8% and 22.3% respectively. Serious AEs were less reported in PF-1332/ritonavir arm than placebo arm, i.e. 1.9% and 6.8% respectively. Grade ≥3 TEAEs were also less reported in PF-1332/ritonavir arm than placebo arm, i.e. 3.1% and 8.6% respectively.

No AE leading to study discontinuation occurred in PF-1332/ritonavir arm and occurred at 1.5% subjects in placebo arm. AEs leading to drug interruption were more reported in placebo arm than PF-1332/ritonavir arm, 4.3% and 2.4% respectively. The rate of AEs leading to treatment modifications is however missing in the overview of AEs.

Table 45 - Treatment-emergent adverse events (all causalities) – DAIDS Grade – safety analysis set (protocol C4671005_45IA)

Number (%) of Participants	PF-07321332 300 mg + Ritonavir 100 mg (N=672) n (%)	Placebo (N=677) n (%)
Participants evaluable for adverse events	672	677
Number of adverse events	263	262
Participants with adverse events	133 (19.8)	151 (22.3)
Participants with serious adverse events	13 (1.9)	46 (6.8)
Participants with Maximum Grade 3 or 4 adverse events	21 (3.1)	48 (7.1)
Participants with Maximum Grade 5 adverse events	0	10 (1.5)
Participants discontinued from study due to adverse events[a]	0	10 (1.5)
Participants discontinued study drug due to AE and continue Study[b]	16 (2.4)	29 (4.3)
Participants with dose reduced or temporary discontinuation due to adverse events	1 (0.1)	4 (0.6)

Includes AEs that started on or prior to Day 34 visit.
MedDRA v24.0 coding dictionary applied.
Except for the Number of Adverse Events participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
a. Participants who have an AE record that indicates that the AE caused the participant to be discontinued from the study
b. Participants who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Participant to be discontinued from Study
PFIZER CONFIDENTIAL SDTM Creation: 29OCT2021 (16:07) Source Data: adae Table Generation: 30OCT2021 (19:13)
(Data cutoff date : 26OCT2021 Database snapshot date : 29OCT2021) Output File: ./nda_unblinded/C4671005_45IA/adae_s020

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Treatment-related TEAEs were highly reported in PF-1335/ritonavir arm compared to placebo, i.e. 7.3% and 4.3% respectively. Despite the higher incidence of treatment-related TEAEs with PF-1335/ritonavir, only 1 (0.1%) treatment-related TEAE was considered as serious and 3 (0.4%) were Grade ≥3. None of the AE leading to study discontinuation or treatment interruption was a treatment-related AE.

Table 46 - Treatment-emergent adverse events (treatment related) – DAIDS Grade – safety analysis set (protocol C4671005_45IA)

Number (%) of Participants	PF-07321332 300 mg + Ritonavir 100 mg (N=672) n (%)	Placebo (N=677) n (%)
Participants evaluable for adverse events	672	677
Number of adverse events	74	35
Participants with adverse events	49 (7.3)	29 (4.3)
Participants with serious adverse events	1 (0.1)	0
Participants with Maximum Grade 3 or 4 adverse events	3 (0.4)	4 (0.6)
Participants with Maximum Grade 5 adverse events	0	0
Participants discontinued from study due to adverse events[a]	0	0
Participants discontinued study drug due to AE and continue Study[b]	7 (1.0)	3 (0.4)
Participants with dose reduced or temporary discontinuation due to adverse events	0	3 (0.4)

Includes AEs that started on or prior to Day 34 visit.
MedDRA v24.0 coding dictionary applied.
Except for the Number of Adverse Events participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
a. Participants who have an AE record that indicates that the AE caused the participant to be discontinued from the study
b. Participants who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Participant to be discontinued from Study
MedDRA v24.0 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 29OCT2021 (16:07) Source Data: adae Table Generation: 30OCT2021 (19:13)
(Data cutoff date : 26OCT2021 Database snapshot date : 29OCT2021) Output File: ./nda_unblinded/C4671005_45IA/adae_t021

Updated safety database (n=1881)

AEs occurred at similar rate across the two treatment groups in the updated safety database, i.e. 19.3% in the PF-07321332/ritonavir group and 20.7% in the placebo group. No additional death was reported in the safety dataset.

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Table 47 - Updated safety database

Treatment Emergent Adverse Events

	PF-07321332 300 + Ritonavir 100 mg	Placebo
Participants	945	936
Number of adverse events	339	320
Participants with adverse events	182 (19.3%)	194 (20.7%)
With serious adverse events	16 (1.7%)	62 (6.6%)
With Maximum Grade 3 or 4 AEs	27 (2.9%)	71 (7.6%)
Deaths	0	10 (1.1%)
Discontinued study drug due to AE and continue Study	20 (2.1%)	38 (4.1%)

Analysis of AEs

- All causality TEAEs

The most frequently reported TEAEs in the PF-07321332/ritonavir group (≥1%) were Dysgeusia (4.8%), Diarrhoea (3.9%), Nausea (1.9%), Headache (1.5%), Vomiting (1.3%), and Pyrexia (1.2%), some reported TEAEs may be associated to COVID-19 symptoms. Of these, Dysgeusia, Diarrhoea, Vomiting, and Pyrexia were reported at a higher frequency in the PF-07321332/ritonavir group compared with the placebo group (0.1%, 1.9%, 0.3%, and 1.0%, in the placebo group, respectively).

Hypertension occurred at a low frequency overall (0.9% and 0.1%, in the PF- 07321332/ritonavir and placebo group, respectively, but was more frequent in the PF- 07321332/ritonavir group. A total of 7 AEs of Hypertension were reported; 6 participants in the PF-07321332/ritonavir group and 1 participant in the placebo group. The AEs of Hypertension were non-serious, transient in nature, did not lead to treatment discontinuation and all were assessed as not related to study intervention by the investigator. The AEs were mild or moderate (Grade 1-2) in severity and were resolved/resolving, with exception of 1 participant in the PF-07321332/ritonavir group: This participant had an event of severe (Grade 3) hypertension. The participant also had 2 SAEs (abscess and sepsis), which were not considered by the investigator to be related to study intervention and resolved. The event of severe hypertension was not resolved (Study 1005).

Reported TEAEs with PF-07321332/ritonavir were mostly Grade 1-2.

A summary of all-causality TEAEs that started on or prior to the Day 34 visit, reported by SOC, PT and maximum severity grade is provided in table 48.

Table 48 – Summary of treatment-emergent adverse events by MedDRA system organ class, preferred term, and maximum DAIDS Grade (all causalities) – safety analysis set (protocol C4671005_45IA)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Participants with events	111 (16.5)	15 (2.2)	6 (0.9)	0	1 (0.1)	133 (19.8)	93 (13.7)	37 (5.5)	11 (1.6)	10 (1.5)	0	151 (22.3)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (0.3)	0	0	0	0	2 (0.3)	1 (0.1)	0	1 (0.1)	0	0	2 (0.3)
Leukocytosis	2 (0.3)	0	0	0	0	2 (0.3)	0	0	0	0	0	0
Lymphadenopathy mediastinal	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Microcytic anaemia	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
CARDIAC DISORDERS	1 (0.1)	1 (0.1)	0	0	0	2 (0.3)	4 (0.6)	0	0	0	0	4 (0.6)
Palpitations	1 (0.1)	1 (0.1)	0	0	0	2 (0.3)	2 (0.3)	0	0	0	0	2 (0.3)
Pericardial effusion	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Sinus tachycardia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
EAR AND LABYRINTH DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	2 (0.3)	0	0	0	0	2 (0.3)
Hyperacusis	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Vertigo	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
EYE DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Eye pain	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
GASTROINTESTINAL DISORDERS	48 (7.1)	0	0	0	0	48 (7.1)	35 (5.2)	1 (0.1)	0	0	0	36 (5.3)
Abdominal pain	2 (0.3)	0	0	0	0	2 (0.3)	2 (0.3)	0	0	0	0	2 (0.3)
Abdominal pain lower	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Abdominal pain upper	1 (0.1)	0	0	0	0	1 (0.1)	2 (0.3)	0	0	0	0	2 (0.3)
Colitis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Constipation	1 (0.1)	0	0	0	0	1 (0.1)	2 (0.3)	0	0	0	0	2 (0.3)
Diarrhoea	26 (3.9)	0	0	0	0	26 (3.9)	13 (1.9)	0	0	0	0	13 (1.9)
Dry mouth	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Dyspepsia	5 (0.7)	0	0	0	0	5 (0.7)	3 (0.4)	0	0	0	0	3 (0.4)
Faeces soft	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Gastrooesophageal reflux disease	3 (0.4)	0	0	0	0	3 (0.4)	2 (0.3)	0	0	0	0	2 (0.3)
Hiatus hernia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Hyperchlorhydria	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Large intestine polyp	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Nausea	13 (1.9)	0	0	0	0	13 (1.9)	13 (1.9)	1 (0.1)	0	0	0	14 (2.1)
Rectal haemorrhage	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Vomiting	9 (1.3)	0	0	0	0	9 (1.3)	2 (0.3)	0	0	0	0	2 (0.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	16 (2.4)	0	0	0	0	16 (2.4)	11 (1.6)	1 (0.1)	0	0	0	12 (1.8)
Asthenia	3 (0.4)	0	0	0	0	3 (0.4)	0	1 (0.1)	0	0	0	1 (0.1)
Catheter site pain	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Chest discomfort	2 (0.3)	0	0	0	0	2 (0.3)	0	0	0	0	0	0
Chest pain	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Chills	5 (0.7)	0	0	0	0	5 (0.7)	0	0	0	0	0	0

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	Grade 1-2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	Total n (%)	Grade 1-2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	Total n (%)
Fatigue	2 (0.3)	0	0	0	0	2 (0.3)	5 (0.7)	0	0	0	0	5 (0.7)
Non-cardiac chest pain	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Oedema due to cardiac disease	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Pain	0	0	0	0	0	0	3 (0.4)	0	0	0	0	3 (0.4)
Pyrexia	8 (1.2)	0	0	0	0	8 (1.2)	7 (1.0)	0	0	0	0	7 (1.0)
HEPATOBILIARY DISORDERS	2 (0.3)	1 (0.1)	0	0	0	3 (0.4)	1 (0.1)	0	0	0	0	1 (0.1)
Cholestasis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Hepatitis toxic	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Hyperbilirubinaemia	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Liver injury	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
IMMUNE SYSTEM DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Seasonal allergy	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
INFECTIONS AND INFESTATIONS	9 (1.3)	5 (0.7)	1 (0.1)	0	0	15 (2.2)	14 (2.1)	20 (3.0)	6 (0.9)	7 (1.0)	0	47 (6.9)
Abscess	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Atypical pneumonia	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Bronchitis	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
COVID-19	2 (0.3)	1 (0.1)	0	0	0	3 (0.4)	4 (0.6)	5 (0.7)	1 (0.1)	2 (0.3)	0	12 (1.8)
COVID-19 pneumonia	2 (0.3)	3 (0.4)	0	0	0	5 (0.7)	4 (0.6)	10 (1.5)	4 (0.6)	5 (0.7)	0	23 (3.4)
Mumps	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	Grade 1-2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	Total n (%)	Grade 1-2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	Total n (%)
Oral herpes	1 (0.1)	0	0	0	0	1 (0.1)	2 (0.3)	0	0	0	0	2 (0.3)
Oropharyngeal candidiasis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Pneumonia	1 (0.1)	1 (0.1)	0	0	0	2 (0.3)	1 (0.1)	5 (0.7)	1 (0.1)	0	0	7 (1.0)
Pneumonia viral	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Respiratory tract infection bacterial	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Respiratory tract infection viral	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Sepsis	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0
Urinary tract infection	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Viral rhinitis	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Viral sepsis	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Vulvovaginal candidiasis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	0	0	0	0	2 (0.3)	0	1 (0.1)	0	0	3 (0.4)
Craniocerebral injury	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Eye injury	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Fall	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Head fracture	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)	0	0	2 (0.3)
Road traffic accident	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Wrist fracture	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
INVESTIGATIONS	17 (2.5)	7 (1.0)	5 (0.7)	0	0	29 (4.3)	25 (3.7)	10 (1.5)	5 (0.7)	0	0	40 (5.9)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Activated partial thromboplastin time prolonged	2 (0.3)	0	0	0	0	2 (0.3)	1 (0.1)	0	0	0	0	1 (0.1)
Alanine aminotransferase increased	4 (0.6)	0	0	0	0	4 (0.6)	7 (1.0)	3 (0.4)	0	0	0	10 (1.5)
Aspartate aminotransferase increased	2 (0.3)	0	0	0	0	2 (0.3)	1 (0.1)	1 (0.1)	1 (0.1)	0	0	3 (0.4)
Blood creatine phosphokinase increased	0	0	1 (0.1)	0	0	1 (0.1)	1 (0.1)	1 (0.1)	0	0	0	2 (0.3)
Blood fibrinogen decreased	0	2 (0.3)	0	0	0	2 (0.3)	0	0	0	0	0	0
Blood glucose increased	1 (0.1)	0	1 (0.1)	0	0	2 (0.3)	2 (0.3)	1 (0.1)	1 (0.1)	0	0	4 (0.6)
Blood thyroid stimulating hormone increased	2 (0.3)	0	0	0	0	2 (0.3)	1 (0.1)	0	0	0	0	1 (0.1)
Breath sounds abnormal	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
C-reactive protein increased	2 (0.3)	1 (0.1)	0	0	0	3 (0.4)	1 (0.1)	1 (0.1)	0	0	0	2 (0.3)
Creatinine renal clearance abnormal	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Creatinine renal clearance decreased	0	2 (0.3)	1 (0.1)	0	0	3 (0.4)	0	3 (0.4)	1 (0.1)	0	0	4 (0.6)
Differential white blood cell count abnormal	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Fibrin D dimer increased	3 (0.4)	0	0	0	0	3 (0.4)	10 (1.5)	0	1 (0.1)	0	0	11 (1.6)
Glomerular filtration rate abnormal	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Glomerular filtration rate decreased	0	1 (0.1)	0	0	0	1 (0.1)	0	1 (0.1)	1 (0.1)	0	0	2 (0.3)
Glycosylated haemoglobin increased	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Haematocrit increased	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Haemoglobin decreased	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0
Haptoglobin increased	2 (0.3)	0	0	0	0	2 (0.3)	1 (0.1)	0	0	0	0	1 (0.1)
Hepatic enzyme increased	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	1 (0.1)	0	0	0	2 (0.3)
International normalised ratio abnormal	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Neutrophil count increased	2 (0.3)	0	0	0	0	2 (0.3)	0	0	0	0	0	0
Oxygen saturation decreased	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Platelet count increased	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Prothrombin time prolonged	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0
Serum ferritin increased	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Thyroxine increased	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
White blood cell count decreased	1 (0.1)	0	0	0	0	1 (0.1)	0	1 (0.1)	0	0	0	1 (0.1)
White blood cell count increased	2 (0.3)	0	0	0	0	2 (0.3)	0	0	0	0	0	0
METABOLISM AND NUTRITION DISORDERS	8 (1.2)	2 (0.3)	0	0	1 (0.1)	11 (1.6)	7 (1.0)	2 (0.3)	0	0	0	9 (1.3)
Decreased appetite	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Dehydration	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Diabetes mellitus	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Diabetes mellitus inadequate control	0	1 (0.1)	0	0	0	1 (0.1)	0	1 (0.1)	0	0	0	1 (0.1)
Hyperglycaemia	1 (0.1)	0	0	0	1 (0.1)	2 (0.3)	0	1 (0.1)	0	0	0	1 (0.1)
Hypertriglyceridaemia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Hypokalaemia	2 (0.3)	0	0	0	0	2 (0.3)	2 (0.3)	0	0	0	0	2 (0.3)
Hyponatraemia	2 (0.3)	0	0	0	0	2 (0.3)	0	0	0	0	0	0
Hypophosphataemia	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Impaired fasting glucose	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Type 2 diabetes mellitus	1 (0.1)	0	0	0	0	1 (0.1)	2 (0.3)	0	0	0	0	2 (0.3)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	7 (1.0)	0	0	0	0	7 (1.0)	8 (1.2)	0	0	0	0	8 (1.2)
Arthralgia	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Back pain	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Intervertebral disc degeneration	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Intervertebral disc protrusion	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Muscle spasms	0	0	0	0	0	0	2 (0.3)	0	0	0	0	2 (0.3)
Musculoskeletal stiffness	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Myalgia	4 (0.6)	0	0	0	0	4 (0.6)	2 (0.3)	0	0	0	0	2 (0.3)
Pain in extremity	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Spinal osteoarthritis	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Colon adenoma	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
NERVOUS SYSTEM DISORDERS	44 (6.5)	1 (0.1)	0	0	0	45 (6.7)	19 (2.8)	0	0	0	0	19 (2.8)
Anosmia	3 (0.4)	0	0	0	0	3 (0.4)	0	0	0	0	0	0
Dizziness	3 (0.4)	0	0	0	0	3 (0.4)	5 (0.7)	0	0	0	0	5 (0.7)
Dysgeusia	31 (4.6)	1 (0.1)	0	0	0	32 (4.8)	1 (0.1)	0	0	0	0	1 (0.1)
Facial paralysis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Headache	10 (1.5)	0	0	0	0	10 (1.5)	11 (1.6)	0	0	0	0	11 (1.6)
Hypersomnia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Migraine	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Restless legs syndrome	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Syncope	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
PSYCHIATRIC DISORDERS	3 (0.4)	0	0	0	0	3 (0.4)	4 (0.6)	0	0	0	0	4 (0.6)
Anxiety	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Confusional state	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Insomnia	1 (0.1)	0	0	0	0	1 (0.1)	2 (0.3)	0	0	0	0	2 (0.3)
Stress	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Vaginal haemorrhage	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	12 (1.8)	1 (0.1)	0	0	0	13 (1.9)	11 (1.6)	10 (1.5)	1 (0.1)	3 (0.4)	0	25 (3.7)
Acute respiratory distress syndrome	0	0	0	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)
Acute respiratory failure	0	1 (0.1)	0	0	0	1 (0.1)	0	2 (0.3)	1 (0.1)	1 (0.1)	0	4 (0.6)
Asthma	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Cough	5 (0.7)	0	0	0	0	5 (0.7)	4 (0.6)	2 (0.3)	0	0	0	6 (0.9)
Dyspnoea	3 (0.4)	0	0	0	0	3 (0.4)	3 (0.4)	3 (0.4)	0	0	0	6 (0.9)
Hiccups	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Hypoxia	0	0	0	0	0	0	3 (0.4)	1 (0.1)	0	1 (0.1)	0	5 (0.7)
Interstitial lung disease	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Nasal congestion	2 (0.3)	0	0	0	0	2 (0.3)	0	0	0	0	0	0
Oropharyngeal pain	3 (0.4)	0	0	0	0	3 (0.4)	0	0	0	0	0	0
Pneumonitis	0	0	0	0	0	0	0	2 (0.3)	0	0	0	2 (0.3)
Respiratory failure	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Rhinorrhoea	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3 (0.4)	2 (0.3)	0	0	0	5 (0.7)	6 (0.9)	1 (0.1)	0	0	0	7 (1.0)
Acne	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Alopecia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Erythema	0	0	0	0	0	0	4 (0.6)	0	0	0	0	4 (0.6)
Hyperhidrosis	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Hyperkeratosis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Pruritus	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Rash	2 (0.3)	0	0	0	0	2 (0.3)	1 (0.1)	1 (0.1)	0	0	0	2 (0.3)
Rash macular-papular	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Urticaria	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
SOCIAL CIRCUMSTANCES	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Disease risk factor	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
UNCODED TERM	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
INCREASED PROCALCITONIN VALUE - 0.28 NG/ML - MORE THAN 3X UNL	0	[illegible]	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
VASCULAR DISORDERS	5 (0.7)	1 (0.1)	0	0	0	6 (0.9)	5 (0.7)	0	0	0	0	5 (0.7)
Hyperaemia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Hypertension	5 (0.7)	1 (0.1)	0	0	0	6 (0.9)	1 (0.1)	0	0	0	0	1 (0.1)
Hypotension	1 (0.1)	0	0	0	0	1 (0.1)	2 (0.3)	0	0	0	0	2 (0.3)
Orthostatic hypotension	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)

Includes AEs that started on or prior to Day 34 visit.
MedDRA v24.0 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 29OCT2021 (16:07) Source Data: adae Table Generation: 30OCT2021 (19:14)
(Data cutoff date : 26OCT2021 Database snapshot date : 29OCT2021) Output File: /ads_unblinded/C4671005_4SLA/adae_s062

Updated safety database (n=1881)

No major difference was noted regarding the most reported TEAEs remained similar between the updated (n=1881) and the initial (n=1349) safety analyses.

Table 49 - Updated safety database

Specific AEs indicating treatment differences

	PF-07321332 300 + Ritonavir 100 mg	Placebo
GI	58 (6.1%)	42 (4.5%) (diarrhea, vomiting)
Dysgeusia	54 (5.7%)	2 (0.2%)
Respiratory AEs	17 (1.8%)	33 (3.5%) (cough, dyspnea, hypoxia)
Hypertension	7 (0.7%)	1 (0.1)%
Pneumonia	2	12
COVID/COVID-19 pneumonia	7	30
COVID-19	3	12

- Treatment-related TEAEs

The most frequently reported treatment-related TEAEs in the PF-07321332/ritonavir group (≥1%) were Dysgeusia (3.7%), and Diarrhoea (1.9%). Of note, dysgeusia and diarrhoea were both reported with ritonavir and mentioned in section 4.8 of SmPC of ritonavir 100 mg at very common frequency. Both of these treatment-related TEAEs were reported with a higher incidence in the PF-07321332/ritonavir group compared with the placebo group (Dysgeusia: 3.7% in the PF-07321332/ritonavir group versus 0.1% in the placebo group, and Diarrhoea: 1.9% in the PF-07321332/ritonavir group versus 0.3% in the placebo group). Most of the treatment related TEAEs experienced by participants in both treatment groups were mild to moderate (Grade 1-2) in severity. One participant in the placebo treatment group had a potentially life-threatening (Grade 4) event (Blood glucose increased) that was considered related to treatment. No participants in either treatment group had an event of death related to an AE (Grade 5).

Table 50 - Summary of treatment-emergent adverse events by MedDRA system organ class, preferred term and maximum DAIDS grade (treatment related) – safety analysis set (protocol C4671005_45IA)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	46 (6.8)	3 (0.4)	0	0	0	49 (7.3)	25 (3.7)	3 (0.4)	1 (0.1)	0	0	29 (4.3)
CARDIAC DISORDERS	0	1 (0.1)	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Palpitations	0	1 (0.1)	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
EAR AND LABYRINTH DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Vertigo	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
GASTROINTESTINAL DISORDERS	26 (3.9)	0	0	0	0	26 (3.9)	12 (1.8)	1 (0.1)	0	0	0	13 (1.9)
Abdominal pain upper	1 (0.1)	0	0	0	0	1 (0.1)	2 (0.3)	0	0	0	0	2 (0.3)
Colitis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Diarrhoea	13 (1.9)	0	0	0	0	13 (1.9)	2 (0.3)	0	0	0	0	2 (0.3)
Dry mouth	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Dyspepsia	5 (0.7)	0	0	0	0	5 (0.7)	2 (0.3)	0	0	0	0	2 (0.3)
Faeces soft	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Gastroesophageal reflux disease	2 (0.3)	0	0	0	0	2 (0.3)	1 (0.1)	0	0	0	0	1 (0.1)
Nausea	6 (0.9)	0	0	0	0	6 (0.9)	6 (0.9)	1 (0.1)	0	0	0	7 (1.0)
Vomiting	5 (0.7)	0	0	0	0	5 (0.7)	1 (0.1)	0	0	0	0	1 (0.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Chest discomfort	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Pyrexia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
INVESTIGATIONS	1 (0.1)	0	0	0	0	1 (0.1)	5 (0.7)	1 (0.1)	1 (0.1)	0	0	7 (1.0)
Activated partial thromboplastin time prolonged	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Alanine aminotransferase increased	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Blood glucose increased	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Blood thyroid stimulating hormone increased	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Fibrin D dimer increased	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Haptoglobin increased	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Hepatic enzyme increased	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
METABOLISM AND NUTRITION DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Decreased appetite	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Myalgia	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
NERVOUS SYSTEM DISORDERS	26 (3.9)	1 (0.1)	0	0	0	27 (4.0)	3 (0.4)	0	0	0	0	3 (0.4)
Dizziness	2 (0.3)	0	0	0	0	2 (0.3)	0	0	0	0	0	0
Dysgeusia	24 (3.6)	1 (0.1)	0	0	0	25 (3.7)	1 (0.1)	0	0	0	0	1 (0.1)
Headache	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Hypersomnia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)

RETURN TO PACKAGE TABLE

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants by SYSTEM ORGAN CLASS	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
PSYCHIATRIC DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Anxiety	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Confusional state	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (0.3)	0	0	0	0	2 (0.3)	0	0	0	0	0	0
Dyspnoea	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Hiccups	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.1)	1 (0.1)	0	0	0	2 (0.3)	3 (0.4)	1 (0.1)	0	0	0	4 (0.6)
Acne	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Alopecia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Erythema	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Rash	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	1 (0.1)	0	0	0	2 (0.3)
Rash maculo-papular	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
VASCULAR DISORDERS	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Orthostatic hypotension	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)

Includes AEs that started on or prior to Day 34 visit.
MedDRA v24.0 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 29OCT2021 (16:07) Source Data: adae Table Generation: 30OCT2021 (19:14)
(Data cutoff date : 26OCT2021 Database snapshot date : 29OCT2021) Output File: /ada unblinded/C4671005 4.5IA/adae s068

Adverse events leading to study discontinuation

- AEs leading to treatment discontinuation

The AEs leading to treatment discontinuation were more reported in placebo arm than PF-07321332/ritonavir arm, i.e. 4.3% and 2.4% respectively. The most frequently reported AEs leading to discontinuation with PF-07321332/ritonavir treatment were Nausea (0.7%) and Vomiting (0.6%), see table 51.

Table 51 - Summary of treatment-emergent adverse events leading to treatment discontinuation by MedDRA system organ class, preferred term, and maximum DAIDS grade (all causalities) – safety analysis set (protocol C5671005_45IA)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Participants with events	8 (1.2)	7 (1.0)	1 (0.1)	0	0	16 (2.4)	5 (0.7)	18 (2.7)	6 (0.9)	0	0	29 (4.3)
CARDIAC DISORDERS	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Palpitations	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
GASTROINTESTINAL DISORDERS	7 (1.0)	0	0	0	0	7 (1.0)	2 (0.3)	1 (0.1)	0	0	0	3 (0.4)
Abdominal pain lower	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Colitis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Diarrhoea	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Nausea	5 (0.7)	0	0	0	0	5 (0.7)	1 (0.1)	1 (0.1)	0	0	0	2 (0.3)
Vomiting	4 (0.6)	0	0	0	0	4 (0.6)	0	0	0	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Chest discomfort	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
INFECTIONS AND INFESTATIONS	0	2 (0.3)	0	0	0	2 (0.3)	2 (0.3)	10 (1.5)	3 (0.4)	0	0	15 (2.2)
COVID-19	0	1 (0.1)	0	0	0	1 (0.1)	2 (0.3)	2 (0.3)	0	0	0	4 (0.6)
COVID-19 pneumonia	0	1 (0.1)	0	0	0	1 (0.1)	0	7 (1.0)	3 (0.4)	0	0	10 (1.5)
Pneumonia	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
INVESTIGATIONS	1 (0.1)	3 (0.4)	1 (0.1)	0	0	5 (0.7)	1 (0.1)	2 (0.3)	2 (0.3)	0	0	5 (0.7)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Blood glucose increased	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Creatinine renal clearance decreased	0	2 (0.3)	0	0	0	2 (0.3)	0	1 (0.1)	0	0	0	1 (0.1)
Differential white blood cell count abnormal	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Glomerular filtration rate abnormal	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Glomerular filtration rate decreased	0	0	0	0	0	0	0	1 (0.1)	1 (0.1)	0	0	2 (0.3)
Haemoglobin decreased	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0
Oxygen saturation decreased	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
White blood cell count decreased	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Myalgia	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
NERVOUS SYSTEM DISORDERS	2 (0.3)	0	0	0	0	2 (0.3)	1 (0.1)	0	0	0	0	1 (0.1)
Dizziness	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Dysgeusia	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Restless legs syndrome	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
PSYCHIATRIC DISORDERS	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Insomnia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0

RETURN TO PACKAGE TABLE

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Vaginal haemorrhage	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	0	5 (0.7)	2 (0.3)	0	0	7 (1.0)
Acute respiratory failure	0	0	0	0	0	0	0	1 (0.1)	1 (0.1)	0	0	2 (0.3)
Cough	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Dyspnoea	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Hypoxia	0	0	0	0	0	0	0	1 (0.1)	1 (0.1)	0	0	2 (0.3)
Interstitial lung disease	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Respiratory failure	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	1 (0.1)	0	0	0	1 (0.1)	0	1 (0.1)	0	0	0	1 (0.1)
Rash	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Rash maculo-papular	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0

Includes AEs that started on or prior to Day 34 visit
MedDRA v24.0 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 29OCT2021 (16:07) Source Data: adae Table Generation: 30OCT2021 (19:14)
(Data cutoff date : 26OCT2021 Database snapshot date : 29OCT2021) Output File: /nda_unblinded/C4671005_45IA/adae_s062d

Updated safety data (n=1881)

The updated safety data showed that the rate of discontinuation from study drug due to AE was slightly decreased, i.e. 2.1% (20/945) in PF-07321332/ritonavir arm and 4.1% (38/936) in placebo arm.

- AEs leading to study discontinuation

No participant in the PF-07321332/ritonavir group discontinued the study due to TEAEs (all causalities) compared with 10 participants (1.5%) in the placebo group.

Adverse event of special interest (AESI)

There were pre-specified AESIs in Study 1005 including hemodynamic events, inflammatory events, and thyroid-related events to be reviewed as part of routine safety data review procedures throughout the study and as part of signal detection processes. Analyses of AESI were not provided in the submitted data and will be provided in the final analysis to be provided at the time of MAA once all participants have completed their Day 34 visit.

All AESIs were expected to be reported as an AE or SAE.

Vital signs measurements did not suggest clinically meaningful changes relative to hemodynamic events across treatment groups and cardiac disorders were reported in 2 (0.3%) subject in PF-07321332/ritonavir group (2 cases of palpitations) and 4 (0.6%) subjects in placebo group (2 cases of palpitations, one pericardial effusion and one sinus tachycardia)

The increase of fibrinogen relative to inflammatory events was more reported in placebo arm than PF-07321332/ritonavir, i.e. 21.8% and 14.3% respectively.

No thyroid-related event was reported as AE based on the submitted summary of TEAEs table for study 1005 and the occurrence of TSH and T4 (free) elevations was comparable in the 2 treatment groups.

Serious adverse events (SAE)

All causality SAEs occurred in 13 (1.9%) subjects in the PF-07321332/ritonavir treatment group according to the Clinical Overview while there were 14 subjects having a SAE listed in the table of content of C4671005 Interim Analysis Narratives. SAEs were more reported in placebo arm, i.e. 46 (6.8%) subjects.

Table 52 - Summary of treatment-emergent serious adverse events by MedDRA system organ class, preferred term, and maximum DAIDS grade (all causalities) – safety analysis set (protocol C4671005_45IA)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Participants with events	4 (0.6)	6 (0.9)	3 (0.4)	0	0	13 (1.9)	5 (0.7)	24 (3.5)	7 (1.0)	10 (1.5)	0	46 (6.8)
CARDIAC DISORDERS	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Palpitations	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
GASTROINTESTINAL DISORDERS	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Rectal haemorrhage	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Chest discomfort	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
INFECTIONS AND INFESTATIONS	3 (0.4)	4 (0.6)	1 (0.1)	0	0	8 (1.2)	4 (0.6)	18 (2.7)	6 (0.9)	7 (1.0)	0	35 (5.2)
Abscess	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Atypical pneumonia	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
COVID-19	1 (0.1)	1 (0.1)	0	0	0	2 (0.3)	1 (0.1)	3 (0.4)	1 (0.1)	2 (0.3)	0	7 (1.0)
COVID-19 pneumonia	1 (0.1)	3 (0.4)	0	0	0	4 (0.6)	2 (0.3)	10 (1.5)	4 (0.6)	5 (0.7)	0	21 (3.1)
Pneumonia	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	5 (0.7)	1 (0.1)	0	0	7 (1.0)
Sepsis	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0

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Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Craniocerebral injury	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Eye injury	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Head fracture	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Road traffic accident	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Wrist fracture	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
INVESTIGATIONS	0	1 (0.1)	2 (0.3)	0	0	3 (0.4)	1 (0.1)	1 (0.1)	1 (0.1)	0	0	3 (0.4)
Alanine aminotransferase increased	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Creatinine renal clearance decreased	0	0	1 (0.1)	0	0	1 (0.1)	0	1 (0.1)	1 (0.1)	0	0	2 (0.3)
Haemoglobin decreased	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0
Oxygen saturation decreased	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Colon adenoma	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
NERVOUS SYSTEM DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Facial paralysis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	0	8 (1.2)	1 (0.1)	3 (0.4)	0	12 (1.8)
Acute respiratory distress syndrome	0	0	0	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)
Acute respiratory failure	0	0	0	0	0	0	0	2 (0.3)	1 (0.1)	1 (0.1)	0	4 (0.6)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Dyspnoea	1 (0.1)	0	0	0	0	1 (0.1)	0	2 (0.3)	0	0	0	2 (0.3)
Hypoxia	0	0	0	0	0	0	1 (0.1)	1 (0.1)	0	1 (0.1)	0	3 (0.4)
Interstitial lung disease	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Pneumonitis	0	0	0	0	0	0	0	2 (0.3)	0	0	0	2 (0.3)
Respiratory failure	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)

Includes AEs that started on or prior to Day 34 visit.
MedDRA v24.0 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 29OCT2021 (16:07) Source Data: adae Table Generation: 30OCT2021 (19:14)
(Data cutoff date : 26OCT2021 Database snapshot date : 29OCT2021) Output File: ./ads unblinded/C4671005 45IA/adae s062s

- Deaths

There were no deaths in PF-07321332 + ritonavir arm according to the provided data on Study 1005. A total of 10 deaths were reported in the placebo arm, all related to COVID-19 and respiratory event (hypoxia, acute respiratory distress/failure).

- Other SAEs

The most frequently reported treatment emergent SAEs in the PF-07321332/ritonavir group (≥2 participants) were COVID-19 (2 participants, 0.3% [compared with 7 participants, 1% in the placebo group]), and COVID-19 pneumonia (4 participants, 0.6% [compared with 21 participants, 3.1% in the placebo group]). All of these SAEs were considered related to the disease under study.

Regarded the non-COVID-19 related SAEs occurring with PF-07321332/ritonavir, it was reported one case of Chest discomfort, Dyspnoea, Palpitations (resolved at Day 5), one case of Facial paralysis

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(recovered with sequelae at Day 37), one case of Abscess, Sepsis (resolved at Day 9), one case of Haemoglobin decreased (resolved at Day 7) and one case of Creatinine renal clearance decreased (Low creatinine was a pre-existing condition that the participant was unaware of, SAE ongoing at the time of the last available report.).

Of the SAEs reported with PF-07321332/ritonavir, one case was considered by the investigator as reasonably possible to be related to the treatment In the opinion of the investigator of this case, there was a reasonable possibility that the events of Chest discomfort, Dyspnoea, and Palpitations were related to the study intervention (ritonavir); there was not a reasonable possibility that the events were related to the study intervention (PF-07321332), concomitant drug or clinical trial procedure.

Overall the reported SAEs with PF-07321332/ritonavir treatment were mostly related to COVID-19. Among the non-related COVID-19 SAEs reported, one case was considered as treatment related. The SAEs occurring with PF-07321332/ritonavir treatment in study 1005 were manageable. The majority of the reported SAEs with PF-07321332/ritonavir were considered as resolved/recovered; 2 subjects withdrew from the study and 2 cases were ongoing at the time of the report. The safety profile currently based on the 1349 participants from the safety analysis set from the interim analysis, will be further substantiated on the basis of the data from the approximately 1000 additional patients having achieved primary analysis. This will be analysed at the time of the MAA.

Laboratory findings

The clinical safety laboratory tests were to be performed at baseline, Day 5 then Days 14 and 34 required only if clinically relevant abnormal laboratory values were present from a sample drawn at the previous study visit.

The overall incidence of laboratory test abnormalities occurring within 34 days of first dose was comparable between both treatment groups. No major hematological and clinical chemistry abnormalities were detected in both PF-07321332/ritonavir and placebo arms. The most frequently occurring laboratory test abnormalities (occurring in ≥5% participants in any treatment group) were fibrinogen (<0.75 x baseline; >1.25 x baseline), aPTT (>1.1 x ULN), D-Dimer (>1.5 x ULN), neutrophils (>1.2 x ULN), glucose (>1.5 x ULN), thyrotropin (>1.2 x ULN), creatine kinase (>2 x ULN), and bicarbonate (<0.9 x LLN).

Elevations of hepatic transaminases >3xULN were reported at similar rates in both PF-07321332/ritonavir and placebo arms, i.e ASAT at 1.4% and 1.6% respectively; ALAT at 3.3% and 4.3% respectively.

Hemodynamic and inflammatory effects were considered as AESIs. Changes in haemoglobin and platelets were similar between the two arms and reported at low rate. No significative difference was reported in the increase of aPTT and PT between PF-07321332/ritonavir and placebo arms, nevertheless D-dimer increase (>1.5 x ULN) was more reported in placebo arm compared to PF-07321332/ritonavir, i.e. 19.7% and 10.8% respectively. The increase of fibrinogen (> 1.25 x ULN) was more reported in placebo arm than PF-07321332/ritonavir, i.e. 21.8% and 14.3% respectively.

Thyroid-related events were also including among AESIs; TSH and T4 increases (> 1.2 x ULN) were comparable in both treatment groups, i.e. TSH > 1.2 x ULN were reported in 7.1% in PF-07321332/ritonavir arm and 8.1% in placebo arm, and T4 (free) > 1.2 x ULN were reported in 1.1% in PF-07321332/ritonavir arm and 0.8% in placebo arm.

Table 53 - Incidence of laboratory test abnormalities (without regard to baseline abnormalities) – safety analysis set (protocol C467100_45IA)

Laboratory Abnormalities: Number of Participants Evaluable for Laboratory Abnormalities: Number (%) of Participants with Laboratory Abnormalities:			PF-07321332 300 mg + Ritonavir 100 mg 635 451 (71.0%)		Placebo 634 475 (74.9%)	
Group	Parameter (Unit)	Primary Criteria	N	n (%)	N	n (%)
HEMATOLOGY	Hemoglobin (g/dL)	<0.8x LLN	537	1 (0.2)	553	4 (0.7)
	Erythrocytes (10^12/L)	<0.8x LLN	537	6 (1.1)	553	8 (1.4)
	Platelets (10^9/L)	<0.5x LLN	530	0	547	3 (0.5)
		>1.75x ULN	530	1 (0.2)	547	4 (0.7)
	Leukocytes (10^9/L)	<0.6x LLN	537	1 (0.2)	553	6 (1.1)
		>1.5x ULN	537	9 (1.7)	553	5 (0.9)
	Lymphocytes (10^9/L)	<0.8x LLN	534	8 (1.5)	546	22 (4.0)
		>1.2x ULN	534	6 (1.1)	546	4 (0.7)
	Neutrophils (10^9/L)	<0.8x LLN	532	14 (2.6)	543	24 (4.4)
		>1.2x ULN	532	30 (5.6)	545	18 (3.3)
	Eosinophils (10^9/L)	>1.2x ULN	534	5 (0.9)	546	5 (0.9)
	Monocytes (10^9/L)	>1.2x ULN	534	4 (0.7)	546	1 (0.2)
	Activated Partial Thromboplastin Time (sec)	>1.1x ULN	580	109 (18.8)	576	95 (16.5)
	Prothrombin Time (sec)	>1.1x ULN	582	28 (4.8)	575	25 (4.3)
CLINICAL CHEMISTRY	Bilirubin (mg/dL)	>1.5x ULN	633	4 (0.6)	630	2 (0.3)
	Aspartate Aminotransferase (U/L)	>3.0x ULN	632	9 (1.4)	630	10 (1.6)
	Alanine Aminotransferase (U/L)	>3.0x ULN	632	21 (3.3)	630	27 (4.3)
	Lactate Dehydrogenase (U/L)	>3.0x ULN	631	1 (0.2)	631	2 (0.3)
	Alkaline Phosphatase (U/L)	>3.0x ULN	632	0	632	1 (0.2)
	Protein (g/dL)	>1.5x ULN	632	1 (0.2)	630	0
	Albumin (g/dL)	<0.8x LLN	635	0	634	1 (0.2)
	Urea Nitrogen (mg/dL)	>1.3x ULN	634	21 (3.3)	633	24 (3.8)
	Creatinine (mg/dL)	>1.3x ULN	634	1 (0.2)	633	3 (0.5)
	Sodium (mEq/L)	<0.95x LLN	634	1 (0.2)	633	2 (0.3)
	Potassium (mEq/L)	<0.9x LLN	630	8 (1.3)	633	8 (1.3)
		>1.1x ULN	630	11 (1.7)	633	14 (2.2)
	Chloride (mEq/L)	<0.9x LLN	634	1 (0.2)	632	1 (0.2)
	Calcium (mg/dL)	<0.9x LLN	630	6 (1.0)	632	6 (0.9)
	Bicarbonate (mEq/L)	<0.9x LLN	632	51 (8.1)	630	52 (8.3)

Laboratory Abnormalities: Number of Participants Evaluable for Laboratory Abnormalities: Number (%) of Participants with Laboratory Abnormalities:			PF-07321332 300 mg + Ritonavir 100 mg 635 451 (71.0%)		Placebo 634 475 (74.9%)	
Group	Parameter (Unit)	Primary Criteria	N	n (%)	N	n (%)
	Thyroxine, Free (ng/dL)	<0.8x LLN	630	7 (1.1)	625	5 (0.8)
		>1.2x ULN	630	3 (0.5)	625	7 (1.1)
	Thyrotropin (mIU/L)	<0.8x LLN	632	9 (1.4)	628	11 (1.8)
		>1.2x ULN	632	45 (7.1)	628	56 (8.9)
	Glucose (mg/dL)	<0.6x LLN	631	2 (0.3)	630	0
		>1.5x ULN	631	46 (7.3)	630	42 (6.7)
	Creatine Kinase (U/L)	>2.0x ULN	633	36 (5.7)	630	29 (4.6)
	Fibrinogen (mg/dL)	<0.75x Baseline	623	188 (30.2)	623	184 (29.5)
		>1.25x Baseline	623	89 (14.3)	623	136 (21.8)
	D-Dimer (ng/mL)	>1.5x ULN	622	67 (10.8)	620	122 (19.7)

NOTE: N = total number of participants with at least one observation of the given laboratory test while on study treatment or during lag time.
n = number of participants with a laboratory abnormality meeting specified criteria while on study treatment or during lag time.
Percentages are displayed for the laboratory tests having a category with ≥ 1 evaluable participants.
PFIZER CONFIDENTIAL SDTM Creation: 29OCT2021 (16:07) Source Data: adlb Table Generation: 30OCT2021 (19:17)
(Data cutoff date : 26OCT2021 Database snapshot date : 29OCT2021) Output File: ../ads_sublisted/C4671005_45IA/adlb_s301

Vital signs

Baseline values for systolic and diastolic blood pressure, heart rate, oxygen saturation (%), body temperature, and respiratory rate, were similar across both treatment groups, and there were no clinically meaningful differences between treatment groups in the mean changes from baseline in vital signs assessments (Study 1005).

- The mean maximum change from baseline in vital signs were comparable for participants in the PF-07321332/ritonavir treatment group compared with the placebo group (Study 1005 Table 14.3.5.3).
- The incidence of participants with diastolic blood >90 mmHg or systolic blood pressure >140 mmHg was comparable across treatment groups.

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Table 54 - Categorization of vital signs data – safety analysis set (protocol C4671005_45IA)

		PF-07321332 300 mg + Ritonavir 100 mg		Placebo	
Parameter (units)	Criteria	N	n (%)	N	n (%)
Diastolic Blood Pressure (mmHg)	Value > 90 mmHg	656	69 (10.5)	657	79 (12.0)
Systolic Blood Pressure (mmHg)	Value > 140 mmHg	656	68 (10.4)	657	88 (13.4)

ECGs

No thorough QT study was performed. ECG data were collected in Study 1005 and to be assessed by the E-DMC for the sentinel cohort consisting of the first 60 participants in study. On 12 Aug 2021, the E-DMC reviewed the unblinded safety data for the sentinel cohort of 68 participants which included ECG data for 59 participants. There was no clinically relevant difference between active and placebo groups in changes of QTcF according to the company but the study Blinded Sentinel Safety Summary and Sentinel Cohort ECG Tables were not submitted.

In addition, the Study 1001 Part 5 aimed to evaluate QTc of PF-07321332/ritonavir at supratherapeutic dose. The upper bounds of 90% CI for ΔΔQTcF estimates across the entire concentration range (supratherapeutic, 2 x therapeutic exposure and therapeutic exposure) were all less than 10 ms suggesting no clinically relevant effect of PF-07321332/ritonavir on QTcF interval.

Table 55 - Model-derived ΔΔQTcF prediction for concentrations of interest

	Concentration (ng/mL)	Mean ΔΔQTcF (90% CI) (ms)
Therapeutic exposure[a]	4140	-0.37 (-1.84, 1.1)
2x Therapeutic exposure[a]	8280	-0.15 (-1.37, 1.07)
2250 mg mean C_{max} in PART-5: Study 1001	15944	0.27 (-1.42, 1.96)

a. Projected steady-state C_{max} at Phase 2/3 dosing regimen ie, PF-07321332/ritonavir 300/100 q12h

Pregnancy

At the time of the data cut-off in Study 1005 (26 Oct 2021), there was one (1) reported pregnancy in the safety database. This participant was in the placebo group and will continue to be followed for pregnancy outcomes.

Hepatotoxicity

Detailed narratives on all participants included in the safety population from the 45% interim analysis (database cut-off 26 October 2021) with hepatotoxicity in study 1005 were provided upon FDA request on 10 November 2021. Indeed a risk of hepatotoxicity is associated with ritonavir and is mentioned in the section 4.8 of the SmPC of ritonavir 100 mg, i.e. Hepatic transaminase elevations exceeding five times the upper limit or normal, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir alone or in combination with other antiretrovirals.

Hepatotoxicity cases occurred at similar rate in both arms in Study 1005 and were reported in 7 (1.04%) subjects in PF-07321332/ritonavir arm and 11 (1.62%) subjects in placebo arm. The majority of hepatotoxicity cases reported in the safety population were hepatic transaminase elevation > 5xULN, which might be related to the disease under study.

Post marketing safety data

Not applicable.

Supportive safety data from Phase 1 studies

- Study 1001
    - Part 1 – SAD (n=13)

The median duration of treatment was 1 day for all 9 treatment groups in each period. All participants received treatment for 1 day in PART-1.

There were no TEAEs reported in the PF-07321332 150 mg (suspension, fasted) group, PF-07321332 250 mg (suspension)/ritonavir 100 mg (fed) group and the PF-07321332 750 mg (suspension)/ritonavir 100 mg (fasted) group. Out of 12 TEAEs, 7 were observed in placebo (alone or enhanced with ritonavir) treatment groups, and 5 were observed in the PF-07321332 500 mg, 1500 mg and 250 mg/ritonavir treatment groups.

The SOCs with participants reporting all-causality TEAEs across all treatment groups, including placebo, were Nervous system disorders (4 events; 2 placebo and 2 treated), Gastrointestinal disorders (3 events; all placebo), General disorders and administration site conditions (2 events; 1 placebo and 1 treated), Psychiatric disorders (2 events; 1 placebo and 1 treated) and Investigations (1 event; treated).

None of the TEAEs in PART-1 were treatment-related. No participant had an SAE, severe AE, or dose reduced or temporary discontinuation due to AEs in PART-1.

- Part 2 – MAD (n=29)

The median duration of treatment was 10 days for all 6 treatment groups. Almost all participants received treatment for 10 days in PART-2 except 1 participant in the placebo/ritonavir 100 mg BID (fasted) group received study treatment for 7 days. The numbers of all-causality TEAEs and treatment-related TEAEs were similar between the 6 treatment arms in PART-2.

The SOCs with the greatest number of participants reporting all-causality TEAEs were Gastrointestinal disorders (13 events; 1 placebo and 12 treated), followed by General disorder and administration site conditions (8 events; 2 placebo and 6 treated), Nervous system disorders (6 events; all treated) and Investigations (5 events; 2 placebo and 3 treated).

The numbers of treatment-related TEAEs were also similar between the 6 treatment arms in PART-2.

No participant had an SAE, severe AE, discontinuation from study due to AEs, or dose reduced or temporary discontinuation due to AEs in PART-2.

- Part 3 – RBA/FE (n=12)

The duration of treatment was 1 day for all participants in each period.

TEAEs were reported at similar rate in PF- 07321332 250 mg (suspension), fasted and PF- 07321332 250 mg (tablet), fasted group (3/12, 25.0% in each group) and in 1/12 (8.3%) subjects included in the PF- 07321332 250 mg (tablet), fed group.

The SOCs with participants reporting all-causality or treatment-related TEAEs were General disorders and administration site conditions (5 events, 1 treatment-related), and Nervous system disorders (3 events, all treatment-related).

Table 56 - Treatment-emergent adverse event by system organ class and preferred term (all causalities) – part-3: rBA/FE (safety analysis set) (protocol C4671001)

Number of Participants Evaluable for AEs	PF-07321332 250 mg (Suspension), Fasted (N=12)	PF-07321332 250 mg (Tablet), Fasted (N=12)	PF-07321332 250 mg (Tablet), Fed (N=12)
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)
With Any Adverse Event	3 (25.0)	3 (25.0)	1 (8.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (16.7)	2 (16.7)	1 (8.3)
Chest discomfort	1 (8.3)	0	0
Vessel puncture site haematoma	0	2 (16.7)	1 (8.3)
Vessel puncture site haemorrhage	1 (8.3)	0	0
NERVOUS SYSTEM DISORDERS	1 (8.3)	1 (8.3)	0
Dizziness	1 (8.3)	0	0
Headache	1 (8.3)	0	0
Hypertonia	0	1 (8.3)	0

Participants were only counted once per treatment per event.
Included all data collected since the first dose of study drug.
MedDRA v24.0 coding dictionary applied.

Table 57 - Treatment-emergent adverse event by system organ class and preferred term (treatment related) – part-3: rBA/FE (safety analysis set) (protocol C4671001)

Number of Participants Evaluable for AEs	PF-07321332 250 mg (Suspension), Fasted (N=12)	PF-07321332 250 mg (Tablet), Fasted (N=12)	PF-07321332 250 mg (Tablet), Fed (N=12)
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)
With Any Adverse Event	2 (16.7)	1 (8.3)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (8.3)	0	0
Chest discomfort	1 (8.3)	0	0
NERVOUS SYSTEM DISORDERS	1 (8.3)	1 (8.3)	0
Dizziness	1 (8.3)	0	0
Headache	1 (8.3)	0	0
Hypertonia	0	1 (8.3)	0

Participants were only counted once per treatment per event.
Included all data collected since the first dose of study drug.
MedDRA v24.0 coding dictionary applied.

Of note the case of Chest discomfort reported with PF- 07321332 was considered as treatment-related similarly to the SAE case reported in Study 1005.

No participant had an SAE, severe AE, discontinuation from study due to AEs, or dose reduced or temporary discontinuation due to AEs in PART-3.

- Part 4 – M&E (n=6)

The duration of treatment was 1 day for all participants. Only 1 all-causality TEAE (Nasopharyngitis) was reported in PART-4. This AE was not treatment related.

- Part 5 – SE (n=10)

The duration of treatment was 1 day for all participants in each period. The incidences of all-causality and treatment-related TEAEs were the same between the 2 groups, treated and placebo in PART-5. The most frequently reported SOC of TEAE was Gastrointestinal disorders (6 events, 2 treatment-related).

Table 58 - Treatment-emergent adverse event by system organ class and preferred term (all causalities) – part-5: SE (safety analysis set) (protocol C4671001)

Number of Participants Evaluable for AEs	Placebo (Suspension)/ ritonavir 100 mg (N=10)	PF-07321332 2250 mg (Suspension)/ ritonavir 100 mg (N=10)
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**
With Any Adverse Event	3 (30.0)	3 (30.0)
EYE DISORDERS	0	1 (10.0)
Photopsia	0	1 (10.0)
GASTROINTESTINAL DISORDERS	2 (20.0)	2 (20.0)
Abdominal pain	1 (10.0)	1 (10.0)
Change of bowel habit	1 (10.0)	0
Diarrhoea	0	1 (10.0)
Nausea	0	1 (10.0)
Vomiting	1 (10.0)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (10.0)	0
Application site erythema	1 (10.0)	0
Application site pruritus	1 (10.0)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (10.0)	0
Back pain	1 (10.0)	0
Pain in extremity	1 (10.0)	0
NERVOUS SYSTEM DISORDERS	1 (10.0)	0
Headache	1 (10.0)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (10.0)	0
Dermatitis contact	1 (10.0)	0

PF-07321332 2250 mg divided into three doses of 750 mg administrated at 0h, 2h and 4h; Ritonavir dosed at -12h, 0h and 12h post-dose.
Participants received first split dose of PF-07321332/placebo oral suspension at least 2h after the morning breakfast.
Participants were only counted once per treatment per event.
Included all data collected since the first dose of study drug.

Table 59 - Treatment-emergent adverse event by system organ class and preferred term (treatment related) – part-5: SE (safety analysis set) (protocol C4671001)

Number of Participants Evaluable for AEs	Placebo (Suspension)/ ritonavir 100 mg (N=10)	PF-07321332 2250 mg (Suspension)/ ritonavir 100 mg (N=10)
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)
With Any Adverse Event	1 (10.0)	1 (10.0)
GASTROINTESTINAL DISORDERS	1 (10.0)	1 (10.0)
Nausea	0	1 (10.0)
Vomiting	1 (10.0)	0

PF-07321332 2250 mg divided into three doses of 750 mg administrated at 0h, 2h and 4h; Ritonavir dosed at -12h, 0h and 12h post-dose.
Participants received first split dose of PF-07321332/placebo oral suspension at least 2h after the morning breakfast.
Participants were only counted once per treatment per event.
Included all data collected since the first dose of study drug.

No participant had an SAE, severe AE, discontinuation from study due to AEs, or dose reduced or temporary discontinuation due to AEs in PART-5.

- Study 1011 (Renal impairment)

All-causality AEs were reported by 2 participants in the normal renal function group and by 1, 1 and 5 participants in the mild, moderate, and severe renal impairment groups, respectively. Treatment related AEs were reported by 2 participants in the severe renal impairment group. One participant in the severe renal impairment had 3 SAEs, including 1 severe SAE (Pulmonary oedema), and 2 moderate SAEs (1 Acute kidney injury, 1 Pneumonia), and all 3 were considered not treatment related. This participant discontinued study due to the SAE of Acute kidney injury. There were no deaths in this study.

All-causality AEs were most frequently reported under the SOCs of Gastrointestinal disorders, General disorders and administration site conditions, and Nervous system disorders. Headache was the most frequently reported AE: 2 participants with normal renal function and 1 participant in the moderate renal impairment group reported headache. In addition, Dysgeusia was reported in 2 participants in the severe renal impairment group. All-causality AEs of other SOCs were reported in 1 participant each. All the all-causality AEs reported in participants with normal renal function, and mild or moderate renal impairment were mild. Most of the all-causality AEs (17 out of 22) were reported by participants in the severe renal impairment group.

There were 4 treatment related AEs under the SOCs of Gastrointestinal disorders (2 participants had Dry mouth) and Nervous system disorders (2 participants had Dysgeusia). All 4 AEs occurred in the severe renal impairment group and were mild in severity

- Study 1014

All 12 participants took at least 1 dose of study intervention and were included in the safety analysis.

In Period 1 (PF-07321332 300 mg/ritonavir 100 mg as a single oral dose), 4 AEs were reported in 4 (33.3%) participants, and 1 AE was considered treatment related. The TEAEs reported by PT were

Vessel puncture site haematoma, Dysgeusia, Sciatica and Polyuria (1 participant each, 8.3%). All 4 TEAEs were mild in severity (Table 14.3.1.2.3). One participant had a treatment related TEAE of Dysgeusia.

In Period 2 (Carbamazepine on a titration schedule for 15 days + PF-07321332 300 mg/ritonavir 100 mg as single dose at Day 14), 18 AEs were reported in 9 (75.0%) participants, and 8 AEs reported in 6 (50%) participants were considered treatment related. One participant discontinued from study due to treatment related AE. The most frequently reported all-causality TEAEs by PT, regardless of SOC, were Transaminases increased (5 participants, 41.7%). The majority of the TEAEs (17/18) were mild in severity. There was 1 moderate TEAE of Inappropriate antidiuretic hormone secretion (Hyponatremia/SIADH). Eight TEAEs reported by 6 participants were considered treatment related. The most frequently reported treatment related TEAEs by PT were Transaminases increased (5 participants, 41.7%).

No participants had SAE, severe AE, or dose reduced or temporary discontinuation due to

AEs in Period 1 or Period 2. In Period 2 there was 1 participant discontinued from study due to a moderate AE of Inappropriate antidiuretic hormone secretion (Hyponatremia/SIADH), which was considered treatment related.

- Study 1015

Twelve participants received at least 1 study treatment and were thus included in the safety analysis. Except for 1 participant, who withdrew informed consent in Period 1, the remaining 11 participants completed the assigned treatment in both periods (period 1: PF-07321332/ritonavir 300/100 mg; period 2: Itraconazole 200 mg QD + PF-07321332/ritonavir 300/100 mg BID).

All-causality 26 and 48 AEs were reported by 7 and 10 participants in Periods 1 and 2, respectively. None of the AEs were considered serious or severe by the investigator. No participants discontinued from the study or study treatment or had dose reductions due to AEs.

Among the all-causality TEAEs, 24 out of 26 AEs in Period 1 and 43 out of 48 AEs in Period 2 were considered treatment related.

Most of the reported AEs were mild in severity. Among the all-causality AEs, 4 participants reported moderate AEs: 2 participants reported 4 moderate AEs in Period 1 and 2 participants reported 5 moderate AEs in Period 2:

In Period 1, 1 participant reported Vomiting and Headache (both related to study treatment); 1 participant reported Dizziness (not related to study treatment) and Headache (related to study treatment).

In Period 2, 1 participant reported Constipation (related to study treatment); and 1 participant reported Anorectal discomfort, Constipation, Diarrhoea, and Gastrointestinal motility disorder (all related to study treatment).

All AEs, with concomitant medications given when necessary, were resolved before the end of study, except 1 event of Constipation, which was reported as resolving at the time of the last report.

One participant experienced the event of Atrioventricular block first degree on Study Day 3 in Period 1, which continued through Period 2. The event resolved on Study Day 13. No severe AEs or SAEs were reported.

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Overall no notable safety signal was detected with PF- 07321332/ritonavir in Phase 1 studies. Cases of transaminases increases and hyponatremia/SIADH were reported with PF- 07321332/ritonavir + Carbamazepine in Study 1014; both of these reported TEAEs are mentioned in the SmPC of carbamazepine. One case of Atrioventricular block was reported with PF-07321332/ritonavir in study 1015 and one case of Chest discomfort was reported with PF- 07321332 in Study 1001 and considered as treatment-related. Taking into account the SAE of Palpitations, Chest discomfort and dyspnea that occurred with Paxlovid in Study 1005, the risk of cardiovascular events should be further discussed by the company during the MAA.

Conditions of use

Three adverse reactions (dysgeusia, diarrhoea and vomiting) have been included in section 6 in Conditions of Use based on Phase 2/3 study 1005 and considered related to Paxlovid according to the presented interim analysis. The proposed list of adverse reactions is agreed based on the submitted data.

However, in section 4.8 of the SmPC of Norvir (ritonavir) a whole range of additional adverse reactions are listed. Taking into account the differences in posology and duration of ritonavir treatment between Norvir and Paxlovid, it is considered unlikely at this stage to identify which of these adverse reactions are related to the dosage of 100 mg ritonavir twice daily. As a conservative measure the CHMP decided to include the adverse reactions from the SmPC of Norvir in the CoU in addition to the adverse reactions reported in the clinical study (467-1005). Nevertheless it is clearly stated in the CoU that the type, severity and frequency of adverse reactions corresponding to higher dose and use for longer duration in the context of chronic HIV infection might not apply to the use of ritonavir during 5 days in Paxlovid.

Discussion on Safety

Demonstrated risks

The safety data was based on the 45% interim analysis of the pivotal Phase II/III Study 1005 (treatment in patients COVID-19 positive at High Risk) which includes 1349 participants (safety analysis set) enrolled through 29 Sep 2021 with the database cut-off on 26 Oct 2021. A total of 672 subjects were enrolled in the PF-07321332/ritonavir arm and 677 subjects were enrolled in the placebo arm. The administered treatment was intended at the posology of PF- 07321332 300mg and ritonavir 100mg Q12h for 5 days, however the extent of exposure was not provided in the submitted data. The safety follow-up period was planned through Day 34. A presentation on updated safety data on a larger safety analysis set (N=1881) was provided during this procedure.

Based on the provided safety data, no major concern was identified in the safety profile of PF-07321332/ritonavir combination which appears comparable to placebo with manageable toxicities. From a non-clinical point of view, there were no adverse findings in toxicity studies in rats and cynomolgus monkeys. The incidence of TEAEs was slightly lower in PF-07321332/ritonavir compared to placebo, i.e. 19.8% and 22.3% respectively, and the majority of the adverse events occurring in the study may be confounded with COVID-19 symptoms. The majority of the reported TEAEs with PF-07321332/ritonavir were low grade severity; Grade 3-4 TEAEs were reported in 3.1% of subjects in the PF-07321332/ritonavir arm and 7.1% in subjects in placebo arm. The most reported TEAEs in the PF-07321332/ritonavir group were Dysgeusia (4.8%), Diarrhoea (3.9%), Nausea (1.9%), Headache (1.5%), Vomiting (1.3%), and Pyrexia (1.2%). It is highlighted that these most reported TEAEs were both reported with ritonavir and mentioned in section 4.8 of SmPC of ritonavir 100 mg at very common frequency except for pyrexia (common). The most frequently reported treatment-related TEAEs in the PF-07321332/ritonavir group (≥1%) were Dysgeusia (3.7%), and Diarrhoea (1.9%). Among the cases

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of dysgeusia reported with PF-07321332/ritonavir, one led to treatment discontinuation. Most of the treatment-related TEAEs experienced by participants in both treatment groups were mild to moderate (Grade 1-2) in severity.

Hypertension occurred at a low frequency overall (0.9% and 0.1%, in the PF-07321332/ritonavir and placebo group, respectively, but was more frequent in the PF-07321332/ritonavir group. A total of 7 AEs of Hypertension were reported; 6 participants in the PF-07321332/ritonavir group and 1 participant in the placebo group. One participant in the PF-07321332/ritonavir group had an event of severe (Grade 3) hypertension which was not resolved. The number of cases were limited, and causality remains unclear. Ongoing studies are expected to provide more data regarding this issue. Further details should be provided during the MAA such as whether the cases occurred in patients who already had hypertension at baseline, and how often blood pressure was measured.

The AEs leading to treatment discontinuation were more reported in placebo arm than PF-07321332/ritonavir arm, i.e. 4.3% and 2.4% respectively. The most frequently reported AEs leading to discontinuation with PF-07321332/ritonavir treatment were Nausea (0.7%) and Vomiting (0.6%). No participant in the PF-07321332/ritonavir group discontinued the study due to TEAEs (all causalities) compared with 10 participants (1.5%) in the placebo group.

The SAEs were less reported in PF-07321332/ritonavir than placebo and were mostly related to COVID-19. No death occurred in the PF-07321332/ritonavir group while a total of 10 deaths were reported in the placebo arm, all related to COVID-19. Of the SAEs reported with PF-07321332/ritonavir, one case of Chest discomfort, dyspnoea and palpitations was considered by the investigator as reasonably possible to be related to the treatment (ritonavir), the treatment was permanently discontinued on Day 2 and the events were reported as resolved on Day 5.

The overall incidence of laboratory test abnormalities occurring within 34 days of first dose was comparable between both treatment groups. No major hematological and clinical chemistry abnormalities were detected in both PF-07321332/ritonavir and placebo arms.

No in-depth QT study was performed. ECG data were collected in Study 1005 and no clinically relevant difference between active and placebo groups in changes of QTcF was identified by the Applicant according to the Clinical Overview, however the C4671005 Blinded Sentinel Safety Summary and C4671005 Sentinel Cohort ECG Tables were missing. In addition, the Study 1001 Part 5 aimed to evaluate QTc of PF-07321332/ritonavir at supratherapeutic dose and the ΔΔQTcF estimates suggested no clinically relevant effect of PF-07321332/ritonavir on QTcF interval.

Due to the risk of hepatotoxicity associated with ritonavir, the company provided detailed narratives on all participants with hepatotoxicity, i.e. Hepatic transaminase elevations exceeding five times the upper limit or normal, clinical hepatitis, and jaundice. Hepatotoxicity cases were reported at similar rate in PF-07321332/ritonavir arm and in placebo arm, i.e. 1.04% and 1.62% respectively. The majority of hepatotoxicity cases that occurred in the safety population were hepatic transaminase elevation > 5xULN. Among the 7 cases of hepatotoxicity reported in the PF-07321332/ritonavir arm, 3 of them had elevations of ALT and/or AST at baseline and there was no hepatotoxicity case considered as related to study intervention by the investigator.

In light of the nonclinical findings, use of Paxlovid is not recommended during pregnancy and in women of childbearing potential not using contraception. This is reflected in section 5.5 of the Conditions for Use.

Uncertainty about risks

Ritonavir is principally metabolized and eliminated by the liver and the primary route of elimination of PF-07321332 when administered with ritonavir was renal excretion of intact drug. Participants with known medical history of active liver disease or acute liver failure and participants receiving dialysis or have known moderate to severe renal impairment were excluded from the pivotal study 1005. There remains uncertainties on the impact of hepatic impairment and severe renal impairment on the safety profile of PF-07321332/ritonavir combination.

Even though Paxlovid is only administered for 5 days, a cardiovascular risk especially in patients with cardiovascular co-morbidities based on the ritonavir component cannot be completely ruled out, especially since only a limited number patients with CVD were included in the Paxlovid group. Therefore, the company will have to discuss at the time of the MAA whether the risk of cardiovascular events should be included as an important potential risk in the RMP.

Some data were missing from the submission and need to be addressed in the MAA, i.e. study drug exposure (duration of exposure, dose intensity, relative dose intensity), AESI analyses, Sentinel Cohort ECG data.

Two still ongoing clinical studies albeit performed in other patients' populations (patients at standard risk of progressing to severe COVID-19 and in Post exposure population) are still ongoing that will provide additional information regarding the safety profile and possible rare adverse reactions.

The Committee considered that this medicine, once it is authorised for use, should be subject to additional monitoring. This enables to stimulate the ADR reporting in order for new safety information to be identified quickly. It is expected that Healthcare Professionals report any suspected adverse reactions

Overall, the safety data submitted are considered sufficient for supporting the use of Paxlovid in an emergency setting.

3. Benefit-risk balance

This procedure, triggered under Article 5(3) of Regulation (EC) No 726/2004, intends to provide a harmonised scientific opinion at EU level on currently available information on Paxlovid and on potential conditions of use with a view to supporting national decisions before a formal marketing authorisation based on the available quality, preclinical and clinical data on the potential use of Paxlovid for the treatment of confirmed COVID-19 in adult patients. This is particularly relevant in the clinical setting in view of the current pandemic situation and the public health interest.

Benefit

The clinical data supporting the use of Paxlovid for treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19 is based on the results of the phase 2/3 study randomized, double blind placebo controlled study (C467- 1005 or EPIC-HR study) with a requiring primary endpoint, difference in percentage of patients with hospitalization for COVID-19 or death for any cause through day 28.

The pre specified interim analysis on 45% of enrolled patients showed an absolute difference in percentage of patients with hospitalization for COVID-19 or death for any cause through day 28 with PF-07321332/ritonavir in comparison with placebo treatment of6.317% (95% CI: -9.041% to -3.593%; p<0.0001) in the primary analysis (mITT). The results in the clinically relevant population, of value for the generalizability to clinical practice (i.e patients who start treatment within 5 days of onset of symptoms) represented by the mITT1 population of analysis were consistent, both the mITT and

mITT are presented in the CoU. On this basis the DSMB recommended to stop the study. The data are considered to support the indication for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

Of note, patients receiving oxygen for other diseases than COVID-19 should not be prevented from being treated with Paxlovid.

It has to be underlined that preliminary presentation of the results of the final analysis were made available at latest stage of the Art5(3) procedure in parallel to the public communication of the company. According to this preliminary presentation the effect size in both the interim and final analyses seem consistent. However, given the high level presentation, no conclusion could be drawn on this final analysis for the CoU, only the results of the interim data are therefore reported in the CoU. The applicant should provide an adequate report of the final analysis at the time of the MAA.

However, some uncertainties regarding the assessment of the data remain and will be further addressed during the MAA.

As regards its pharmacodynamic properties, Paxlovid seems to have a limited barrier to resistance, observed at 10 passages but only based on *in vitro* resistance selection study with murine hepatitis virus (MHV)-3CL protease and are reported in the CoU (requiring caution in interpretation). The resistance pattern (including signature mutations) of SARS-CoV-2 under treatment with Paxlovid remains to be determined. Therefore, *in vitro* data on antiviral resistance to PF-07321332 with SARS-CoV-2 need to be provided at the time of the MAA and will notably enable to substantiate the resistance pattern and the genetic barrier.

Adherence to the treatment schedule is critical to reduce the risk of resistance development. PF-07321332 must be coadministered with ritonavir. Failure to correctly coadministered PF-07321332 with ritonavir will result in plasma levels of PF-07321332 that will be insufficient to achieve the desired therapeutic effect. The recommended dosage is 300 mg PF-07321332 (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally every 12 hours for 5 days. Paxlovid should be administered as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset.

It is noteworthy, that more than half of the enrolled population was seropositive for SARS-CoV-2 (56%) although SARS-COV-2 vaccination and prior episode of SARS-CoV-2 infection were part of the exclusion criteria and scarce use of mAb is reported (only one patient in Paxlovid arm). This will be further scrutinized at the time of the MAA (notably with discriminant IgG/IgM serology to be provided), given the potential impact for generalizability to vaccinated subjects.

As regards the relevant subgroup of patients at high risk, obese patients represented a limited proportion of patients (app 37%), the same applies for patients >65 y/o (11.4%), patients >75 y/o age (app 3%) with a number of patients >80 y/o, being likely scarce and finally for diabetic patients (app 13%). As a matter of fact, among comorbidities cigarette smokers (app 37%) and hypertension (app 30%) were mostly reported.

The complex interaction profile driven by ritonavir is expected to be a notable limiting factor of its use in the target population (likely requiring co-medications, notably for old patients).

Due to the lack of a relevant PK population model integrating PK data from patients, a contra-indication for patient with severe renal impairment and hepatic impairment has been added to the Conditions of Use.

Moreover, based on the available non clinical data, the use in pregnant women is not recommended as well as in WOCBP not using contraception. Moreover, due to the ritonavir driven ddI combined

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contraception, use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Therefore, as stated in the CoU, patients using combined hormonal contraceptives should be advised to use an effective alternative contraceptive method or an additional barrier method of contraception during treatment with Paxlovid, and until one menstrual cycle after stopping Paxlovid.

In vitro Data on VOC were provided, with no significant impact on antiviral activity observed against SARS-CoV-2 isolates belonging to the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2) Lambda (C.37) variants. This is reflected in the CoU.

However, recently, sublineages of the Delta (B.1.617.2) variant carrying non-silent mutations in different areas of the genome, have emerged. Clinical data have shown that the 5/6 patients with an event in the treated group were all infected with the Delta (21J) subvariant which harbours mutations in the ORF1a that encodes for nsp5 (the 3CL-protease) in contrast to the 21A subvariant. Albeit patients enrolled in the clinical study were almost exclusively infected by the Delta variant (98%) with the vast majority with the sublineage 21J (73%) the applicant will have to provide at the time of MAA adequate *in vitro* data to further investigate this issue, since the clinical data may point to a potential loss of efficacy in VOCs harbouring mutations in ORF1a., In vitro study in a substantial number of representative sequences of the Delta variant and its sublineages (based on GISAID) will have to be provided at the time of the MAA.

In vitro experiment on Mu variant is ongoing with results to be provided at the time of the MAA.

As a critical caveat given the highly increasing circulation of Omicron VOC, the applicant could not provide *in vitro* data for the EU harmonized recommendation for the Article 5(3) (as reflected in the CoU). This will have to be provided at the time of the MAA.

Safety

As regards the security profile, no overlapping or additive toxicities between PF-07321332 and ritonavir are expected since no target organs have been identified after PF-07321332 administration rats and monkeys up to 1 month duration.

Based on the currently limited safety data base (678 patients treated at the recommended dose), the common adverse advents are dysgueusia (being a known AE of ritonavir, with unknown contribution of PF-07321332) diarrhea and vomiting.

The frequency of some adverse events are of higher in the placebo arm, likely reflecting the limited impact on disease progression in this comparator arm.

Overall, based on the provided safety data, the safety profile of PF-07321332/ritonavir combination appears comparable to placebo and manageable with no major concern identified. However there remains uncertainties on the impact of hepatic impairment and severe renal impairment on the safety profile of PF-07321332/ritonavir combination. Additional safety data are expected in the final analysis (from app 1000 additional patients) to be provided at the time of the MAA. This will further substantiate the safety profile of Paxlovid.

Overall conclusion

Considering the data provided by the company on quality aspects, preclinical aspects and the provided clinical dataset from the interim analysis of the phase 2/3 study randomized, double blind placebo controlled study (C467- 1005 or EPIC-HR study), Paxlovid could provide clinical benefit for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19 in the context of this procedure and the COVID-19 pandemic, when used in accordance with the conditions of use.

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In view of safety reporting for product distribution in the EU supported by CHMP Opinion under Art 5(3) of Reg (EC) No 726/2004, Member States and the company should submit to EudraVigilance Post-Authorisation Module (EVPM) any individual case safety reports (serious non-EEA; serious and non-serious EEA) related to Paxlovid (PF-07321332 - ritonavir) and reported directly to them by patients and healthcare professionals.

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Document 2A.9

EMA Conditions of Use, Conditions for Distribution and Patients Targeted and Conditions for Safety Monitoring Addressed to Member States for Unauthorized Product Paxlovid (PF-07321332 150 mg and ritonavir 100 mg) Available for Use

Document URL

https://www.ema.europa.eu/en/documents/referral/paxlovid-pf-07321332-ritonavir-covid-19-article-53-procedure-conditions-use-conditions-distribution_en.pdf

Reference website URL

https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/article-53-opinions-any-scientific-matter-human-medicines#use-of-paxlovid-(pf-07321332-and-ritonavir)-for-treating-covid-19-section

License

Not applicable

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ANNEX I

CONDITIONS OF USE, CONDITIONS FOR DISTRIBUTION AND PATIENTS TARGETED AND CONDITIONS FOR SAFETY MONITORING ADDRESSED TO MEMBER STATES

FOR UNAUTHORISED PRODUCT

PAXLOVID (PF-07321332 150 mg and ritonavir 100 mg)

AVAILABLE FOR USE

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1. MEDICINAL PRODUCT FOR USE

- **Name of the medicinal product for use:** PAXLOVID
- **Active substance(s):** PF-07321332 and ritonavir
- **Pharmaceutical form:** Film-coated tablets
- **Route of administration:** Oral use
- **Strength:** 150 mg PF-07321332, 100 mg ritonavir

2. NAME AND CONTACT DETAILS OF THE COMPANY

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

[Contact details will be added at the National level]

3. TARGET POPULATION

PAXLOVID is indicated for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19 (see section 6).

4. CONDITIONS FOR DISTRIBUTION

Medicinal product subject to medical prescription.

5. CONDITIONS OF USE

5.1 Posology

PF-07321332 must be coadministered with ritonavir. Failure to correctly coadminister PF-07321332 with ritonavir will result in plasma levels of PF-07321332 that will be insufficient to achieve the desired therapeutic effect.

- **Dosing recommendations and treatment duration**

The recommended dosage is 300 mg PF-07321332 (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally every 12 hours for 5 days.

PAXLOVID should be administered as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset.

- **Specific populations**

Paediatric population

The safety and efficacy of PAXLOVID in paediatric patients younger than 18 years of age have not yet been established. No data are available.

Renal impairment

Mild
No dose adjustment is needed in patients with mild renal impairment.

Moderate
In patients with moderate renal impairment, the dose of PAXLOVID should be reduced to PF-07321332/ritonavir 150 mg/100 mg every 12 hours for 5 days to avoid increased toxicity due to over-exposure (this dose adjustment has not been clinically tested).

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The daily blister contains two separated parts each containing 2 tablets of PF-07321332 and one tablet of ritonavir corresponding to the daily administration at the standard dose.
Therefore, patients with **moderate** renal impairment should be alerted on the fact that only **one tablet of PF-07321332** with the tablet of ritonavir should be taken **every 12 hours**.

Severe
Appropriate dose for patients with severe renal impairment has not yet been determined (see section 6). PAXLOVID is contraindicated in patients with severe renal impairment (eGFR < 30 mL/min) until more data are available; the appropriate dosage for patients with severe renal impairment has not been determined (see section 5.2).

Hepatic impairment

Mild and moderate
No dosage adjustment of PAXLOVID is needed for patients with either mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.

Severe
No pharmacokinetic or safety data are available regarding the use of PF-07321332 or ritonavir in subjects with severe hepatic impairment (Child-Pugh Class C), therefore, PAXLOVID is contraindicated in patients with severe hepatic impairment (see section 5.2).

- **Method of administration**

For oral use.

PAXLOVID can be taken with or without food. The tablets should be swallowed whole and not chewed, broken or crushed.

5.2 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 5.11.

PAXLOVID is contraindicated in patients with severe hepatic impairment.

PAXLOVID is contraindicated in patients with severe renal impairment.

PAXLOVID is contraindicated with medicinal products that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions. PAXLOVID is also contraindicated with medicinal products that are potent CYP3A inducers where significantly reduced PF-07321332/ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance.

Table 1: Medicinal products that are contraindicated for concomitant use with PAXLOVID

Medicinal product class	Medicinal products within class	Rationale
Concomitant medicinal product levels increased or decreased		
α1-Adrenoreceptor Antagonist	Alfuzosin	Increased plasma concentrations of alfuzosin which may lead to severe hypotension (see section 5.4).
Analgesics	Pethidine, piroxicam, propoxyphene	Increased plasma concentrations of norpethidine, piroxicam and propoxyphene. Thereby, increasing the risk of serious respiratory depression or haematologic abnormalities, or other serious adverse effects from these agents.
Antianginal	Ranolazine	Increased plasma concentrations of ranolazine which may increase the potential for serious and/or life-threatening reactions (see section 5.4).

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Table 1: Medicinal products that are contraindicated for concomitant use with PAXLOVID

Medicinal product class	Medicinal products within class	Rationale
Anticancer	Neratinib	Increased plasma concentrations of neratinib which may increase the potential for serious and/or life-threatening reactions including hepatotoxicity (see section 5.4).
	Venetoclax	Increased plasma concentrations of venetoclax. Increased risk of tumour lysis syndrome at the dose initiation and during the dose-titration phase (see section 5.4).
Antiarrhythmics	Amiodarone, bepridil, dronedarone, encainide, flecanide, propafenone, quinidine	Increased plasma concentrations of amiodarone, bepridil, dronedarone, encainide, flecanide, propafenone, quinidine. Thereby, increasing the risk of arrhythmias or other serious adverse reactions from these agents.
Antibiotic	Fusidic Acid	Increased plasma concentrations of fusidic acid and ritonavir.
Anti-gout	Colchicine	Potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment (see sections 5.4).
Antihistamines	Astemizole, terfenadine	Increased plasma concentrations of astemizole and terfenadine. Thereby, increasing the risk of serious arrhythmias from these agents.
Antipsychotics/Neuroleptics	Lurasidone	Increased plasma concentrations of lurasidone which may increase the potential for serious and/or life-threatening reactions (see section 5.4).
	Clozapine, pimozide	Increased plasma concentrations of clozapine and pimozide. Thereby, increasing the risk of serious haematologic abnormalities, or other serious adverse effects from these agents.
	Quetiapine	Increased plasma concentrations of quetiapine which may lead to coma. The concomitant administration with quetiapine is contraindicated (see section 5.4).
Ergot Derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Increased plasma concentrations of ergot derivatives leading to acute ergot toxicity, including vasospasm and ischaemia.
Lipid-modifying agents HMG Co-A Reductase Inhibitors	Lovastatin, simvastatin	Increased plasma concentrations of lovastatin and simvastatin; thereby, increasing the risk of myopathy including rhabdomyolysis (see section 5.4).
Microsomal triglyceride transfer protein (MTTP) inhibitor	Lomitapide	Increased plasma concentrations of lomitapide (see section 5.4).

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Table 1: Medicinal products that are contraindicated for concomitant use with PAXLOV

Medicinal product class	Medicinal products within class	Rationale
PDE5 inhibitors	Avanafil	Increased plasma concentrations of avanafil (see section 5.4).
	Sildenafil	Contraindicated when used for the treatment of pulmonary arterial hypertension (PAH) only. Increased plas concentrations of sildenafil. Thereby, increasing the potential for sildenafil associated adverse events (which include hypotension and syncope). See section 5 for coadministration of sildenafil in patie with erectile dysfunction.
	Vardenafil	Increased plasma concentrations of vardenafil (see section 5.4).
Sedatives/hypnotics	Clorazepate, diazepam, estazolam, flurazepam, oral midazolam and triazolam	Increased plasma concentrations of clorazepate, diazepam, estazolam, flurazepam, oral midazolam and triazola Thereby, increasing the risk of extreme sedation and respiratory depression from these agents. (For caution on parenteral administered midazolam, see section 5.4
PF-07321332/ritonavir level decreased		
Herbal Preparation	St. John's wort	Herbal preparations containing St John's wort (*Hypericum perforatum)* due to the risk of decreased plasma concentrations and reduced clinical effects of PF-073213 and ritonavir (see section 5.4).
Anticonvulsant Antiinfective	Carbamazepine[a], Rifampin	Decreased plasma concentration and reduced clinical effects of PF-07321332 a ritonavir.

a. See section 6, Interaction studies conducted with PF-07321332/ritonavir.

5.3 Special warnings and precautions for use

Risk of serious adverse reactions due to interactions with other medicinal products

Initiation of PAXLOVID, a CYP3A inhibitor, in patients receiving medicinal products metabolised by CYP3A or initiation of medicinal products metabolised by CYP3A in patients already receiving PAXLOVID, may increase plasma concentrations of medicinal products metabolised by CYP3A.

Initiation of medicinal products that inhibit or induce CYP3A may increase or decrease concentratio of PAXLOVID, respectively.

These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening or fata events from greater exposures of concomitant medicinal products.
- Clinically significant adverse reactions from greater exposures of PAXLOVID.
- Loss of therapeutic effect of PAXLOVID and possible development of viral resistance.

See Table 1 for medicinal products that are contraindicated for concomitant use with PF-07321332/ritonavir (see section 5.2) and Table 2 for potentially significant interactions with oth medicinal products (see section 5.4). Potential for interactions should be considered with other medicinal products prior to and during PAXLOVID therapy; concomitant medicinal products should b reviewed during PAXLOVID therapy and the patient should be monitor for the adverse reactions associated with the concomitant medicinal products.

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Hepatotoxicity

Hepatic transaminase elevations, clinical hepatitis and jaundice have occurred in patients receiving ritonavir. Therefore, caution should be exercised when administering PAXLOVID to patients with pre-existing liver diseases, liver enzyme abnormalities or hepatitis.

Risk of HIV-1 resistance development

Because PF-07321332 is coadministered with ritonavir, there may be a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection.

Excipients

PF-07321332 contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

PF-07321332 and ritonavir each contain less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

5.4 Interaction with other medicinal products and other forms of interaction

PAXLOVID (PF-07321332/ritonavir) is an inhibitor of CYP3A and may increase plasma concentrations of medicinal products that are primarily metabolised by CYP3A. Medicinal products that are extensively metabolised by CYP3A and have high first-pass metabolism appear to be the most susceptible to large increases in exposure when coadministered with PF-07321332/ritonavir. Thus, coadministration of PF-07321332/ritonavir with medicinal products highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated (see Table 1, section 5.2).

PF-07321332 does not reversibly inhibit CYP2D6, CYP2C9, CYP2C19, CYP2C8, or CYP1A2 *in vitro* at clinically relevant concentrations. *In vitro* study results showed PF-07321332 may be inducer of CYP3A4, CYP2B6, CYP2C8, and CYP2C9. The clinical relevance is unknown. Based on *in vitro* data, PF-07321332 has a low potential to inhibit BCRP, MATE2K, OAT1, OAT3, OATP1B3 and OCT2. There is a potential for PF-07321332 to inhibit MDR1, MATE1, OCT1 and OATP1B1 at clinically relevant concentrations.

Ritonavir has a high affinity for several cytochrome P450 (CYP) isoforms and may inhibit oxidation with the following ranked order: CYP3A4 > CYP2D6. Ritonavir also has a high affinity for P-glycoprotein (P-gp) and may inhibit this transporter. Ritonavir may induce glucuronidation and oxidation by CYP1A2, CYP2C8, CYP2C9 and CYP2C19 thereby increasing the biotransformation of some medicinal products metabolised by these pathways and may result in decreased systemic exposure to such medicinal products, which could decrease or shorten their therapeutic effect.

Coadministration of other CYP3A4 substrates that may lead to potentially significant interaction should be considered only if the benefits outweigh the risks (see Table 2).

PF-07321332 and ritonavir are CYP3A substrates; therefore, medicinal products that induce CYP3A may decrease PF-07321332 and ritonavir plasma concentrations and reduce PAXLOVID therapeutic effect.

Only two drug-drug interaction studies have been performed with PAXLOVID (see the paragraph Interaction studies conducted with PF-07321332/ritonavir in section 6).

The drug-drug interactions listed in Table 1 (section 5.2) and Table 2 correspond to drug-drug interactions related to ritonavir. As a conservative approach they should also apply for PAXLOVID.

Medicinal products listed in Table 1 (section 5.2) and Table 2 are a guide and not considered a comprehensive list of all possible medicinal products that may interact with PF-07321332/ritonavir. The healthcare provider should consult appropriate references for comprehensive information.

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Table 2: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
α1-adrenoreceptor antagonist	↑Alfuzosin	Increased plasma concentrations of alfuzosin may lead to severe hypotension and is therefore contraindicated (see section 5.2).
Amphetamine derivatives	↑Amphetamine	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of amphetamine and its derivatives. Careful monitoring of adverse effects is recommended when these medicines are coadministered with PAXLOVID.
Analgesics	↑Buprenorphine (57%, 77%), ↑Norbuprenorphine (33%, 108%)	The increases of plasma levels of buprenorphine and its active metabolite did not lead to clinically significant pharmacodynamic changes in a population of opioid tolerant patients. Adjustment to the dose of buprenorphine may therefore not be necessary when the two are dosed together.
	↑Pethidine, ↑Piroxicam, ↑Propoxyphene	Increased plasma concentrations of norpethidine, piroxicam and propoxyphene may result in serious respiratory depression or haematologic abnormalities (see section 5.2).
	↑Fentanyl	Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of fentanyl. Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended when fentanyl is concomitantly administered with ritonavir.
	↓Methadone (36%, 38%)	Increased methadone dose may be necessary when coadministered with ritonavir dosed as a pharmacokinetic enhancer due to induction of glucuronidation. Dose adjustment should be considered based on the patient's clinical response to methadone therapy.
	↓Morphine	Morphine levels may be decreased due to induction of glucuronidation by coadministered ritonavir dosed as a pharmacokinetic enhancer.
Antianginal	↑Ranolazine	Due to CYP3A inhibition by ritonavir, concentrations of ranolazine are expected to increase. The concomitant administration with ranolazine is contraindicated (see section 5.2).
Antiarrhythmics	↑amiodarone, ↑dronedarone, ↑flecainide, ↑propafenone, ↑quinidine	Ritonavir coadministration is likely to result in increased plasma concentrations of amiodarone, dronedarone, flecainide, propafenone and quinidine and is

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Table 2: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
	↑digoxin	therefore contraindicated (see section 5.2). This interaction may be due to modification of P-gp mediated digoxin efflux by ritonavir dosed as a pharmacokinetic enhancer.
Antiasthmatic	↓Theophylline (43%, 32%)	An increased dose of theophylline may be required when coadministered with ritonavir, due to induction of CYP1A2.
Anticancer agents	↑Afatinib	Serum concentrations may be increased due to Breast Cancer Resistance Protein (BCRP) and acute P-gp inhibition by ritonavir. The extent of increase in AUC and Cmax depends on the timing of ritonavir administration. Caution should be exercised in administering afatinib with PAXLOVID (refer to the afatinib SmPC). Monitor for ADRs related to afatinib.
	↑Abemaciclib	Serum concentrations may be increased due to CYP3A4 inhibition by ritonavir. Coadministration of abemaciclib and PAXLOVID should be avoided. If this coadministration is judged unavoidable, refer to the abemaciclib SmPC for dosage adjustment recommendations. Monitor for ADRs related to abemaciclib.
	↑Apalutamide	Apalutamide is a moderate to strong CYP3A4 inducer and this may lead to a decreased exposure of PF-07321332/ritonavir and potential loss of virologic response. In addition, serum concentrations of apalutamide may be increased when coadministered with ritonavir resulting in the potential for serious adverse events including seizure. Concomitant use of PAXLOVID with apalutamide is not recommended.
	↑Ceritinib	Serum concentrations of ceritinib may be increased due to CYP3A and P-gp inhibition by ritonavir. Caution should be exercised in administering ceritinib with PAXLOVID. Refer to the ceritinib SmPC for dosage adjustment recommendations. Monitor for ADRs related to ceritinib.
	↑Dasatinib, ↑nilotinib, ↑vincristine, ↑vinblastine	Serum concentrations may be increased when coadministered with ritonavir resulting in the potential for increased incidence of adverse events.
	↑Encorafenib	Serum concentrations of encorafenib may be increased when coadministered with ritonavir which may increase the risk of

Table 2: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		toxicity, including the risk of serious adverse events such as QT interval prolongation. Coadministration of encorafenib and ritonavir should be avoided. If the benefit is considered to outweigh the risk and ritonavir must be used, patients should be carefully monitored for safety.
	↑Fostamatinib	Coadministration of fostamatinib with ritonavir may increase fostamatinib metabolite R406 exposure resulting in dose-related adverse events such as hepatotoxicity, neutropenia, hypertension or diarrhoea. Refer to the fostamatinib SmPC for dose reduction recommendations if such events occur.
	↑Ibrutinib	Serum concentrations of ibrutinib may be increased due to CYP3A inhibition by ritonavir, resulting in increased risk for toxicity including risk of tumour lysis syndrome. Coadministration of ibrutinib and ritonavir should be avoided. If the benefit is considered to outweigh the risk and ritonavir must be used, reduce the ibrutinib dose to 140 mg and monitor patient closely for toxicity.
	↑Neratinib	Serum concentrations may be increased due to CYP3A4 inhibition by ritonavir. Concomitant use of neratinib with PAXLOVID is contraindicated due to serious and/or life-threatening potential reactions including hepatotoxicity (see section 5.2).
	↑Venetoclax	Serum concentrations may be increased due to CYP3A inhibition by ritonavir, resulting in increased risk of tumour lysis syndrome at the dose initiation and during the ramp-up phase (see section 5.2 and refer to the venetoclax SmPC). For patients who have completed the ramp-up phase and are on a steady daily dose of venetoclax, reduce the venetoclax dose by at least 75% when used with strong CYP3A inhibitors (refer to the venetoclax SmPC for dosing instructions).
Anticoagulants	↑rivaroxaban (153%, 53%)	Inhibition of CYP3A and P-gp lead to increased plasma levels and pharmacodynamic effects of rivaroxaban which may lead to an increased bleeding risk. Therefore, the use of ritonavir is not recommended in patients receiving rivaroxaban.

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Table 2: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
	↑Vorapaxar	Serum concentrations may be increased due to CYP3A inhibition by ritonavir. The coadministration of vorapaxar with PAXLOVID is not recommended (refer to the vorapaxar SmPC).
	Warfarin, ↑↓S-Warfarin (9%, 9%), ↓↔R-Warfarin (33%)	Induction of CYP1A2 and CYP2C9 lead to decreased levels of R-warfarin while little pharmacokinetic effect is noted on S-warfarin when coadministered with ritonavir. Decreased R-warfarin levels may lead to reduced anticoagulation, therefore it is recommended that anticoagulation parameters are monitored when warfarin is coadministered with ritonavir.
Anticonvulsants	Carbamazepine	Carbamazepine is strong CYP3A4 inducer, and this may lead to a decreased exposure of PF-07321332 and ritonavir and potential loss of virologic response. Concomitant use of carbamazepine with PAXLOVID is contraindicated (see section 5.2).
	↓Divalproex, lamotrigine, phenytoin	Ritonavir dosed as a pharmacokinetic enhancer induces oxidation by CYP2C9 and glucuronidation and as a result is expected to decrease the plasma concentrations of anticonvulsants. Careful monitoring of serum levels or therapeutic effects is recommended when these medicines are coadministered with ritonavir. Phenytoin may decrease serum levels of ritonavir.
Antidepressants	↑Amitriptyline, fluoxetine, imipramine, nortriptyline, paroxetine, sertraline	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of imipramine, amitriptyline, nortriptyline, fluoxetine, paroxetine or sertraline. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir (see section 5.4).
	↑Desipramine (145%, 22%)	The AUC and C_{max} of the 2-hydroxy metabolite were decreased 15% and 67%, respectively. Dosage reduction of desipramine is recommended when coadministered with ritonavir.

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Table 2: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
Anti-gout	↑Colchicine	Concentrations of colchicine are expected to increase when coadministered with ritonavir. Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and ritonavir (CYP3A4 and P-gp inhibition). Concomitant use of colchicine with PAXLOVID is contraindicated (see section 5.2).
Antihistamines	↑Fexofenadine	Ritonavir may modify P-gp mediated fexofenadine efflux when dosed as a pharmacokinetic enhancer resulting in increased concentrations of fexofenadine.
	↑Loratadine	Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A and as a result is expected to increase the plasma concentrations of loratadine. Careful monitoring of therapeutic and adverse effects is recommended when loratadine is coadministered with ritonavir.
Anti-infectives	↑Fusidic Acid	Ritonavir coadministration is likely to result in increased plasma concentrations of both fusidic acid and ritonavir and is therefore contraindicated (see section 5.2).
	↑Rifabutin (4-fold, 2.5-fold) ↑25-*O*-desacetyl rifabutin metabolite (38-fold, 16-fold)	Due to the large increase in rifabutin AUC, reduction of the rifabutin dose to 150 mg 3 times per week may be indicated when coadministered with ritonavir as a pharmacokinetic enhancer.
	Rifampicin	Rifampicin is strong CYP3A4 inducer, and this may lead to a decreased exposure of PF-07321332/ritonavir and potential loss of virologic response. Concomitant use of rifampicin with PAXLOVID is contraindicated (see section 5.2).
	↓Voriconazole (39%, 24%)	Coadministration of voriconazole and ritonavir dosed as a pharmacokinetic enhancer should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.
	↑Ketoconazole (3.4-fold, 55%)	Ritonavir inhibits CYP3A-mediated metabolism of ketoconazole. Due to an increased incidence of gastrointestinal and hepatic adverse reactions, a dose reduction of ketoconazole should be considered when coadministered with ritonavir.
	↑Itraconazole[a], ↑Erythromycin	Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A4 and as a result is expected to increase the plasma

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Table 2: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		concentrations of itraconazole and erythromycin. Careful monitoring of therapeutic and adverse effects is recommended when erythromycin or itraconazole is coadministered with ritonavir.
	↓Atovaquone	Ritonavir dosed as a pharmacokinetic enhancer induces glucuronidation and as a result is expected to decrease the plasma concentrations of atovaquone. Careful monitoring of serum levels or therapeutic effects is recommended when atovaquone is coadministered with ritonavir.
	↑Bedaquiline	No interaction study is available with ritonavir only. Due to the risk of bedaquiline related adverse events, coadministration should be avoided. If the benefit outweighs the risk, coadministration of bedaquiline with ritonavir must be done with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended (see bedaquiline Summary of Product Characteristics)
	Delamanid	No interaction study is available with ritonavir only. In a healthy volunteer drug interaction study of delamanid 100 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily for 14 days, the exposure of the delamanid metabolite DM-6705 was 30% increased. Due to the risk of QTc prolongation associated with DM-6705, if coadministration of delamanid with ritonavir is considered necessary, very frequent ECG monitoring throughout the full delamanid treatment period is recommended (see section 4.4 and refer to the delamanid Summary of Product Characteristics).
	↑Clarithromycin (77%, 31%), ↓14-OH clarithromycin metabolite (100%, 99%)	Due to the large therapeutic window of clarithromycin no dose reduction should be necessary in patients with normal renal function. Clarithromycin doses greater than 1 g per day should not be coadministered with ritonavir dosed as a pharmacokinetic enhancer. For patients with renal impairment, a clarithromycin dose reduction should be considered: for patients with creatinine clearance of 30 to 60 ml/min the dose should be reduced by 50%, for patients with creatinine clearance less than 30 ml/min the dose should be reduced by 75%.

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Table 2: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
	Sulfamethoxazole/Trimethoprim	Dose alteration of sulfamethoxazole/trimethoprim during concomitant ritonavir therapy should not be necessary.
Anti-HIV protease inhibitors	↑Amprenavir (64%, 5-fold)	Ritonavir increases the serum levels of amprenavir as a result of CYP3A4 inhibition. For further information, physicians should refer to the Summary of Product Characteristics for amprenavir.
	↑Atazanavir (86%, 11-fold)	Ritonavir increases the serum levels of atazanavir as a result of CYP3A4 inhibition. For further information, physicians should refer to the Summary of Product Characteristics for atazanavir.
	↑Darunavir (14-fold)	Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir must be given with ritonavir to ensure its therapeutic effect. For further information, refer to the Summary of Product Characteristics for darunavir.
	↑Fosamprenavir (2.4-fold, 11-fold) measured as amprenavir)	Ritonavir increases the serum levels of amprenavir (from fosamprenavir) as a result of CYP3A4 inhibition. Fosamprenavir must be given with ritonavir to ensure its therapeutic effect. For further information, physicians should refer to the Summary of Product Characteristics for fosamprenavir.
Anti-HIV	↑Efavirenz (21%)	A higher frequency of adverse reactions (e.g., dizziness, nausea, paraesthesia) and laboratory abnormalities (elevated liver enzymes) have been observed when efavirenz is coadministered with ritonavir.
	↑Maraviroc (161%, 28%)	Ritonavir increases the serum levels of maraviroc as a result of CYP3A inhibition. Maraviroc may be given with ritonavir to increase the maraviroc exposure. For further information, refer to the Summary of Product Characteristics for maraviroc.
	↓Raltegravir (16%, 1%)	Coadministration of ritonavir and raltegravir results in a minor reduction in raltegravir levels
	↓Zidovudine (25%, ND)	Ritonavir may induce the glucuronidation of zidovudine, resulting in slightly decreased levels of zidovudine. Dose alterations should not be necessary.
Antipsychotics	↑Clozapine, ↑pimozide	Ritonavir coadministration is likely to result in increased plasma concentrations of clozapine or pimozide and is therefore contraindicated (see section 5.2).

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Table 2: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
	↑Haloperidol, ↑Risperidone, ↑Thioridazine	Ritonavir is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of haloperidol, risperidone and thioridazine. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir.
	↑Lurasidone	Due to CYP3A inhibition by ritonavir, concentrations of lurasidone are expected to increase. The concomitant administration with lurasidone is contraindicated (see section 5.2).
	↑quetiapine	Due to CYP3A inhibition by ritonavir, concentrations of quetiapine are expected to increase. Concomitant administration of PAXLOVID and quetiapine is contraindicated as it may increase quetiapine-related toxicity (see section 5.2).
β2-agonist (long acting)	↑salmeterol	Ritonavir inhibits CYP3A4 and as a result a pronounced increase in the plasma concentrations of salmeterol is expected. Therefore, concomitant use is not recommended.
Calcium channel antagonist	↑amlodipine, ↑diltiazem, ↑nifedipine	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of calcium channel antagonists. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with ritonavir.
Endothelin Antagonists	↑Bosentan	Coadministration of bosentan and ritonavir may increase steady-state bosentan maximum concentrations (C_{max}) and area under the curve (AUC).
	↑Riociguat	Serum concentrations may be increased due to CYP3A and P-gp inhibition by ritonavir. The coadministration of riociguat with PAXLOVID is not recommended (refer to riociguat SmPC).
Ergot Derivatives	↑Dihydroergotamine, ↑Ergonovine, ↑Ergotamine, ↑Methylergonovine	Ritonavir coadministration is likely to result in increased plasma concentrations of ergot derivatives and is therefore contraindicated (see section 5.2)

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Table 2: Interaction with other medicinal products and other forms of interaction

Medicinal product class	**Medicinal product within class (AUC change, C_{max} Change)**	**Clinical comments**
HCV Direct Acting Antiviral	↑Glecaprevir/pibrentasvir	Serum concentrations may be increased due to P-gp, BCRP and OATP1B inhibition by ritonavir. Concomitant administration of glecaprevir/pibrentasvir and PAXLOVID is not recommended due to an increased risk of ALT elevations associated with increased glecaprevir exposure.
HMG Co-A Reductase	↑Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin	HMG-CoA reductase inhibitors which are highly dependent on CYP3A metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when coadministered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer. Since increased concentrations of lovastatin and simvastatin may predispose patients to myopathies, including rhabdomyolysis, the combination of these medicinal products with ritonavir is contraindicated (see section 5.2). Atorvastatin is less dependent on CYP3A for metabolism. While rosuvastatin elimination is not dependent on CYP3A, an elevation of rosuvastatin exposure has been reported with ritonavir coadministration. The mechanism of this interaction is not clear, but may be the result of transporter inhibition. When used with ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent, the lowest possible doses of atorvastatin or rosuvastatin should be administered. The metabolism of pravastatin and fluvastatin is not dependent on CYP3A, and interactions are not expected with ritonavir. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.
Hormonal Contraceptive	↓Ethinyl Estradiol (40%, 32%)	Due to reductions in ethinyl estradiol concentrations, barrier or other non-hormonal methods of contraception should be considered with concomitant ritonavir use when dosed as an antiretroviral agent or as a pharmacokinetic enhancer. Ritonavir is likely to change the uterine bleeding profile and reduce the effectiveness of estradiol-containing contraceptives.

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Table 2: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
Immunosupressants	↑Cyclosporine ↑Tacrolimus ↑Everolimus	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of cyclosporine, tacrolimus or everolimus. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with ritonavir.
Lipid-modifying agents	↑Lomitapide	CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Due to CYP3A inhibition by ritonavir, concentrations of lomitapide are expected to increase. Concomitant use of PAXLOVID with lomitapide is contraindicated (see prescribing information for lomitapide) (see section 5.2).
Phosphodiesterase (PDE5) Inhibitors	↑Avanafil (13-fold, 2.4-fold)	Concomitant use of avanafil with PAXLOVID is contraindicated (see section 5.2).
	↑Sildenafil (11-fold, 4-fold)	Concomitant use of sildenafil for the treatment of erectile dysfunction with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer should be with caution and in no instance should sildenafil doses exceed 25 mg in 48 hours. Concomitant use of sildenafil with PAXLOVID is contraindicated in pulmonary arterial hypertension patients (see section 5.2).
	↑Tadalafil (124%, ↔)	The concomitant use of tadalafil for the treatment of erectile dysfunction with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer should be with caution at reduced doses of no more than 10 mg tadalafil every 72 hours with increased monitoring for adverse reactions.
	↑Vardenafil (49-fold, 13-fold)	Concomitant use of vardenafil with PAXLOVID is contraindicated (see section 5.2).
Sedatives/hypnotics	↑Clorazepate, ↑Diazepam, ↑Estazolam, ↑Flurazepam, ↑Oral and parenteral midazolam	Ritonavir coadministration is likely to result in increased plasma concentrations of clorazepate, diazepam, estazolam and flurazepam and is therefore contraindicated (see section 5.2). Midazolam is extensively metabolised by CYP3A4. Coadministration with PAXLOVID may cause a large increase in the concentration of midazolam. Plasma concentrations of midazolam are expected to be significantly higher when

Table 2: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		midazolam is given orally. Therefore, PAXLOVID should not be coadministered with orally administered midazolam (see section 5.2), whereas caution should be used with coadministration of PAXLOVID and parenteral midazolam. Data from concomitant use of parenteral midazolam with other protease inhibitors suggests a possible 3 – 4 fold increase in midazolam plasma levels. If PAXLOVID is coadministered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.
	↑Triazolam (> 20-fold, 87%)	Ritonavir coadministration is likely to result in increased plasma concentrations of triazolam and is therefore contraindicated (see section 5.2)
	↓Pethidine (62%, 59%), ↑Norpethidine metabolite (47%, 87%)	The use of pethidine and ritonavir is contraindicated due to the increased concentrations of the metabolite, norpethidine, which has both analgesic and CNS stimulant activity. Elevated norpethidine concentrations may increase the risk of CNS effects (e.g., seizures) (see section 5.2).
	↑Alprazolam (2.5-fold, ↔)	Alprazolam metabolism is inhibited following the introduction of ritonavir. Caution is warranted during the first several days when alprazolam is coadministered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer, before induction of alprazolam metabolism develops.
	↑Buspirone	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma concentrations of buspirone. Careful monitoring of therapeutic and adverse effects is recommended when buspirone concomitantly administered with ritonavir.
Sleeping agent	↑Zolpidem (28%, 22%)	Zolpidem and ritonavir may be coadministered with careful monitoring for excessive sedative effects.

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Table 2: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
Smoke cessation	↓Bupropion (22%, 21%)	Bupropion is primarily metabolised by CYP2B6. Concurrent administration of bupropion with repeated doses of ritonavir is expected to decrease bupropion levels. These effects are thought to represent induction of bupropion metabolism. However, because ritonavir has also been shown to inhibit CYP2B6 *in vitro*, the recommended dose of bupropion should not be exceeded. In contrast to long-term administration of ritonavir, there was no significant interaction with bupropion after short-term administration of low doses of ritonavir (200 mg twice daily for 2 days), suggesting reductions in bupropion concentrations may have onset several days after initiation of ritonavir coadministration.
Steroids	Inhaled, injectable or intranasal fluticasone propionate, budesonide, triamcinolone	Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression (plasma cortisol levels were noted to be decreased 86%) have been reported in patients receiving ritonavir and inhaled or intranasal fluticasone propionate; similar effects could also occur with other corticosteroids metabolised by CYP3A e.g., budesonide and triamcinolone. Consequently, concomitant administration of ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid, which is not a substrate for CYP3A4 (e.g., beclomethasone). Moreover, in case of withdrawal of glucocorticoids progressive dose reduction may be required over a longer period.
	↑Dexamethasone	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma concentrations of dexamethasone. Careful monitoring of therapeutic and adverse effects is recommended when dexamethasone is concomitantly administered with ritonavir.
	↑Prednisolone (28%, 9%)	Careful monitoring of therapeutic and adverse effects is recommended when

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Table 2: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		prednisolone is concomitantly administered with ritonavir. The AUC of the metabolite prednisolone increased by 37 and 28% after 4 and 14 days ritonavir, respectively.
Thyroid hormone replacement therapy	Levothyroxine	Post-marketing cases have been reported indicating a potential interaction between ritonavir containing products and levothyroxine. Thyroid-stimulating hormone (TSH) should be monitored in patients treated with levothyroxine at least the first month after starting and/or ending ritonavir treatment.

Abbreviations: ATL=alanine aminotransferase.
a. See section 6, Interaction studies conducted with PF-07321332/ritonavir.

5.5 Pregnancy and lactation

Women of childbearing potential

There are no human data on the use of PAXLOVID during pregnancy to inform the drug-associated risk of adverse developmental outcomes; women of childbearing potential should avoid becoming pregnant during treatment with PAXLOVID.

Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Patients using combined hormonal contraceptives should be advised to use an effective alternative contraceptive method or an additional barrier method of contraception during treatment with PAXLOVID, and until one menstrual cycle after stopping PAXLOVID (see section 5.4).

Pregnancy

There are no data from the use of PF-07321332 in pregnant women. Animal data with PF-07321332 have shown reproductive toxicity (see section 6).

A large number of pregnant women exposed to ritonavir during pregnancy indicate no increase in the rate of birth defects compared to rates observed in population-based birth defect surveillance systems. However, animal data with ritonavir have shown reproductive toxicity (see section 6).

PAXLOVID is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

There are no human data on the use of PAXLOVID in breast-feeding.

It is unknown whether PF-07321332 is present in human or animal milk, and the effects of it on the breast-fed newborn/infant, or the effects on milk production are also unknown. Limited published data reports that ritonavir is present in human milk. There is no information on the effects of ritonavir on the breast-fed newborn/infant or the effects of the medicinal product on milk production. A risk to the newborn/infant cannot be excluded. Breast-feeding should be interrupted during treatment with PAXLOVID.

Fertility

There are no human data on the effect of PAXLOVID on fertility.

No human data on the effect of PF-07321332 on fertility are available. PF-07321332 produced no effects on fertility in rats (see section 6).

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There are no human data on the effect of ritonavir on fertility. Ritonavir produced no effects on fertility in rats.

5.6 Incompatibilities

Not applicable.

5.7 Overdose

Treatment of overdose with PAXLOVID should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with PAXLOVID.

5.8 Shelf life

12 months.

5.9 Storage conditions

Do not refrigerate or freeze. Do not store above 25 °C

5.10 Special precautions for disposal

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

5.11 List of excipients

PF-07321332

Tablet core:
Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Colloidal silicon dioxide
Sodium stearyl fumarate

Film coat:
Hydroxy propyl methylcellulose
Titanium dioxide
Polyethylene glycol
Iron oxide red

Ritonavir

Tablet core:
Copovidone
Sorbitan laureate
Silica, colloidal anhydrous
Calcium hydrogen phosphate, anhydrous
Sodium stearyl fumarate

Film coat:
Hypromellose
Titanium dioxide
Macrogol
Hydroxy propyl cellulose
Talc
Silica, colloidal anhydrous
Polysorbate 80

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6. OTHER INFORMATION

- **Undesirable effects**

Summary of the safety profile

The most commonly reported adverse reactions reported during treatment with PAXLOVID (PF-07321332/ritonavir 300 mg/100 mg) every 12 hours for 5 days and during 34 days after the last dose were dysgeusia (4.8%), diarrhoea (3.9%) and vomiting (1.3%).

Tabulated summary of adverse reactions

The adverse reactions in Table 3 are listed below by system organ class and frequency. Frequencies are defined as follows: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); not known (frequency cannot be estimated from the available data).

Table 3a: Adverse reactions with PAXLOVID

System organ class	Frequency category	Adverse reactions
Nervous system disorders	Common	Dysgeusia
Gastrointestinal disorders	Common	Diarrhoea, vomiting

Adverse reactions with ritonavir

The type, severity and frequency of adverse reactions corresponding to higher dose and use for longer duration in the context of chronic HIV infection listed below might not apply to the use of ritonavir during 5 days in PAXLOVID. Events noted as having a frequency not known were identified via post-marketing surveillance

Table 3b: Adverse reactions with ritonavir

Adverse reactions in clinical studies and post-marketing in adult patients		
System Order Class	**Frequency**	**Adverse reaction**
Blood and lymphatic system disorders	Common	Decreased white blood cells, decreased haemoglobin, decreased neutrophils, increased eosinophils, thrombocytopenia
	Uncommon	Increased neutrophils
Immune system disorders	Common	Hypersensitivity, including urticaria and face oedema.
	Rare	Anaphylaxis
Metabolism and nutrition disorders	Common	Hypercholesterolaemia, hypertriglyceridaemia, gout, oedema and peripheral oedema, dehydration (usually associated with gastrointestinal symptoms)
	Uncommon	Diabetes mellitus
	Rare	Hyperglycaemia
Nervous system disorders	Very common	Dysgeusia, oral and peripheral paraesthesia, headache, dizziness, peripheral neuropathy
	Common	Insomnia, anxiety, confusion, disturbance in attention, syncope, seizure
Eye disorders	Common	Blurred vision
Cardiac disorders	Uncommon	Myocardial infarction

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Adverse reactions in clinical studies and post-marketing in adult patients		
System Order Class	**Frequency**	**Adverse reaction**
Vascular disorders	Common	Hypertension, hypotension including orthostatic hypotension, peripheral coldness
Respiratory, thoracic and mediastinal disorders	Very common	Pharyngitis, oropharyngeal pain, cough
Gastrointestinal disorders	Very common	Abdominal pain (upper and lower), nausea, diarrhoea (including severe with electrolyte imbalance), vomiting, dyspepsia
	Common	Anorexia, flatulence, mouth ulcer, gastrointestinal haemorrhage, gastroesophageal reflux disease, pancreatitis
Hepatobiliary disorders	Common	Hepatitis (including increased AST, ALT, GGT), blood bilirubin increased (including jaundice)
Skin and subcutaneous tissue disorders	Very common	Pruritus, rash (including erythematous and maculopapular)
	Common	Acne
	Rare	Stevens Johnson syndrome, toxic epidermal necrolysis (TEN)
Musculoskeletal and connective tissue disorders	Very common	Arthralgia and back pain
	Common	Myositis, rhabdomyolysis, myalgia, myopathy/CPK increased
Renal and urinary disorders	Common	Increased urination, renal impairment (e.g., oliguria, elevated creatinine)
	Uncommon	Acute renal failure
	Not known	Nephrolithiasis
Reproductive system and breast disorders	Common	Menorrhagia
General disorders and administration site conditions	Very common	Fatigue including asthenia, flushing, feeling hot
	Common	Fever, weight loss
Investigations	Common	Increased amylase, decreased free and total thyroxine
	Uncommon	Increased glucose, increased magnesium, increased alkaline phosphatase

Description of selected adverse reactions for ritonavir

Hepatic transaminase elevations exceeding five times the upper limit or normal, clinical hepatitis and jaundice have occurred in patients receiving ritonavir alone or in combination with other antiretrovirals.

Metabolic parameters

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Weight and levels of blood lipids and glucose may increase during antiretroviral therapy.

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and can occur many months after initiation of treatment.

Pancreatitis has been observed in patients receiving ritonavir therapy, including those who developed hypertriglyceridaemia. In some cases, fatalities have been observed. Patients with advanced HIV disease may be at risk of elevated triglycerides and pancreatitis.

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

- **Summary of relevant pharmacological properties**

Mechanism of action

PF-07321332 is a peptidomimetic inhibitor of the coronavirus 3C-like (3CL) protease, including the SARS-CoV-2 3CL protease. Inhibition of the 3CL protease renders the protein incapable of processing polyprotein precursors which leads to the prevention of viral replication.

Ritonavir inhibits the CYP3A-mediated metabolism of PF-07321332, thereby providing increased plasma concentrations of PF-07321332.

Antiviral activity

PF-07321332 exhibited antiviral activity against SARS-CoV-2 infection of dNHBE cells, a primary human lung alveolar epithelial cell line (EC_{50} value of 61.8 nM and EC_{90} value of 181 nM) after 3 days of drug exposure. PF-07321332 had cell culture antiviral activity (with EC50 values in the low nanomolar range ≤ 3-fold relative to USA-WA1/2020) against SARS-CoV-2 isolates belonging to the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2) Lambda (C.37) variants. The Beta (B.1.351) variant was the least susceptible tested variant with approximately 4-fold reduced susceptibility relative to the USA-WA1/2020 isolate.

There is no *in vitro* data available on the antiviral activity against Omicron variant.

Resistance
No information on antiviral resistance is currently available to PF-07321332 with SARS-CoV-2. Studies to evaluate selection of resistance to PF-07321332 with SARS-CoV-2 in cell culture and clinical studies have not been completed. Only *in vitro* resistance selection study with murine hepatitis virus (MHV)-3CL protease is available. It showed a 4.4- to 5-fold decrease in PF-07321332 susceptibility against mutant viruses with 5 mutations (Pro55Leu, Ser144Ala, Thr129Met, Thr50Lys, Pro15Ala) in the MHV-3CL protease following 10 passages in cell culture. The relevance for this to SARS-CoV-2 is not known.

Pharmacodynamic effects

Cardiac electrophysiology
No clinically relevant effect of PF-07321332 on QTcF interval was observed in a double-blind, randomised, placebo-controlled, cross-over study in 10 healthy adults. The model predicted upper bound of 90% confidence interval (CI) for baseline and ritonavir adjusted QTcF estimate was 1.96 ms at approximately 4-fold higher concentration than the mean steady-state peak concentration after a therapeutic dose of PF-07321332/ritonavir 300 mg/100 mg.

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Pharmacokinetic properties

The pharmacokinetics of PF-07321332/ritonavir have been studied in healthy participants.

Ritonavir is administered with PF-07321332 as a pharmacokinetic enhancer resulting in higher systemic concentrations of PF-07321332. In healthy participants in the fasted state, the mean half-life ($t_{1/2}$) of a single dose of 150 mg PF-07321332 administered alone was approximately 2 hours compared to 7 hours after administration of a single dose of 250 mg/100 mg PF-07321332/ritonavir thereby supporting a twice-daily administration regimen.

Upon administration of single dose of PF-07321332/ritonavir 250 mg/100 mg as oral suspension formulation to healthy participants in the fasted state, the geometric mean (CV%) maximum concentration (C_{max}) and area under the plasma concentration-time curve from 0 to the time of last measurement (AUC_{last}) was 2.88 ug/mL (25%) and 27.6 ug*hr/mL (13%), respectively. Upon repeat-dose of PF-07321332/ritonavir 75 mg/100 mg, 250 mg/100 mg, and 500 mg/100 mg administered twice daily, the increase in systemic exposure at steady-state appears to be less than dose proportional. Multiple dosing over 10 days achieved steady-state on Day 2 with approximately 2-fold accumulation. Systemic exposures on Day 5 were similar to Day 10 across all doses.

Absorption

Following oral administration of PF-07321332/ritonavir 300 mg/100 mg after a single dose, the geometric mean PF-07321332 (CV%) C_{max} and area under the plasma concentration-time curve from 0 to infinity (AUC_{inf}) was 2.21 µg/mL (33) and 23.01 µg*hr/mL (23), respectively. The median (range) time to C_{max} (T_{max}) was 3.00 hrs (1.02-6.00). The arithmetic mean (+SD) terminal elimination half-life was 6.1 (1.8) hours.

Following oral administration of PF-07321332/ritonavir 300 mg/100 mg after a single dose, the geometric mean ritonavir (CV%) C_{max} and AUC_{inf} was 0.36 µg/mL (46) and 3.60 µg*hr/mL (47), respectively. The median (range) time to C_{max} (T_{max}) was 3.98 hrs (1.48-4.20). The arithmetic mean (+SD) terminal elimination half-life was 6.1 (2.2) hours.

Effect of food on oral absorption
Dosing with a high fat meal modestly increased the exposure of PF-07321332 (approximately 15% increase in mean C_{max} and 1.6% increase in mean AUC_{last}) relative to fasting conditions following administration of a suspension formulation of PF-07321332 coadministered with ritonavir tablets.

Distribution

The protein binding of PF-07321332 in human plasma is approximately 69%.

The protein binding of ritonavir in human plasma is approximately 98-99%.

Biotransformation

In vitro studies assessing PF-07321332 without concomitant ritonavir suggest that PF-07321332 is primarily metabolised by CYP3A4. PF-07321332 does not reversibly inhibit CYP2D6, CYP2C9, CYP2C19, CYP2C8 or CYP1A2 *in vitro* at clinically relevant concentrations. PF-07321332 is not an inducer or substrate of other CYP enzymes. Administration of PF-07321332 with ritonavir inhibits the metabolism of PF-07321332. In plasma, the only drug-related entity observed was unchanged PF-07321332. Minor oxidative metabolites were observed in the faeces and urine.

In vitro studies utilising human liver microsomes have demonstrated that cytochrome P450 3A (CYP3A) is the major isoform involved in ritonavir metabolism, although CYP2D6 also contributes to the formation of oxidation metabolite M–2.

Low doses of ritonavir have shown profound effects on the pharmacokinetics of other protease inhibitors (and other products metabolised by CYP3A4) and other protease HIV inhibitors may influence the pharmacokinetics of ritonavir.

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Elimination

The primary route of elimination of PF-07321332 when administered with ritonavir was renal excretion of intact drug. Approximately 49.6% and 35.3% of the administered dose of PF-07321332 300 mg was recovered in urine and faeces, respectively. PF-07321332 was the predominant drug-related entity with small amounts of metabolites arising from hydrolysis reactions in excreta. In plasma, the only drug related entity quantifiable was unchanged PF-07321332.

Human studies with radiolabelled ritonavir demonstrated that the elimination of ritonavir was primarily via the hepatobiliary system; approximately 86% of radiolabel was recovered from stool, part of which is expected to be unabsorbed ritonavir.

Specific populations

The pharmacokinetics of PF-07321332/ritonavir based on age and gender have not been evaluated.

Racial or ethnic groups
Systemic exposure in Japanese participants was numerically lower but not clinically meaningfully different than those in Western participants.

Patients with renal impairment
Compared to healthy controls with no renal impairment, the C_{max} and AUC of PF-07321332 in patients with mild renal impairment was 30% and 24% higher, in patients with moderate renal impairment was 38% and 87% higher, and in patients with severe renal impairment was 48% and 204% higher, respectively.

Patients with hepatic impairment
The pharmacokinetics of PF-07321332/ritonavir have not been evaluated in patients with hepatic impairment.

Interaction studies conducted with PF-07321332/ritonavir

CYP3A4 was the major contributor to the oxidative metabolism of PF-07321332, when PF-07321332 was tested alone in human liver microsomes. Ritonavir is an inhibitor of CYP3A and increases plasma concentrations of PF-07321332 and other drugs that are primarily metabolised by CYP3A. Despite being coadministered with ritonavir as a pharmacokinetic enhancer, there is potential for strong inhibitors and inducers to alter the pharmacokinetics of PF-07321332.

The effects of coadministration of PAXLOVID with itraconazole (CYP3A inhibitor) and carbamazepine (CYP3A inducer) on the PF-07321332 AUC and C_{max} are summarised in Table 4 (effect of other medicinal products on PF-07321332).

Table 4: Interactions with other medicinal products: pharmacokinetic parameters for PF-07321332 in the presence of the coadministered medicinal products

Coadministered medicinal product	Dose (schedule)		N	Ratio (in combination with coadministered medicinal product/alone) of PF-07321332 pharmacokinetic parameters (90% CI); no effect=1.00	
	Coadministered medicinal product	PF-07321332/ ritonavir		C_{max}	AUC[a]
Carbamazepine[b]	300 mg twice daily (16 doses)	300 mg/100 mg twice daily (5 doses)	9	56.82 (47.04, 68.62)	44.50 (33.77, 58.65)
Itraconazole	200 mg once daily (8 doses)	300 mg/100 mg twice daily (5 doses)	11	118.57 (112.50, 124.97)	138.82 (129.25, 149.11)

Abbreviations: AUC=area under the plasma concentration-time curve; CI=confidence interval; C_{max}=maximum plasma concentrations.
a. For carbamazepine, AUC=AUC_{inf}, for itraconazole, AUC=AUC_{tau}.

Table 4: Interactions with other medicinal products: pharmacokinetic parameters for PF-07321332 in the presence of the coadministered medicinal products

b. Carbamazepine titrated up to 300 mg twice daily on Day 8 through Day 15 (e.g., 100 mg twice daily on Day 1 through Day 3 and 200 mg twice daily on Day 4 through Day 7).

- **Summary of relevant clinical properties**

The efficacy of PAXLOVID is based on the *interim* analysis of EPIC-HR, a Phase 2/3, randomised, double-blind, placebo-controlled study in non-hospitalised symptomatic adult participants with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Preliminary presentation of the final analysis of the primary endpoint has been made available and shows consistent level of efficacy. The study report of the final analysis is awaited.

Eligible participants were 18 years of age and older with at least 1 of the following risk factors for progression to severe disease: diabetes, overweight (BMI > 25), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease, hypertension, sickle cell disease, neurodevelopmental disorders, active cancer, medically-related technological dependence, or were 60 years of age and older regardless of comorbidities. The study excluded individuals with vaccination or a known history of prior COVID-19 infection.

Participants with COVID-19 symptom onset of ≤ 5 days were included in the study.

The primary efficacy endpoint is the proportion of participants with COVID-19 related hospitalisation or death from any cause through Day 28 in the modified intent-to-treat (mITT) analysis set (all treated participants with onset of symptoms ≤ 3 days who had at least one post-baseline visit and did not receive nor were expected to receive COVID-19 therapeutic mAb treatment).

Secondary efficacy endpoints included assessments of COVID-19 hospitalisation or death from any cause through Day 28 in the mITT1 analysis set (all treated participants with onset of symptoms ≤ 5 days who had at least one post-baseline visit, and did not receive nor were expected to receive COVID-19 therapeutic mAb treatment). Participants either receiving or expected to receive COVID-19 therapeutic monoclonal antibody treatment at the time of randomisation were excluded from the mITT and mITT1 analyses (8.2%).

A total of 1361 participants were randomised to receive either PAXLOVID or placebo. At baseline, mean age was 45 years with 11.4 % of participants 65 years of age and older (2.9% 75 years of age and older); 52% were male; 63% were White, 5% were Black, 48% were Hispanic or Latino and 20% were Asian; 63% of participants had onset of symptoms ≤ 3 days from initiation of study treatment; 79.4% had a BMI > 25 kg/m2 (36.7% a BMI > 30 kg/m2); 32.4% had hypertension; 12.9% had diabetes mellitus; 55.6% of participants were serological positive at baseline. The mean (SD) baseline viral load was 4.71 $\log_{10}$ copies/mL (2.78).

Overall, the baseline demographic and disease characteristics were balanced between the PAXLOVID and placebo groups.

Table 5: Progression of COVID-19 (hospitalisation or death) through Day 28 in symptomatic adults at increased risk of progression to severe illness; mITT analysis set

	PAXLOVID 300 mg/100 mg	**Placebo**
Number of patients (%)	389	385
Patients with hospitalisation or death[a] (%)	3 (0.8%)	27 (7.0%)
Estimated proportion over 28 days [95% CI], %	0.78 (0.25, 2.39)	7.09 (4.92, 10.17)
Reduction relative to placebo [95% CI]* p-value**	-6.32 (-9.04, -3.59) p<0.0001	

*95% two-sided confidence interval *unadjusted* for multiplicity. The 95% two-sided confidence interval *adjusted* for multiplicity for the interim analysis is [-10.61% to -2.02%].
**Two-sided significance level of 0.002.
Abbreviations: CI=confidence interval; mITT=modified intent-to-treat. All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, with at least 1 post-baseline visit through Day 28, who at baseline did not receive nor were expected to receive

Table 5: Progression of COVID-19 (hospitalisation or death) through Day 28 in symptomatic adults at increased risk of progression to severe illness; mITT analysis set

COVID-19 therapeutic monoclonal antibody treatment, and were treated ≤ 3 days after COVID-19 symptom onset.
a. Covid-19 related hospitalisation or death from any cause.

No deaths were reported in the PAXLOVID group compared with 7 deaths in the placebo group.

mITT1 analyses are considered more representative for the population of interest (initiated within 5 days of symptom onset and dosing recommendation).

Table 6: Progression of COVID-19 (hospitalisation or death) through Day 28 in symptomatic adults at increased risk of progression to severe illness; mITT1 analysis set

	PAXLOVID 300 mg/100 mg	**Placebo**
Number of patients	N=607	N=612
Patients with hospitalisation or death[a] (%) Estimated proportion over 28 days [95% CI], % Reduction relative to placebo [95% CI] p-value	6 (1.0%) 1.00 (0.45, 2.21) -5.77 (-7.92, -3.61) p<0.0001	41 (6.7%) 6.76 (5.03, 9.04)
Serology Negative	n=256	n=272
Patients with hospitalisation or death[a] (%) Estimated proportion over 28 days [95% CI], % Difference from placebo [95% CI], % p-value	5 (2.0%) 1.98 (0.83, 4.69) -11.45 (-15.89, -7.02) p<0.0001	36 (13.2%) 13.43 (9.88, 18.13)
Serology Positive	n=344	n=332
Patients with hospitalisation or death[a] (%) Estimated proportion over 28 days [95% CI], % Difference from placebo [95% CI], % p-value	1 (0.3%) 0.29 (0.04, 2.05) -1.22 (-2.66, 0.21) p=0.0947	5 (1.5%) 1.51 (0.63, 3.60)

Abbreviations: CI=confidence interval; mITT1=A modified intent-to-treat analysis set that includes all participants randomly assigned to study intervention, who took at least 1 dose of study intervention, with at least 1 post-baseline visit through Day 28, who at baseline did not receive nor were expected to receive COVID-19 therapeutic monoclonal antibody treatment and were treated ≤ 5 days after COVID-19 symptom onset.
a. Covid-19 related hospitalisation or death from any cause.

No deaths were reported in the PAXLOVID group compared with 10 deaths in the placebo group.

Table 7: Progression of COVID-19 (hospitalisation or death) through Day 28 in symptomatic adults at increased risk of progression to severe illness; mITT1 patients with treatment initiated > 3 days from symptom onset

	PAXLOVID 300 mg/100 mg	**Placebo**
Number of patients	N=218	N=227
Patients with hospitalisation or death[a] (%) Estimated proportion over 28 days [95% CI], % Reduction relative to placebo [95% CI] p-value	3 (1.4%) 1.40 (0.45, 4.29) -4.79 (-8.31, -1.28) 0.0076	14 (6.2%) 6.19 (3.72, 10.24)

Abbreviations: CI=confidence interval; mITT1=A modified intent-to-treat analysis set that includes all participants randomly assigned to study intervention, who took at least 1 dose of study intervention, with at least 1 post-baseline visit through Day 28, who at baseline did not receive nor were expected to receive COVID-19 therapeutic monoclonal antibody treatment and were treated ≤ 5 days after COVID-19 symptom onset.
a. Covid-19 related hospitalisation or death from any cause.

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Efficacy results for mITT1 were consistent across subgroups of participants including age (≥ 65 years) and BMI (BMI > 25 and BMI > 30).

- **Preclinical safety data**

No nonclinical safety studies have been conducted with PF-07321332 in combination with ritonavir.

Toxicology

Repeat-dose toxicity studies up to 1 month duration of PF-07321332 in rats and monkeys resulted in no adverse findings.

Repeat-dose toxicity studies of ritonavir in animals identified major target organs as the liver, retina, thyroid gland and kidney. Hepatic changes involved hepatocellular, biliary and phagocytic elements and were accompanied by increases in hepatic enzymes. Hyperplasia of the retinal pigment epithelium and retinal degeneration have been seen in all of the rodent studies conducted with ritonavir, but have not been seen in dogs. Ultrastructural evidence suggests that these retinal changes may be secondary to phospholipidosis. However, clinical trials revealed no evidence of medicinal product-induced ocular changes in humans. All thyroid changes were reversible upon discontinuation of ritonavir. Clinical investigation in humans has revealed no clinically significant alteration in thyroid function tests.

Renal changes including tubular degeneration, chronic inflammation and proteinurea were noted in rats and are considered to be attributable to species-specific spontaneous disease. Furthermore, no clinically significant renal abnormalities were noted in clinical trials.

Carcinogenesis

PAXLOVID has not been evaluated for the potential to cause carcinogenicity.

PF-07321332 has not been evaluated for the potential to cause carcinogenicity.

Long-term carcinogenicity studies of ritonavir in mice and rats revealed tumourigenic potential specific for these species, but are regarded as of no relevance for humans.

Genotoxicity

PAXLOVID has not been evaluated for the potential to cause genotoxicity.

PF-07321332 was not genotoxic in a battery of assays, including bacterial mutagenicity, chromosome aberration using human lymphoblastoid TK6 cells and *in vivo* rat micronucleus assays.

Ritonavir was found to be negative for mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Reproductive toxicity

PF-07321332
In a fertility and early embryonic development study, there were no PF-07321332-related effects on fertility and reproductive performance at doses up to 1000 mg/kg/day representing 12x/4.3x based on the predicted human C_{max}/AUC_{24} at a twice-daily dose of 300 mg/100 mg PF-07321332/ritonavir.

The potential embryo-foetal toxicity of PF-07321332 was evaluated in rats and rabbits. There was no PF-07321332-related effect on rat embryo-foetal development up to the highest dose of 1000 mg/kg/day (exposure margin of 16x/7.8x based on total C_{max}/AUC_{24} over the predicted human exposures at a dose of 300 mg/100 mg PF-07321332/ritonavir twice daily). In the rabbit EFD study, adverse PF-07321332-related lower foetal body weights were observed at the highest dose of 1000 mg/kg/day in the presence of nonadverse, low magnitude effects on maternal body weight change and food consumption. These findings were not present at the intermediate dose of 300 mg/kg/day (10x/2.8x C_{max}/AUC_{24} over the predicted clinical exposure).

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Ritonavir
Ritonavir produced no effects on fertility in rats.

Developmental toxicity observed in rats (embryolethality, decreased foetal body weight and ossification delays and visceral changes, including delayed testicular descent) occurred mainly at a maternally toxic dosage. Developmental toxicity in rabbits (embryolethality, decreased litter size and decreased foetal weights) occurred at a maternally toxic dosage.

7. CONDITIONS FOR SAFETY MONITORING

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare Professionals are asked to report any suspected adverse reactions. For information on reporting side effects, see section 6.

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Document 2A.10

U.S. FDA Center for Drug Evaluation and Research Application number: 217188Orig1s000 Product Quality Review

Document URL

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/217188Orig1s000ChemR.pdf

Reference website URL

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/217188Orig1s000TOC.cfm

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217188Orig1s000

PRODUCT QUALITY REVIEW(S)

OPQ Joint Review Addendum (Review #3)

Application	NDA 217188
Regulatory Pathway	505(b)(1)
Applicant Name	Pfizer, Inc.
Drug Product Name	PAXLOVID (nirmatrelvir tablets and ritonavir tablets) copackaged, for oral use
Dosage Form	Tablets
Proposed Strength(s)	150 mg nirmatrelvir tablets and 100 mg ritonavir tablets
Indication	Treatment of mild-to-moderate COVID-19 in adult patients
Assessment Cycle Number	1
Clearance History	S. Anand 05/08/2023; E Chikhale 05/08/2023; G Gieser 5/8/2023

Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Katherine Windsor	Paresma Patel
	Drug Product/Labeling	Shalini Anand	David Claffey
	OPMA	Abdollah Koolivand	Hang Guo
	Biopharmaceutics	Gerlie Gieser	Elsbeth Chikhale
	Environmental Assessment	Xiaoqin Wu	James Laurenson
	RBPM	Erica Keafer and Musse Olani	
	ATL	David Claffey	

Assessment Recommendation: Adequate

Updated drug product stability data were provided representing several drug product manufacturing sites. The data continue to support the proposed 24 month drug product expiry period.

Biopharmaceutics:

Reference ID: 5170460

Assessment Recommendation: *Adequate*

Assessment Summary:

SN-158 includes the updated dissolution on stability data of seven [child-resistant (CR) (b) (4) *blister] co-packaged Paxlovid lots from three nirmatrelvir tablet manufacturers (Pfizer-Freiburg, Pfizer-Ascoli and* (b) (4)*). Specifically, the dissolution dataset is updated to include 12-month individual dissolution data for nirmatrelvir & ritonavir (Hetero) batch FX3846, 6-month nirmatrelvir & ritonavir (Hetero) individual dissolution data for batches GE5412, GE5413, GE5414 and 6-week nirmatrelvir & ritonavir (Abbvie) individual dissolution data for batches 3225150, 3225152 and 3225154.*

During up to 12 months of long-term (25°C 60%RH), up to 12 months of intermediate and up to 6 months of accelerated stability testing, these PAXLOVID lots were able to conform to the proposed/recommended nirmatrelvir dissolution acceptance criterion (Q = (b) (4) *% at 30 min) by USP Stage 1 (n=6) testing, as well as to the approved ritonavir dissolution acceptance criterion by USP Stage 1 (n=6) or USP Stage 2 (n=12) testing.*

Additionally, based on this Reviewer's modeling using the "Stability Test" feature of the JMP software (version 16), the nirmatrelvir and ritonavir dissolution data [i.e., from the Paxlovid lot (FX3846) with at least 12 months of long-term (25°C 60%RH) stability data] continue to support the proposed PAXLOVID expiration dating period of 24 months.

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/s/

SHALINI ANAND
05/08/2023 04:25:55 PM

DAVID J CLAFFEY
05/08/2023 04:27:11 PM

OPQ Joint Review Addendum (Review #2)

Application	NDA 217188		
Regulatory Pathway	505(b)(1)		
Applicant Name	Pfizer, Inc.		
Drug Product Name	PAXLOVID (nirmatrelvir tablets and ritonavir tablets) copackaged, for oral use		
Dosage Form	Tablets		
Proposed Strength(s)	150 mg nirmatrelvir tablets and 100 mg ritonavir tablets		
Indication	Treatment of mild-to-moderate COVID-19 in adult patients		
Assessment Cycle Number	1		
Clearance History	K.Windsor 04/11/2023; P. Patel 4/11/2023; E. Chikhale 04/12/2023;S.Anand 04/13/2023		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Katherine Windsor	Paresma Patel
	Drug Product/Labeling	Shalini Anand	David Claffey
	OPMA	Abdollah Koolivand	Hang Guo
	Biopharmaceutics	Gerlie Gieser	Elsbeth Chikhale
	Environmental Assessment	Xiaoqin Wu	James Laurenson
	RBPM	Erica Keafer and Musse Olani	
	ATL	David Claffey	

Assessment Recommendation: Adequate

Information was provided in this amendment to update the drug substance and drug product stability data and provide updates to the dissolution and ritonavir polymorph testing. The data continue to support overall approval recommendation and the drug

substance retest and drug product expiry periods in OPQ Review #1. Refer to the review notes below for more details.

Document(s) Assessed	Date Received
Seq. 0142	March 10, 2023

Highlight Key Issues from Last Cycle and Their Resolution: N/A

UPDATE SUMMARY

Drug substance:

Assessment Recommendation: Adequate.

Assessment Summary: *This addendum provides an assessment of the following drug substance information submitted since the original drug substance review (06-FEB-2023): 9-month stability data fo[redacted] nirmatrelvir drug substance.*

At the time of original drug substance review, long-term (30 °C/75% RH or 30 °C/65% RH) and accelerated (40 °C/75% RH) stability data were provided for 18 batches of [redacted] drug substance: 9 batches through six months and 9 batches through 3 months. Supportive stability data were provided for three batches of [redacted] drug substance through 6 months and one batch each of [redacted] drug substance through 12 months. The totality of the information provided at that time was evaluated and found acceptable to support a [redacted] retest period for nirmatrelvir drug substance for commercial supply stored at either [redacted]

Updated long-term (30 °C/75% RH) stability data for the [redacted] drug substance manufactured at Pfizer Ireland were provided through the 9-month timepoint (data submitted on 10-MAR-2023). No significant changes were noted. [redacted]; however, all stability data remained well within specification. The updated supporting stability data for [redacted] drug substance support the proposed [redacted] retest period for nirmatrelvir drug substance for commercial supply.

Drug product:

Assessment Recommendation: Adequate

Assessment Summary:

<u>Drug Product Stability and Shelf Life-</u>

In the SN-142 amendment, Pfizer submitted the 12-month long-term stability data for 3 EUA supply batches (FL4516, FL4517, FR7229) of PAXLOVID (nirmatrelvir tablets manufactured at Freiburg site and packaged with AbbVie ritonavir tablets in the child resistant blister pack). As discussed in drug product review #1, only nirmatrelvir tablets were tested for these batches beyond 6 months' time points for the long-term (25°C/60%RH) stability studies, due to availability of limited samples of these batches. However, for two of these EUA batches I.e., FL417 and FR7229, Pfizer submitted 12-month intermediate (30°C/ 75%RH) stability data for both ritonavir tablets and nirmatrelvir tablets. The 9-month stability data for the three non-US EUA supply batches of PAXLOVID (nirmatrelvir tablets from Freiburg site and ritonavir batches from Hetero, packaged in (b) (4) blister, lots FX2130, FX2131 and FX3846) were also submitted. In this submission, Pfizer also submitted the 6-month stability data for two PAXLOVID batches (containing nirmatrelvir tablets from Freiburg site and ritonavir tablets from AbbVie –lots 1910752A and 285897) packaged in the proposed child resistant blister pack. The provided data of all these batches met the proposed regulatory specifications. The primary stability batches of nirmatrelvir tablets alone (packaged in the (b) (4) blister pack) were also manufactured at the Freiburg site, the 12-month long term and 6-month accelerated stability data of these batches was found acceptable (Refer drug product review-1 for additional details).

The Applicant also submitted 9-month long term and intermediate stability data for four nirmatrelvir tablets batches (FT3310, FT3301, FT3313 and FT3659) manufactured at the Newbridge site and packaged in (b) (4) blister pack. The 6-month stability data for one PAXLOVID batch containing nirmatrelvir tablets manufactured at the Newbridge site, packaged with ritonavir tablets from AbbVie in (b) (4) blister pack is also submitted. The data met the proposed regulatory specifications and demonstrate that the change in drug product manufacturing site do not impact the quality of the drug product.

In addition, initial time point data for three PAXLOVID batches (3225150, 3225152, 3225154) containing nirmatrelvir tablets manufactured at the (b) (4) site and packaged ritonavir tablets from AbbVie in the proposed commercial child resistant

blister pack were submitted. The data met the proposed regulatory specifications. Pfizer agreed to a post marketing commitment and will submit the 3-month stability data for these three batches via a CBE-0 supplement.

Pfizer submitted the documentation to demonstrate that the (b) (4) *and child resistant blister pack are equivalent in providing protection from moisture and thus stability testing in* (b) (4) *blister pack is representative of child resistant (proposed commercial packaging) blister pack. (Refer to drug product review-1 for additional details). As captured in drug product review-1, the provided data still support the proposed 24-month shelf life for PAXLOVID at controlled room temperature conditions.*

(b) (4) ***Testing of Ritonavir Tablets-***

Pfizer previously submitted the updated release and stability specifications for Hetero and AbbVie ritonavir tablets with inclusion of (b) (4) test on 01-31-2023. The detailed analytical method and validation report are provided in this amendment. The (b) (4) This test is validated as a limit test for impurities and validated for specificity, limit of detection (LOD) and repeatability, as per the FDA guidance- Text on Validation of Analytical Procedures. The proposed LODs for (b) (4) are (b) (4) of the API load, respectively. The proposed LODs were found acceptable by the Drug Product and Biopharmaceutics review teams.

OPMA: NAI

Biopharmaceutics:

Assessment Recommendation: Adequate

Assessment Summary: An updated dissolution on stability dataset was provided in SN-142. During up to 12 months of long-term (25°C 60%RH), up to 12 months of intermediate and up to 6 months of accelerated stability testing, the PAXLOVID lots (consisting of nirmatrelvir 150 mg tablets from various manufacturers and the Abbvie-sourced or Hetero-sourced ritonavir 100 mg tablets co-packaged in child-resistant and (b) (4) foil/foil blisters) were able to conform to the proposed/recommended nirmatrelvir dissolution

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acceptance criterion (Q = (b) (4)% at 30 min) by USP Stage 1 (n=6) testing, as well as to the approved ritonavir dissolution acceptance criterion by USP Stage 1 (n=6) or USP Stage 2 (n=12) testing.

Additionally, based on this Reviewer's modeling using the "Stability Test" feature of the JMP software (version 16), the nirmatrelvir and ritonavir dissolution data during up to 6 to 12 months of long-term (25°C 60%RH) storage continue to support the proposed PAXLOVID expiration dating period of 24 months.

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/s/

DAVID J CLAFFEY
04/17/2023 03:17:58 PM

NDA Executive Summary

1. Application/Product Information

NDA Number.	217188		
Applicant Name	Pfizer		
Drug Product Name	PAXLOVID (nirmatrelvir tablets and ritonavir tablets) copackaged, for oral use		
Dosage Form.	Tablets		
Proposed Strength(s)	150 mg nirmatrelvir tablets and 100 mg ritonavir tablets		
Route of Administration	Oral		
Maximum Daily Dose	Two nirmatrelvir tablets and one ritonavir tablet – twice daily for five days.		
Rx/OTC Dispensed	Rx		
Proposed Indication	Treatment of mild-to-moderate COVID-19 in adult patients		
Drug Product Description	Co-packaged Immediate Release Tablets		
Co-packaged product information	Dose packs of either one or two nirmatrelvir tablets and one ritonavir tablet. 10 Dose packs are contained within a carton.		
Storage Temperature/ Conditions	20ºC to 25ºC (68ºF to 77 ºF); excursions permitted between 15ºC to 30ºC (59ºF to 86ºF)		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Katherine Windsor	Paresma Patel
	Drug Product/ Labeling	Shalini Anand	David Claffey
	Manufacturing	Abdollah Koolivand	Hang Guo

	Biopharmaceutics	Gerlie Geiser	Elsbeth Chikhale
	EA	Xiaoqin Wu	James Laurenson
	RBPM	Erica Keafer and Musse Olani	
	ATL	David Claffey	

2. Final Overall Recommendation - *Approval*

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

PAXLOVID is a co-packaged oral antiviral drug indicated for the treatment of mild-to-moderate COVID-19 in adult patients. The product is currently authorized for emergency use (EUA 105). The drug product blisters contain immediate release tablets of nirmatrelvir, 150 mg and ritonavir,100 mg. The marketing of two dosage presentations is proposed – they differ only in having either one or two nirmatrelvir tablets in each dose pack. The blister packs have been updated since the EUA to contain single doses – instead of the daily dose packs in the EUA product. Nirmatrelvir tablets are manufactured by the Applicant whereas the ritonavir tablets are sourced from two previously approved sources – AbbVie (NDA 22417) and Hetero (ANDA 204587). The NDA contains many updates from the EUA in terms of manufacturing sites, processes and controls. The data provided support the quality and labeling of the proposed product including a (b) (4) retest period for nirmatrelvir and a 24-month expiry period for both nirmatrelvir tablets and ritonavir tablets. The PAXLOVID co-packaged drug product expiry date will reflect the shorter expiry of the two components. Additional site-specific (b) (4) confirmatory nirmatrelvir tablets stability data are subject to a Post Marketing Commitment together with additional Environmental Assessment data.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance - Adequate
Drug Product - Adequate
Quality Labeling - Adequate
Manufacturing - Adequate

Biopharmaceutics - Adequate
Microbiology - N/A

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): Choose Yes or No.

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): Yes
Comments: Three Comparability Protocols were found acceptable (b) (4) all CBE-30 supplements.

Additional Lifecycle Comments: Pfizer committed to submit CBE-0 supplement with the three-month long-term and accelerated stability data for three nirmatrelvir tablets batches manufactured at (b) (4) by 31 JUL 2023. Pfizer also committed to submit additional supporting assay data for the environmental assessment as a CBE-0 submission by 15 DEC 2023. PMC numbers for both commitments remain pending at completion of this assessment document.

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	PAXLOVID (nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use	Adequate
Established name(s)	Nirmatrelvir tablets; Ritonavir tablets	Adequate.
Route(s) of administration	For oral use	Adequate.
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Tablets: nirmatrelvir 150 mg Tablets: ritonavir 100 mg	Adequate
Controlled drug substance symbol (if applicable)	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Tablet: N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

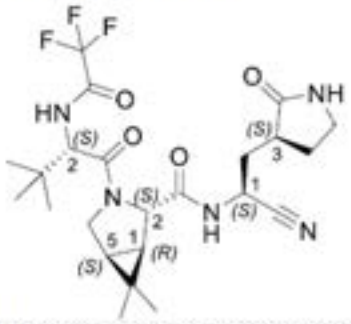
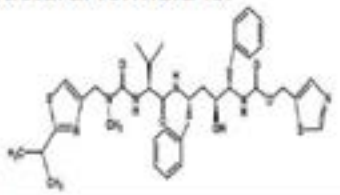
Item	Information Provided in the NDA	Assessor's Comments
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	PAXLOVID (both nirmatrelvir and ritonavir tablets) should be swallowed whole and not chewed, broken, or crushed.	Adequate The USPI of Norvir tablets (Abbvie, NDA 022417) include the following statement – 'Norvir tablets should be swallowed whole and not chewed, broken, or crushed'. The statement included in section 2 of the PAXLOVID USPI is in accordance with USPI of Norvir tablets.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
Available dosage form(s)	[PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets	Adequate.
Strength(s) in metric system	• Nirmatrelvir Tablet- Each tablet contains 150 mg of nirmatrelvir. • Ritonavir Tablet- Each tablet contains 100 mg of ritonavir.	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	• Nirmatrelvir is supplied as oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Each tablet contains 150 mg of nirmatrelvir. • Ritonavir is supplied as white or white to off-white film-coated tablets uniquely identified by the color, shape, and debossing. Each tablet contains 100 mg of ritonavir.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Adequate
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	Adequate

1.2.3 Section 11 Description

Item	Information Provided in the NDA	Assessor's Comments
Proprietary and established name(s)	PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets.	Adequate
Dosage form(s) and route(s) of administration	Nirmatrelvir tablets co-packaged with ritonavir tablets.	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Each nirmatrelvir tablet contains following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, and sodium stearyl fumarate. The following are the ingredients in the film coating: hydroxy propyl methylcellulose, iron oxide red, polyethylene glycol, and titanium dioxide. Each ritonavir tablet contains following inactive ingredients: anhydrous dibasic calcium phosphate, colloidal silicon dioxide, copovidone, sodium stearyl fumarate, and sorbitan monolaurate. The film coating may include the following ingredients: colloidal anhydrous silica, colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, polyethylene glycol, polysorbate 80, talc, and titanium dioxide.	Adequate Hetero and AbbVie ritonavir tablets contain similar inactive ingredients, other than slight difference in the coating material inactive ingredients. The inactive materials of both Hetero and AbbVie tablets coating material are included in section 11.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	Adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	N/A	

Pharmacological/ therapeutic class	Nirmatrelvir is a SARS-CoV-2 main protease (Mpro) inhibitor, and ritonavir is an HIV-1 protease inhibitor and CYP3A inhibitor.	Pharm/ tox team confirmed the accuracy of the therapeutic class (commented in the PI)
Chemical name, structural formula, molecular weight	Nirmatrelvir- The chemical name is: 1R,2S,5S)-N-((1S)-1-Cyano-2-((3S)-2-oxopyrrolidin-3-yl) ethyl)-3-((2S)-3,3-dimethyl-2-(2,2,2 trifluoroacetamido) butanoyl)-6,6-dimethyl-3-azabicyclo [3.1.0]hexane-2-carboxamide] It has a molecular formula of C23H32F3N5O4 and a molecular weight of 499.54. Its structural formula is:  Ritonavir- The chemical name is: 10-Hydroxy-2-methyl-5-(1-methylethyl)-1- [2-(1 methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12- tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]. Its molecular formula is C37H48N6O5S2, and its molecular weight is 720.95. Its structural formula is: 	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	

Other important chemical or physical properties (such as pKa or pH)	N/A	

1.2.4 Section 16 HOW SUPPLIED/STORAGE AND HANDLING section

Item	Information Provided in the NDA	Assessor's Comments
Available dosage form(s)	Tablets	Adequate.
Strength(s) in metric system	Supplied in two different dose packs- • 300 mg nirmatrelvir; 100 mg ritonavir • 150 mg nirmatrelvir; 100 mg ritonavir	Adequate.
Available units (e.g., bottles of 100 tablets)	• 300 mg/100 mg dose pack - Each blister card contains: 2 nirmatrelvir tablets (150 mg each) and 1 ritonavir tablets (100 mg each) - Each carton contains: 30 tablets divided in 10 blister cards • 150 mg/100 mg dose pack- - Each blister card contains: 1 nirmatrelvir tablets (150 mg each) and 1 ritonavir tablets (100 mg each) - Each carton contains: 20 tablets divided in 10 blister cards	Adequate.

Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Ritonavir tablets: White film-coated ovaloid tablets debossed with the “a” logo and the code NK. (AbbVie tablets) Or White film-coated ovaloid tablets debossed with “NK” on one side. (AbbVie tablets) Or White to off-white, capsule-shaped, film-coated tablets debossed with “H” on one side and “R9” on the other side. (Hetero tablets)	Adequate - Pfizer proposed separate NDC number for PAXLOVID dose packs packed with Hetero or AbbVie ritonavir tablets. - Separate NDC numbers are proposed for PAXLOVID 150 mg/ 100 mg and 300 mg/100 mg dose packs. - Per the submission dated 02/08/2023, Pfizer intend to pack AbbVie ritonavir tablets for 150 mg/100mg dose pack. - In the submission dated 01-31-2023, Pfizer included additional description of AbbVie ritonavir tablets without ‘a’ logo (debossed with only NK on one side). Pfizer proposed different NDC codes for AbbVie ritonavir tablets with and without ‘a’ logo. Refer to DP review for additional details about this.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Tablet: N/A	Adequate
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to “Dispense in original container,” provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Tablet: None	Adequate
If the product contains a desiccant, ensure the size and shape differ	N/A	Adequate: Tablets are packaged in blister pack.

from the dosage form and desiccant has a warning such as "Do not eat."		
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at USP controlled room temperature 20ºC to 25ºC (68ºF to 77 ºF); excursions permitted between 15ºC to 30ºC (59ºF to 86ºF).	Adequate Up to 12-month of supporting stability data for nirmatrelvir tablets and 24-month of ritonavir tablets (in HDPE bottles) supports the proposed storage conditions.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	Adequate
Include information about child-resistant packaging	Nirmatrelvir tablets and ritonavir tablets are supplied in separate blister cavities within the same child-resistant blister card.	Adequate

1.2.3 Other Sections of Labeling

1.2.4 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Distributed by: Pfizer Labs, Division of Pfizer Inc., New York, NY 10017	Adequate.

Reviewer's Assessment of Package Insert: Acceptable

The CMC sections of the USPI are acceptable from DP perspective.

2.0 CARTON AND CONTAINER LABELING

IMAGES OF LABEL AND LABELING RECEIVED ON DEC 20, 2022

2.1 Container/Blister Label

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Item	Information provided in the AbbVie 300 mg/100 mg blister label	Information provided in the Hetero 300 mg/100 mg blister label	Information provided in the AbbVie 150mg/100 mg blister label
Proprietary name, established name, and dosage form (font size and prominence	PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use	PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use	PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use
Dosage strength	300 mg; 100 mg	300 mg; 100 mg	150 mg; 100 mg
Route of administration	For oral use	For oral use	For oral use
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	N/A	N/A
Net contents (e.g. tablet count)	3 Tablets	3 Tablets	2 Tablets
"Rx only" displayed on the principal display	Yes	Yes	Yes
NDC number	NDC 0069-5001-06 Or NDC 0069-5321-03 (Blister pack with AbbVie Ritonavir tablets debossed with NK' only)	NDC 0069-5045-06	NDC 0069-5017-04 Or NDC 0069-5317-02 (Blister pack with AbbVie Ritonavir tablets debossed with 'NK' only)
Lot number and expiration date	Yes	Yes	Yes
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Not Included	Not Included	Not Included
Bar code	Yes	Yes	Yes
Name of manufacturer/distributor	Pfizer Labs, Division of Pfizer Inc., New York, NY 10017	Pfizer Labs, Division of Pfizer Inc., New York, NY 10017	Pfizer Labs, Division of Pfizer Inc., New York, NY 10017
Medication Guide (if applicable)	N/A	N/A	N/A
No text on Ferrule and Cap overseal	N/A	N/A	N/A

When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	N/A	N/A
And others, if space is available	Take these 3 tablets together	Take these 3 tablets together	Take these 2 tablets together

2.2 Carton Labeling

(b) (4)

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Item	Information provided in the AbbVie 300 mg/100 mg Carton label	Information provided in the Hetero 300 mg/100 mg Carton label	Information provided in the AbbVie 150mg/100 mg Carton label
Proprietary name, established name, and dosage form (font size and prominence	PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use	PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use	PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use
Dosage strength	300 mg; 100 mg Dose Pack	300 mg; 100 mg Dose Pack	150 mg; 100 mg Dose Pack
Route of administration	For oral use	For oral use	For oral use
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	N/A	N/A
Net contents (e.g. tablet count)	Each carton contains 30 tablets in 10 blister cards Each blister card contains 3 tablets: • 2 nirmatrelvir tablets (150 mg each) • 1 ritonavir tablet (100 mg each)	Each carton contains 30 tablets in 10 blister cards Each blister card contains 3 tablets: • 2 nirmatrelvir tablets (150 mg each) • 1 ritonavir tablet (100 mg each)	Each carton contains 20 tablets in 10 blister cards Each blister card contains 2 tablets: • 1 nirmatrelvir tablet (150 mg each) • 1 ritonavir tablet (100 mg each)
"Rx only" displayed on the principal display	Yes	Yes	Yes
NDC number	NDC 0069-5001-30 Or NDC 0069-5321-30	NDC 0069-5045-30	NDC 0069-5017-20 Or NDC 0069-5317-20
Lot number and expiration date	Yes	Yes	Yes
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).	Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).	Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).
Bar code	Yes	Yes	Yes
Name of manufacturer/distributor	Pfizer Labs, Division of Pfizer Inc., New York, NY 10017	Pfizer Labs, Division of Pfizer Inc., New York, NY 10017	Pfizer Labs, Division of Pfizer Inc., New York, NY 10017
Medication Guide (if applicable)	N/A	N/A	N/A
No text on Ferrule and Cap overseal	N/A	N/A	N/A

When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	N/A	N/A
And others, if space is available	Take all 3 tablets from one blister card together, twice daily (in morning and at bedtime) for 5 days.	Take all 3 tablets from one blister card together, twice daily (in morning and at bedtime) for 5 days.	Take both tablets from one blister card together, twice daily (in morning and at bedtime) for 5 days.

Assessment of Carton and Container Labeling: Adequate

The CMC information on the blister and carton labels are in accordance with information provided in quality sections of the NDA. The provided information is acceptable.

ITEMS FOR ADDITIONAL ASSESSMENT

N/A

Overall Assessment and Recommendation:

Refer to discussion above and recommendations in OND labeling.

Primary Labeling Reviewer Name and Date:

Shalini Anand, PhD, Branch 1; ONDP Division of New Drug Products I; OPQ

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

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David Claffey, PhD, Branch Chief; ONDP Division of New Drug Products I; OPQ

Shalini Anand

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David Claffey

Digitally signed by David Claffey
Date: 2/13/2023 11:50:52AM
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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	NDA 217188* (Associated with EUA 105 & IND 153517)
Drug Product Name/ Strength	PAXLOVID® [Nirmatrelvir Film-Coated Tablets/150 mg, co-packaged with externally sourced Norvir® or Hetero (Ritonavir) Film-Coated Tablets/100 mg]
Route of Administration	Oral
Applicant Name	Pfizer, Inc.
Therapeutic Classification/ OND Division	Nirmatrelvir: SARS-CoV-2 main protease inhibitor; Ritonavir: PK boosting agent of nirmatrelvir / Division of Antivirals
Indication	Treatment of mild-to-moderate COVID-19 in adult patients who are at high risk for progression to severe COVID-19, including hospitalization or death
Dosage	Nirmatrelvir/Ritonavir 300 mg/100 mg twice daily for 5 days, with or without food Swallow tablets whole; do not chew or crush. For patients with moderate renal impairment: Nirmatrelvir/Ritonavir 150 mg/100 mg twice daily, with or without food
*PAXLOVID was previously *authorized* for emergency use under EUA-000105 on 12/20/2021; this NDA requests FDA *approval* for US marketing. Letters of authorization (LOAs) to cross-reference the technical information in Abbvie's NDA 022417 for Norvir® Tablets 100 mg and in Hetero's ANDA 204587 for Ritonavir Tablets 100 mg were provided to the NDA Applicant. This Biopharmaceutics assessment focuses mainly on the nirmatrelvir component of the co-packaged drug product.	

Assessment Recommendation: APPROVAL

Assessment Summary:

Based on the available *in vitro* and *in vivo* data, nirmatrelvir (previously known as PF-07321332) exhibits the characteristics of a low solubility and low permeability drug substance, per BCS criteria.

Based mainly on the submitted *in vitro* dissolution profile data and *in vivo* PK data of target and variant nirmatrelvir 150 mg tablet lots investigated in Relative Bioavailability Study C4671008, the proposed QC dissolution method and acceptance criterion (as tabulated below) are considered adequate for the routine QC of Nirmatrelvir Film-Coated Tablets/150 mg at batch release and during shelf-life/stability testing.

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USP Apparatus	Speed	Medium/Temperature	Volume	Acceptance criterion
II (Paddle)	75 rpm	0.05 M Sodium Phosphate, pH 6.8 with 0.2% Sodium Dodecyl Sulfate (SDS); 37 ± 0.5 °C	900 mL	Q = (b) (4) % at 30 min

There were no formulation and manufacturing process-type changes to the nirmatrelvir tablets after initiation of the main part of the pivotal clinical trial (Study C4671005) that would have necessitated *in vivo* bridging data. Overall, for purposes of bridging to the final commercial nirmatrelvir 150 mg tablet drug product, the provided comparative *in vitro* nirmatrelvir dissolution profile data, additional CMC data and clinical information were deemed adequate to support the minor CMC changes that were introduced after conducting the pivotal clinical trial (specifically those related to the nirmatrelvir 150 mg tablet appearance/manufacturing sites/manufacturing process steps, and the nirmatrelvir drug substance manufacturing process/manufacturing sites, as well as related to the co-packaging of the nirmatrelvir tablets and ritonavir tablets). To support the Applicant's proposal to add suppliers for three nirmatrelvir tablet excipients, no additional dissolution data apart from those generated from routine QC testing are needed, since per the CMC reviewer's assessment there is no corresponding change in the technical grades of the excipients.

Additionally based on the *in vitro* ritonavir dissolution profile data/information provided in the Paxlovid® NDA, as well as the cross-referenced *in vivo* bioequivalence (BE) information that supported the approval of ANDA 204587, the nirmatrelvir PK-boosting performance of the externally sourced Norvir® (ritonavir 100 mg) Tablets (from Abbvie) and Hetero Lab's Ritonavir 100 mg Tablets is expected to be comparable/equivalent. Of note, Hetero's ritonavir tablets were co-administered with the nirmatrelvir tablets in the (double-blinded) pivotal clinical trial (Study C4671005) that supported Paxlovid®'s EUA, and Abbvie's Norvir® tablets was used as the Reference Standard/RLD in the BE study conducted to support the approval of Hetero's ritonavir tablets (ANDA 204587).

Per FDA recommendation, the originally submitted Comparability Protocols (CPs) for post-approval changes (b) (4)

List of Submissions Assessed and Relevant Documents in NDA 217188:

Documents	Date Received
SN-001 Original NDA	6/29/2022
SN-005 (QT Evaluation Report/TQT Waiver Request)	7/29/2022
SN-006 (includes CMC Wave 2)	7/29/2022
SN-012 (Response to Quality Information Request)	8/19/2022
SN-035 (CMC Wave 3)	9/30/2022
SN-053 (Quality IR Response)	10/26/2022
SN-054 (Response to Drug Product IR)	10/25/2022
SN-059 (Response to Biopharm IR)	11/3/2022
SN-063 (Response to Drug Product IR)	11/8/2022
SN-066 (Single Dose Blister Presentation)	11/10/2022
SN-073 (Response to Quality IR – including Biopharm)	11/23/2022
SN-089 (Response to Quality IR)	12/16/2022
SN-091 (CMC Wave 5 - includes dissolution datasets)	12/19/2022
SN-121 (Response to Quality IR – including dissolution)	1/31/2023

B.1 BCS DESIGNATION

Assessment:
This Reviewer agrees with the Applicant's classification of nirmatrelvir as a BCS IV (low solubility, low permeability) drug substance.

Solubility: *Low*
Based on the pH-solubility data in Table 3.2.P.2.2-15, the equilibrium total solubility (b) (4) of nirmatrelvir (b) (4) is pH-independent and low (0.98 to 1.21 mg/mL) across the physiologic pH range of 1.02 – 6.96. As reported in 3.2.S.1.3, the final pH values after 72 hours of solubility testing were all within 0.10 units of the initial pH values. Note that the standard clinical dosage of nirmatrelvir is 300 mg (two 150 mg tablets) when concomitantly administered with 100 mg ritonavir (one 100 mg tablet) taken orally twice daily for 5 days, with or without food.

(b) (4)

(b) (4)

Permeability: ***Low***

Note that nirmatrelvir is a substrate of the CYP3A4 metabolizing enzyme and the P-glycoprotein (P-gp) drug efflux transporter. Co-administration with ritonavir (a CYP3A4 and P-gp inhibitor) is required to increase nirmatrelvir plasma concentrations to therapeutic levels.

Based on the results of the human Mass Balance study (Study 4671001/Part 4), it appears that <85% of the administered dose of nirmatrelvir was systemically absorbed following a single 300 mg dose of an oral suspension (*boosted* with four ritonavir 100 mg doses separated by 12 hours) in six healthy subjects. Per the Applicant, 27.5% of the administered dose was recovered in the feces potentially representing unabsorbed drug. The absolute oral bioavailability of nirmatrelvir 150 mg tablets has not been determined.

In vitro, the apparent passive permeability of nirmatrelvir from the apical to basolateral direction in Madin-Darby Canine Kidney (MDCK) cell line is low (i.e., $P_{app, A \rightarrow B} = 1.71 \times 10^{-6}$ cm/sec). Additionally, nirmatrelvir is a substrate of the P-glycoprotein efflux transporter in the Multidrug Resistance Mutation-1 (MDR1) - MDCK cell line. *In vitro* Caco-2 permeability data for nirmatrelvir were not provided.

Dissolution: ***Not Rapid in Various pH Media Without Surfactant***

Within 30 minutes, approximately 55% to 60% of nirmatrelvir from the 150 mg tablet dissolves in 900 mL volumes of pH 1.2, pH 4.5 and pH 6.8 media, (USP Apparatus 2 at 75 rpm); refer to Figure 3.2.P.2.2-11.

Per the Applicant, *in vitro* and *in vivo* dissolution of nirmatrelvir (b) (4) is (b) (4) influenced by two simultaneous kinetic processes.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment:

DISSOLUTION METHOD - *ADEQUATE*

The proposed commercial QC dissolution method parameters for nirmatrelvir tablets are shown in excerpted Table 3.2.P.2.2-18.

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Table 3.2.P.2.2-18. Proposed Dissolution Method for Nirmatrelvir Tablets

Apparatus	USP Apparatus 2 (paddles)
Medium	0.05M Sodium Phosphate, pH 6.8 with 0.2% (w/v) Sodium Dodecyl Sulfate (SDS)
Volume	900 mL
Agitation rate	75 rpm
Temperature	37 °C
Analytical End Analysis	HPLC with UV detection at (b) (4) nm

Method TM-9379A

(b) (4)

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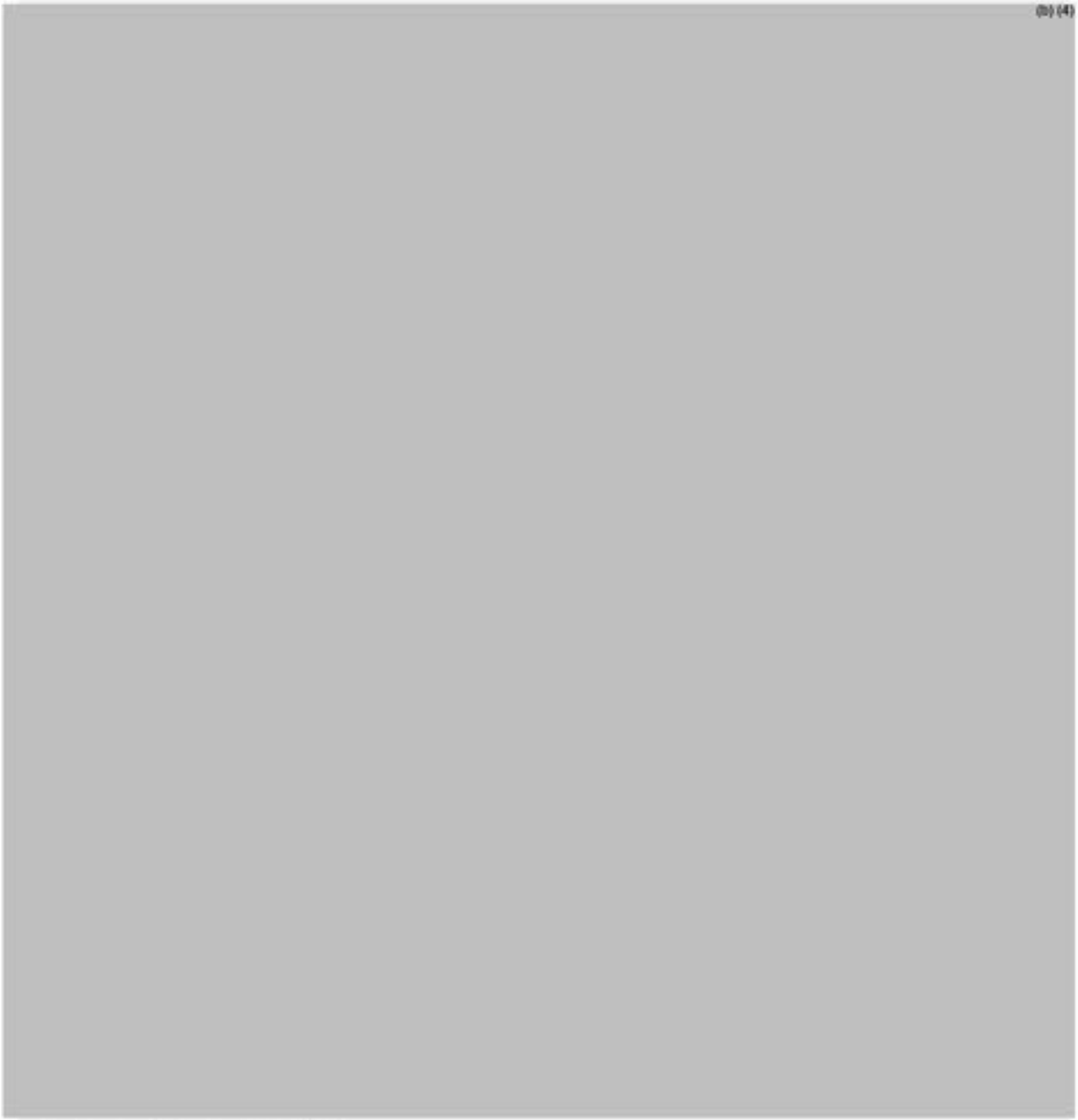

Analytical Method Validation

HPLC with UV detection (b) (4) is used for quantification of nirmatrelvir in the dissolution samples. Analytical method validation included specificity, linearity, accuracy, precision, filter suitability, and analytical solution stability. Per the Applicant, the dissolution method was robust with respect to the following studied dissolution method parameter ranges: Paddle rate: 75 (b) (4) rpm; Medium % SDS: 0.20 (b) (4) %; Medium volume: 900 (b) (4) mL; Medium

Temperature: 37 (b) (4) °C (refer to Table 3.2.P.5.3-46). Per the Drug Product Reviewer (Dr. Shalini Anand), the analytical method validation for dissolution is acceptable.

(b) (4)

DISSOLUTION ACCEPTANCE CRITERION – *Acceptable (for routine QC testing of the target drug product)*

The proposed dissolution acceptance criterion for Nirmatrelvir Film-Coated Tablets/150 mg of "not less than (b) (4) % (Q) of the label claim is dissolved in 30 minutes" is acceptable based mainly on the following supporting data/information:

1. The results of completed Relative BA (rBA) Study 1008 that found comparable nirmatrelvir PK following single dose administrations of the target product and its (b) (4) variant, along with the dissolution profile data of these target/reference and variant tablet lots

(b) (4)

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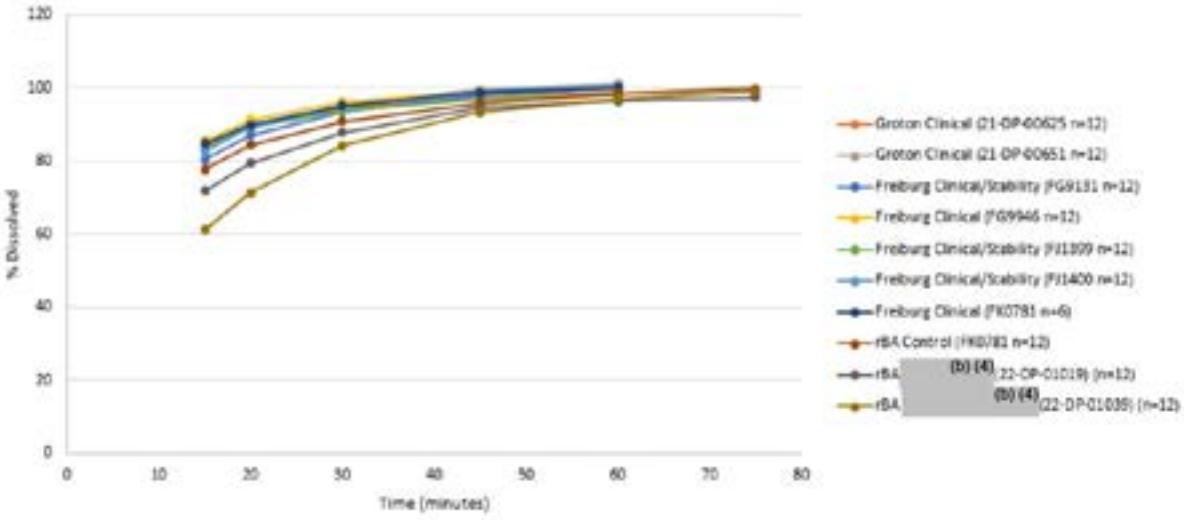
2. The dissolution profile data of the pivotal clinical trial lots, as shown in excerpted Figure 3.2.P.5.6-2 below.

Figure 3.2.P.5.6-2. Mean Dissolution Profile of Nirmatrelvir Film-Coated Tablet Clinical Batches at Release*



*rBA study supplies tested within 30 days of study C4671008 dosing

Although nirmatrelvir is a low solubility drug substance per BCS criteria, this Reviewer determines that a 2nd/early dissolution specification time point is not required (i.e., specifically to guard against premature drug release) based on the following considerations:

(1) As shown in the excerpted Figure above, the clinical lots were rapidly to very rapidly dissolving (i.e., ≥85% within 30 minutes). Note: The (b) (4) variant lot (**Batch 22-DP-01039**) that exhibited comparable PK to the target product in rBA Study 1008 exhibited a mean (range) dissolution of 84% (b) (4) at 30 min.
(2) The proposed drug product is intended for immediate drug release.
(3) Based on the analysis of the ECG data from the supratherapeutic dose cohort of PK Study C467001 and the ECG data from the sentinel cohort of COVID-19 patients in Study C4671005 and Study C4671002, as well as based on the results of nonclinical studies, the Applicant concluded (and the CDER-QT-IRT Team confirmed) that the combination of nirmatrelvir 300 mg and ritonavir 100 mg does not have a clinically meaningful effect on QT; refer to 2.7.4.4.2, as well as SN-5 of the NDA, as well as the CDER QT-IRT Review. Thus,

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nirmatrelvir 150 mg tablet lots with significantly faster dissolution rate are not anticipated to pose a relative safety hazard, based on currently available nonclinical and clinical safety data.

(4) Based on the FDA recommended labeling edits, it appears that the major clinical safety concern related to PAXLOVID is drug-drug interaction potential associated with the ritonavir component. Since anti-COVID efficacy relies upon the nirmatrelvir component, assurance of adequate nirmatrelvir bioavailability (through attainment of a minimum dissolution rate) appears critical.

Dissolution on Stability

Co-Packaged Nirmatrelvir/Ritonavir Tablets in Child-Resistant (CR) Foil/Foil Blister:

Based on up to 9 months of long-term (25°C/60% RH), intermediate (30°C/75% RH) and up to 6 months of accelerated (40°C/75% RH) stability data, the three US EUA supply CR foil/foil blister packaged PAXLOVID Lots FL4516, FL4517, and FR7229 (consisting of Pfizer Freiburg-manufactured nirmatrelvir 150 mg tablets using [(b) (4)] /Ringaskiddy nirmatrelvir drug substance, and Abbvie's ritonavir 100 mg tablets), demonstrated ability to conform to the proposed nirmatrelvir dissolution acceptance criterion (Q = [(b) (4)]% at 30 min) and the approved Norvir® dissolution acceptance criterion (Q = [(b) (4)]% at 120 min) both by USP Stage 1 (n=6) testing. The packaging of these three lots is consistent with that described in Section 3.2.P.7.1 Container Closure System; refer also to Table 3.2.P.8.1-1 in SN-73.

- Using the "Stability Test" analysis feature of JMP 15, this Reviewer's modeling suggests that based on the nirmatrelvir dissolution (at 30 minute) data onbtained during 9 months long-term stability storage of US EUA Supply PAXLOVID (copackaged nirmatrelvir tablets and ritonavir) Lots FL4516, FL4517, and FR7229, the earliest crossing time of the 95% confidence intervals with the nirmatrelvir dissolution tolerance limit of "[(b) (4)]% at 30 min" is approximately 33.8 months (refer to Reviewer Figure 2A below). Using the dissolution data obtained over 7 months of intermediate testing, the earliest crossing time is 44.2 months (refer to Reviewer Figure 2B below). Thus, it appears that the proposed PAXLOVID expiration dating period of 24 months at room temperature storage is supported by the nirmatrelvir dissolution stability modeling results for these three US EUA Supply PAXLOVID lots. Note that modeling could not be performed for the ritonavir component of PAXLOVID because only Month 0 (initial) ritonavir dissolution on long-term stability data were available. However, using ritonavir dissolution data obtained during 6 months intermediate stability storage, the model-predicted an earliest crossing time with the ritonavir dissolution tolerance limit of "Q = [(b) (4)]% at 120 min" at 85.5 months with 95% confidence. *The final determination of the product's shelf-life is deferred to the Drug Product Reviewer.*

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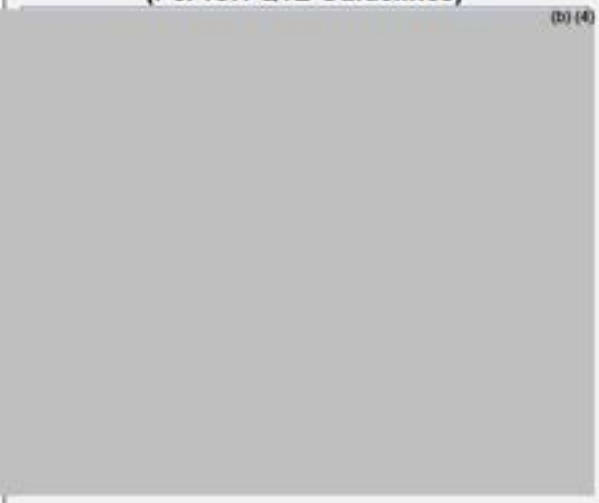
Reviewer Figure 2A PAXLOVID Shelf-life Determination Based on Predicted Nirmatrelvir Dissolution at 30 min Data During Long-Term Storage (Per ICH Q1E Guidelines)	Reviewer Figure 2B PAXLOVID Shelf-life Determination Based on Predicted Nirmatrelvir Dissolution at 30 min Data During Intermediate Stability Storage (Per ICH Q1E Guidelines)
	

Based on 3 months of long-term and accelerated stability data, the co-packaged "Stability" PAXLOVID CR foil/foil co-packaged tablet lot [2858974] consisting of nirmatrelvir tablets manufactured by Freiburg/Germany using (b) (4) nirmatrelvir drug substance, and ritonavir 100 mg tablets supplied by Abbvie, conforms to the approved Norvir® dissolution acceptance criterion (Q = (b) (4)% at 120 min) by USP Stage 1 (n=6) testing.

Three (3) months nirmatrelvir and ritonavir (long-term and accelerated) stability data were submitted for three additional CR foil/foil co-packaged tablet lots [GE5412, GE5413, GE5414] consisting of nirmatrelvir tablets manufactured by Ascoli using (b) (4) nirmatrelvir drug substance, and Hetero Ritonavir 100 mg tablets. Based on up to 3 months dissolution on stability data of these three lots, the nirmatrelvir tablets are able to conform to Q = (b) (4)% at 30 min by USP Stage 1 (n = 6) testing whereas the ritonavir tablets are able to conform to Q = (b) (4)% at 90 min by USP Stage 2 (n = 12) testing.

Co-Packaged Nirmatrelvir/Ritonavir Tablets in (b) (4) Foil/Foil Blister:
Based on up to 6 months of long-term, intermediate, and accelerated stability data for three Non-US emergency supply PAXLOVID (b) (4) foil/foil co-packaged tablet lots [FX2130, FX2131, FX3846] consisting of nirmatrelvir tablets manufactured by Freiburg using (b) (4) nirmatrelvir drug substance, and ritonavir 100 mg tablets supplied by Hetero, the nirmatrelvir tablets in PAXLOVID Lots FX2130, FX2131, FX3846 were able to conform to the proposed dissolution acceptance criterion (Q = (b) (4)% at 30 min) by USP Stage 1 testing. As well, the co-packaged

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Hetero Ritonavir 100 mg Tablets were able to conform to the approved dissolution acceptance criterion [NLT (b)(4)% (Q) at 90 min] by USP Stage 1 testing.

Based on 3 months of long-term, intermediate, and accelerated stability data, the co-packaged "Stability" PAXLOVID (b)(4) foil/foil co-packaged tablet lot [FY1865] consisting of nirmatrelvir tablets manufactured by Newbridge/Ireland using (b)(4) nirmatrelvir drug substance, and ritonavir 100 mg tablets supplied by Abbvie,
demonstrated ability to conform to the proposed nirmatrelvir tablets dissolution acceptance criterion (Q= (b)(4)% at 30 min) and the approved Norvir® dissolution acceptance criterion (Q = % at 120 min), both by USP Stage 1 (n=6) testing.

Per the Applicant, the stability data observed to date for the co-packaged nirmatrelvir 150 mg tablets and ritonavir 100 mg tablets are consistent with those observed for the separately commercially foil/foil blister packaged nirmatrelvir tablets.

The proposed expiration dating period of the PAXLOVID® (nirmatrelvir 150 mg tablets and ritonavir tablets packaged in a common aluminum/aluminum foil blister card) is 24 months when stored under USP Controlled Room Temperature conditions. *Refer to the Drug Product Review for the assessment of the acceptability of the proposed expiration dating period of 24 months for the proposed commercial product.*

B.4 APPLICATION OF DISSOLUTION/IVIVC IN QbD

Assessment: *Adequate*

Dissolution and Nirmatrelvir Drug Substance Particle Size Distribution
The proposed drug substance particle size distribution acceptance criteria (d_{90} NMT (b)(4) µm, d_{50} NMT (b)(4) µm) is supported by the *in vitro* dissolution and *in vivo* PK results of completed rBA Study 1008 that included "(b)(4)" variant nirmatrelvir tablet lots using input (b)(4) drug substance lot (22-AP-00733) manufactured by Pfizer-Groton/USA. For the CMC information of nirmatrelvir DS Lot 22-AP-00733, refer to Table 3.2.S.4.5-4.

The proposed API d_{50} and d_{90} acceptance criteria encompass the particle size of the nirmatrelvir (b)(4) drug substance lots from Pfizer Sandwich/UK that were used to manufacture 150 mg tablets for the pivotal Phase 3 clinical trial, as well as the historical batch ranges as reported by the Applicant (at the time of NDA submission) particularly for those produced using the proposed final nirmatrelvir drug substance manufacturing process (b)(4) by Pfizer Ringaskiddy/Ireland, (b)(4)

Drug Substance Synthetic Process	Nirmatrelvir Drug substance Lot Number	Nirmatrelvir Drug Substance Particle Size Distribution[a]		
		API d_{90} (um)	API d_{50} (um)	API d_{50} (um)
(b) (4)	21-AP-00640		(b) (4)	-
	21-AP-00642			-
	21-AP-00581			-
	21-AP-00594			-
	(e.g., 22-AP-00733)			-

[a] measured by (b) (4)
[b] 3.2.S.4.4. Batch Analyses
Refer to the DS review for further details and evaluation of the particle size distribution acceptance criteria.

B. 12 BRIDGING

Assessment: ***Adequate***

Majority (~98%) of the non-hospitalized COVID-19 patients in the pivotal clinical trial (Study C4671005; EPIC-HR) were administered the 150 mg nirmatrelvir tablets manufactured using the final proposed commercial formulation/process, or placebo treatment. Nirmatrelvir pharmacokinetic (PK) and/or pharmacodynamic (PD) data from healthy subjects and/or mild-to-moderate COVID-19 patients (enrolled in EPIC-HR and other Phase 2/3 clinical trials) when coadministered with ritonavir are also available. Thus, additional *in vivo* clinical PK/PD/efficacy/safety data/information are not needed to establish the bridge from the final pivotal clinical trial product to the proposed commercial EUA formulation/process product. [For the comparison of the formulation compositions and other quality attributes of the immediate release nirmatrelvir tablets that were used during clinical development, refer to Table 3.2.P.2.2-4 and Table 3.2.P.2.2-5. For the comparison of the manufacturing process/site details of the pivotal clinical, registration stability and proposed 150 mg nirmatrelvir tablets, refer to Table 3.2.P.2.3-1. For details regarding the available PK and PD data/information for the final pivotal clinical/commercial nirmatrelvir 150 mg tablet formulation and prior clinical development formulations, refer to the 'Reviewer Note 1' section below.]

As shown in excerpted Table 3.2.P.2.2-5, two of three 150 mg nirmatrelvir tablet lots evaluated in the pivotal Phase 3 clinical trial were manufactured by Pfizer Groton/USA; the third Phase 3 clinical trial lot (which is also 1 of 3 primary registration/stability lots) was manufactured by the final proposed (EUA-stage) drug product manufacturing site, Pfizer Freiburg/Germany, at a similar batch size range

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([redacted]; Lot FG9131). All three primary registration/stability lots were manufactured at the Freiburg site [redacted] using nirmatrelvir API from the clinical supplier (Pfizer Sandwich/UK) synthesized using either drug substance [redacted] (clinical process) or [redacted] (1 of 2 final proposed drug substance processes at the time of authorization of PAXLOVID for emergency use).

For the minor CMC changes that were made to the 150 mg nirmatrelvir tablet at the post-pivotal clinical trial stage, i.e., including changes in the drug product manufacturing site, drug substance synthetic route, tablet appearance, and/or changes/differences in drug product manufacturing [redacted] step or batch size, comparative *in vitro* dissolution profile data (especially as generated by a QC dissolution method that is clinically relevant) and/or CMC data are deemed sufficient for bridging from the clinical/primary stability product to the commercial product. The dissolution profile data of the nirmatrelvir tablet batches that provide support to these minor CMC changes are discussed in more detail below.

Table 3.2.P.2.2-5. Nirmatrelvir Drug Product Clinical Lot Genealogy Table

Drug Product Description	Drug Product Batch Number	Drug Product Manufacturing Site	Drug Substance Batch Number	Drug Substance Synthetic Route	Drug Substance Manufacturing Site	Clinical Study Number
EP oral suspension	N/A	PCRU[a] New Haven, USA and Brussels, BE	21-AP-00525	[redacted]	[redacted]	C4671001, C4671015
250 mg IR tablet core	21-PN-00103	Groton, USA	21-AP-00525			C4671001
100 mg film-coated tablet	21-DP-00508	Groton, USA	21-AP-00521			C4671005[b], C4671010, C4671011, C4671012, C4671013
150 mg film-coated tablet	21-DP-00625	Groton, USA	21-AP-00581		Pfizer Sandwich, UK	C4671005
150 mg film-coated tablet	21-DP-00651	Groton, USA	21-AP-00581		Pfizer Sandwich, UK	C4671002, C4671005, C4671006, C4671014
150 mg film-coated tablet	FG9131[c]	Freiburg, Germany	21-AP-00594		Pfizer Sandwich, UK	C4671005, C4671006
150 mg film-coated tablet	FG9946	Freiburg, Germany	21-AP-00594		Pfizer Sandwich, UK	C4671002, C4671006
150 mg film-coated tablet	FJ1399[d]	Freiburg, Germany	21-AP-00640		Pfizer Sandwich, UK	C4671006, C4671026
150 mg film-coated tablet (debossed)	FJ1400[e]	Freiburg, Germany	21-AP-00642		Pfizer Sandwich, UK	C4671016
150 mg film-coated tablet (debossed)	FK0781	Freiburg, Germany	21-AP-00640 & 21-AP-00642		Pfizer Sandwich, UK	C4671006, C4671008, C4671019, C4671024, C4671026
150 mg film-coated tablet [redacted]	22-DP-01019	Groton, USA	22-AP-00733		Pfizer Sandwich, UK	C4671008
150 mg film-coated tablet [redacted]	22-DP-01039	Groton, USA	22-AP-00733		Pfizer Sandwich, UK	C4671008
PF-07321332 500 mg/g [redacted]	21-PN-00132	Bend, USA	21-AP-00594		Pfizer Sandwich, UK	C4671008
PF-07321332 200 mg/g [redacted]	22-DP-01036	Groton, USA	21-AP-00707		Pfizer Sandwich, UK	C4671024

a. Pfizer Clinical Research Unit (PCRU)
b. Used in the C4671005 sentinel cohort only.
c. 1st registration stability batch.
d. 2nd registration stability batch.
e. 3rd registration stability batch. Debossed with PFE and 3CL.

Note that (as shown in Reviewer Figure 1 above) all the nirmatrelvir 150 mg tablet lots manufactured with these minor CMC changes (as well as additional post-clinical lots manufactured to date) exhibited nirmatrelvir dissolution profiles (at batch release

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or initial time point) that are higher than the dissolution profile of rBA Study 1008's (b) (4) (**22-DP-01039**) (b) (4) .

1) Change in Nirmatrelvir 150 mg Tablet (Drug Product) Manufacturing Site (Pfizer Groton → Pfizer Freiburg + Pfizer Newbridge + Pfizer Ascoli → … + (b) (4) :

At the time of the EUA request, the only proposed commercial nirmatrelvir 150 mg tablet manufacturing site was Pfizer, Freiburg/Germany.

- Since a 150 mg nirmatrelvir tablet lot (FG9131) produced by the Freiburg/Germany site was introduced into the pivotal clinical trial (Study 1005, as confirmed by the Applicant in the EUA/SN-006 IR Response) and in registration stability studies, *in vitro* bridging to the 150 mg tablets produced by the original pivotal clinical trial drug product manufacturer (Pfizer, Groton/USA) is not necessary. Nevertheless, the comparable *in vitro* dissolution profile data of Pivotal Clinical Study 1005 (EPIC-HR) Lot 21-DP-00625 (Groton/USA) and Supportive Phase 2/3 Clinical Study 1006 (EPIC-PEP) Lot FG9946 (Freiburg/Germany) in various pH media (without surfactant) and using the proposed QC dissolution method (with surfactant) confirm the equivalence of the two drug product manufacturing sites, and further supports the use of both Groton- and Freiburg- manufactured 150 mg nirmatrelvir tablets in the pivotal Phase 3 clinical trial (Study 1005). For the supporting comparative dissolution profiles, refer to Figure 3.2.P.2.2-24 through Figure 3.2.P.2.2-27.

- More recently, additional Freiburg-manufactured nirmatrelvir 150 mg tablet lots have been used in other clinical studies [e.g., Phase 2/3 Study C4671002 (EPIC-SR), rBA Study C4671008, Food-Effect Study C4671019, rBA Study C4671024, Phase 2/3 Study C4671026 (EPIC-Peds)], as shown in excerpted Table 3.2.P.2.2-5 above.

Since the granting of the EUA request, three additional nirmatrelvir 150 mg tablet manufacturers/manufacturing sites, i.e., Pfizer/Newbridge (Ireland), (b) (4) and Pfizer Ascoli/Italy have also been authorized.

- Adequate evidence of comparable *in vitro* dissolution profile data to the Freiburg-manufactured nirmatrelvir 150 mg tablet lots in various pH media (without surfactant) and using the proposed QC dissolution method were provided to support the post-EUA addition of these three additional nirmatrelvir 150 mg tablet manufacturing sites; refer to the Biopharmaceutics (bridging) assessments for EUA-105/SN-63, SN-117, and SN-140,

respectively, and Section 3.2.P.2.2.8.4 and Section 3.2.P.2.2.8.5, as well as Reviewer Figure 1 above.

After the original NDA (217188) submission, the addition of [redacted] as an alternate nirmatrelvir 150 mg tablet manufacturing site was proposed.

- Adequate evidence of comparable *in vitro* dissolution profile data to the reference nirmatrelvir 150 mg tablet lot (manufactured by Pfizer Freiburg using input nirmatrelvir drug substance from [redacted]) in various pH media (without surfactant) and using the proposed QC dissolution method were provided to support addition of [redacted] as alternative nirmatrelvir 150 mg tablet manufacturing site, i.,e., when using input nirmatrelvir drug substance from one of the already authorized manufacturers [redacted] Refer to Section 3.2.P.2.2.1.6.

- Relative to the slowest dissolving nirmatrelvir 150 mg tablet Lot 22-DP-01039 in rBA Study 1008, the [redacted] batches exhibited higher mean dissolution profiles and higher minimum individual unit values for dissolution at 30 minutes (refer to Reviewer Figure 1 above).

2) Change in Drug Substance Synthetic Process and Manufacturing Site [redacted]

At the time of the EUA request, the proposed commercial drug substance synthetic routes were [redacted] the proposed commercial drug substance manufacturing sites were Pfizer Ringaskiddy/Ireland and [redacted]

- Nirmatrelvir Drug Substance Manufacturing Process. The comparable *in vitro* dissolution profile data of Primary Registration/Phase 3 Clinical Drug Product Lot # FG9131 (DS Process [redacted] and Primary Registration/Clinical Lot # FJ1399 (DS Process [redacted] (using the proposed QC dissolution method) supports the conclusion that change in drug substance synthetic process from [redacted] is not anticipated to impact drug product performance. Note that these two compared lots were manufactured by Pfizer Freiburg at the same commercial scale using input drug substance from the same supplier, and are both [redacted] tablet lots. [Additionally, evidence of superimposable *in vitro* dissolution profiles in various pH media (without surfactant) and using the proposed QC dissolution method were provided for Freiburg-manufactured [redacted] tablet Lot FG9946 and [redacted] tablet Lot FJ1400 (which used 'Process [redacted] and 'Process [redacted] input drug substance

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lots, respectively); refer to Section 3.2.P.2.2.8.2. As discussed in more detail below further evidence is available to enable this Reviewer to conclude that the presence/absence of [redacted] did not significantly impact the observation of comparable dissolution profiles between these two tablet lots despite the difference in the ingoing drug substance synthetic routes (i.e., [redacted]] Furthermore, notwithstanding the [redacted] differences, the evidence of superimposable *in vitro* dissolution profiles in various pH media (without surfactant) provided for both Freiburg-manufactured tablet lots (FJ1400 and FP4796) both using ingoing Pfizer Sandwich-sourced drug substance produced via "Process [redacted] and "Process [redacted], respectively, supports extension of the bridge to the final commercial drug substance synthetic route [redacted]; refer to Table 3.2.P.2.2-75 and the associated Tables and Figures. [Note that earlier drug substance Processes [redacted] were not used to produce lots for the pivotal clinical trial or primary stability studies; Process [redacted] was used to manufacture the 100 mg nirmatrelvir tablet formulation evaluated in the sentinel cohort of Study 1005 and in one of the (first generation) 150 mg tablet supportive stability batches.]

- Nirmatrelvir Drug Substance Manufacturer/Manufacturing Sites For Route [redacted] and Other Routes used for Pivotal Clinical Trial Supply. Pfizer, Sandwich/UK supplied the ingoing Process [redacted] or Process [redacted] drug substance lots for the Phase 3 clinical trial (Study 1005) and prim ry registration/stability studies. Per the Drug Substance Reviewer, the provided drug substance batch analysis data were adequate to support the EUA manufacturing sites (i.e., Pfizer Ringaskiddy/Ireland and [redacted]) and the two proposed synthetic routes [redacted]

Since the granting of the EUA request, the additions of [redacted] as alternative drug substance manufacturers have been authorized; refer to the Drug Substance Review for EUA-105/SN-60, and Drug Substance Review for EUA-105/SN-134, respectively.

- As shown in excerpted Table 3.2.P.2.2-5 above, drug substance lots using *'Route [redacted] /Pfizer Sandwich* have since emergency authorization of Paxlovid been used to manufacture two nirmatrelvir tablet lots (22-DP-01019 and **22-DP-01039**) that were demonstrated to have comparable PK to the reference (commercial EUA) nirmatrelvir 150 mg tablet lots (based on the results of completed Relative BA Study 1008).

- Note that the already authorized additions of Pfizer Newbridge/Ireland, [redacted] and Pfizer Ascoli/Italy as drug product manufacturers (via EUA-105/SN-63, SN-117, and SN-140, respectively) were supported in part by the *in vitro* dissolution profile data of Pfizer Newbridge-manufactured,

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[(b) (4)]-manufactured and Pfizer Ascoli-manufactured drug product lots using input [(b) (4)] drug substance batches supplied by [(b) (4)] [(b) (4)] Refer to Table 3.2.P.2.2-37 of the NDA for details regarding the ingoing drug substance routes and suppliers used to manufacture the pre-change/reference and post-change/test nirmatrelvir 150 mg tablet lots used in these comparative *in vitro* dissolution studies. For example, the evidence of superimposable *in vitro* dissolution profiles in various pH media (without surfactant) provided for Newbridge-manufactured debossed tablet Lots FR2906 and FR3678 versus reference Freiburg-manufactured debossed tablet Lot FP4796, (all using ingoing [(b) (4)] drug substance) supports use of [(b) (4)] as final commercial drug substance suppliers, in addition to Pfizer Sandwich which (as mentioned above) provided input drug substance for the manufacture of the pivotal clinical and other clinical lots; refer to Table 3.2.P.2.2-75 and the associated tables and figures.

- Additionally as provided in SN-6, the comparative *in vitro* dissolution profile data in various pH media of the nirmatrelvir 150 mg tablet lot (GD4172) produced by Pfizer Freiburg using input nirmatrelvir [(b) (4)] *Pfizer Ringaskiddy* drug substance were comparable to those for the reference Freiburg-manufactured lot (FR6824) using input nirmatrelvir [(b) (4)] drug substance, thereby providing further support for the addition of the Ireland site as a nirmatrelvir [(b) (4)] drug substance manufacturing site. Refer to Figures 3.2.P.2.2-54, -55, and -56. Note also that (as shown in Reviewer Figure 1 above) the mean dissolution profile data and the minimum individual dissolution at 30 min value of Lot GD4172 are both higher than those for rBA Study's [(b) (4)] tablet lot (**22-DP-01039**). Note that nirmatrelvir tablet Lots FR6824 and GD4172 differ in terms of [(b) (4)] and the manufacturing batch sizes; however, as stated above, this Reviewer determined that [(b) (4)] did not contribute to significant nirmatrelvir tablet dissolution changes, and it is noted that the batch size difference is less than 10-fold (i.e., [(b) (4)] kg versus [(b) (4)] kg). Note that per 3.2.P.3.2, the proposed commercial batch size range is [(b) (4)] kg to [(b) (4)] kg).

- In SN-6, evidence was provided that the *in vitro* dissolution profiles in various pH media from nirmatrelvir 150 mg tablet lot (3209523R) produced by [(b) (4)] using input [(b) (4)] nirmatrelvir drug substance sourced from [(b) (4)] were comparable to those from the reference drug product lot (i.e., with f_2 >50 values). Additionally, evidence was provided that the average dissolution profile data and the minimum individual unit dissolution at 30 min value of Lot 3209523R using the proposed QC

dissolution method was not lower than rBA Study 1008's slowest dissolving tablet Lot **22-DP-01039**.

The NDA proposes the addition of [redacted] as a [redacted] nirmatrelvir drug substance manufacturer.

- In SN-35, the dissolution profile data (in various pH media without surfactant and using the QC dissolution method) of Pfizer-Freiburg nirmatrelvir film-coated debossed tablet lot (GH5539) using ingoing drug substance lot sourced from [redacted] were shown to be comparable to those from the reference Pfizer-Freiburg [redacted] tablet lot (FR6824) using ingoing [redacted] drug substance lot sourced from [redacted] [As explained above, data suggest that the [redacted] on the tablet does not significantly influence nirmatrelvir dissolution data.] For the data/information that supported the addition of [redacted] as a "[redacted] nirmatrelvir drug substance manufacturer, refer to Table 3.2.P.2.2-117, the comparative multi-pH dissolution profile data in Figure 3.2.P.2.2-57, Figure 3.2.P.2.2-58, and Figure 3.2.P.2.2-59, as well as the comparative QC dissolution profile data in Reviewer Figure 1. Additionally, at batch release, tablet lot GH5539 was reported to conform to the dissolution acceptance criterion (Q = [redacted]% at 30 min) by USP Stage 1 (n=6) testing. Of note, per the Drug Substance Reviewer, the batch analyses data of the ingoing drug substance lot (0030008161) were not submitted; nevertheless, the data available for three commercial batches of [redacted] drug substance showed that those lots are comparable to those for previously authorized nirmatrelvir DS manufacturers.

3) Changes in Drug Product Appearance and Packaging Presentation:

A summary of the proposed labeling's description of the co-packaged nirmatrelvir tablets and ritonavir tablets is as follows:

Nirmatrelvir is supplied as oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Each tablet contains 150 mg of nirmatrelvir.

Ritonavir is supplied as white [redacted] *Each tablet contains 100 mg of ritonavir.* [redacted]

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PAXLOVID® Tablets are supplied in separate cavities within the same blister card.

(b) (4)

- Based on the comparable dissolution profile data of Primary Registration Drug Product Lots # FJ1399 ((b) (4) and # FJ1400 (debossed), it can be concluded that the change in tablet appearance at the post-clinical stage is not anticipated to impact drug product performance. Note that these two compared lots were manufactured at the Freiburg site using (b) (4) drug substance.
- The proposal to revise the CR-blister packaging presentations (b) (4) to a single dose pack and the introduction of the reduced dose packs, i.e., in order to remediate concerns of medication errors related to dosing of the wrong tablet combination or wrong dose, is acceptable from the Biopharmaceutics perspective. No dissolution profile data are specifically required to support these packaging presentation changes, provided these changes do not result in significant blister material and packaging process changes (per the evaluation of the Drug Product and Process Reviewers), and DMEPA finds the revised blister pack and carton labels/labeling acceptable.

4) Change in Drug Product Manufacturing Step (b) (4)

(b) (4)

(b) (4)

5) Change in Supplier of Excipients (Lactose Monohydrate, Microcrystalline Cellulose, Croscarmellose Sodium)

Note that the Applicant claims (and the Drug Product Reviewer confirmed) that the proposed changes in the suppliers of lactose monohydrate, microcrystalline cellulose, and croscarmellose sodium do not involve a change in technical grades of these three excipients.

- Since there are no excipient technical grade changes involved, in line with the SUPAC-IR Guidance recommendations, evidence that the finished drug product is able to conform to the approved dissolution specifications is considered sufficient to support the proposed change in excipient supplier.

Reviewer Note 1:
Clinical PK of Final Commercial Nirmatrelvir Tablet (150 mg) Formulation, and Bridging to the Earlier Clinical Development Nirmatrelvir Liquid and Solid Oral Formulations

Intensive nirmatrelvir PK data of the proposed commercial 150 mg nirmatrelvir film-coated tablet formulation (when co-administered with ritonavir) in healthy subjects are available mainly via Carbamazepine Drug Interaction Study C4671014 using batch 21-DP-00651; refer to Table 4 of the proposed labeling, and Food-Effect Study 1019 (using Pfizer Freiburg batch FK0781). Nirmatrelvir pharmacokinetics/PK (predicted by population analysis) and nirmatrelvir pharmacodynamics/PD (i.e., changes from baseline viral RNA levels) in mild-to-moderate COVID-19 patients

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treated with PAXLOVID are also summarized in the proposed labeling's Table 5 and Table 2, respectively. Per the Clinical Pharmacology Reviewer (Dr. Cristina Miglis), the nirmatrelvir PK data provided for the final commercial drug product formulation is adequate.

Intensive nirmatrelvir PK data of the 100 mg film-coated nirmatrelvir tablet (co-administered with ritonavir) in healthy subjects are available via PK (in Renal Impairment) Study C4671011 should *in vivo* PK bridging to this earlier developmental nirmatrelvir tablet formulation be needed. Note that the earlier 100 mg tablet and the final 150 mg tablet formulations of nirmatrelvir that were used in Study 1005 do not have the same excipients, so *in vitro* bridging is not considered appropriate. The Applicant reported that the observed plasma nirmatrelvir concentrations in the pivotal clinical trial (Study 1005) were comparable between the sentinel cohort patients who received the 100 mg nirmatrelvir tablet and the non-sentinel cohort patients who received the 150 mg nirmatrelvir tablet (both at the recommended dosage of 300 mg nirmatrelvir and 100 mg ritonavir twice daily for 5 days), as depicted in Figure 2 of the final Population PK study report. Refer to the Clinical Pharmacology Review for the assessment of the sparse nirmatrelvir PK data collected in Study 1005 and the PopPK modeling study report.

PK data are also available for additional earlier pre-EUA stage nirmatrelvir formulations including an extemporaneously prepared nirmatrelvir oral suspension and an uncoated 250 mg nirmatrelvir immediate release tablet formulation (via First in Human Study C4671001/Part 3), as well as a post-EUA investigational nirmatrelvir 500 mg/g (b) (4) formulation administered as an extemporaneous oral suspension in Relative BA Study 1008. [Note that unlike the immediate release oral tablet and suspension dosage forms of nirmatrelvir evaluated during clinical development (pre-EUA) which used (b) (4) of the drug substance, the (b) (4) formulation contains (b) (4) of the nirmatrelvir drug substance in a (b) (4) which enhances oral bioavailability relative to the commercial nirmatrelvir 150 mg tablet (when both are co-administered with ritonavir 100 mg tablets).] Refer to the Clinical Pharmacology Review should it be necessary to compare the PK of these various nirmatrelvir formulations to the commercial nirmatrelvir 150 mg tablet.

Reviewer Note 2:
Ritonavir Over-encapsulation in Pivotal (Double-Blinded) Clinical Trial, and Dissolution Testing of Co-Packaged Norvir® (Ritonavir) 100 mg Tablets and Hetero Ritonavir 100 mg Tablets

Previously in SN-29 of IND 153517 (Figure 1), the Applicant provided comparative *in vitro* ritonavir dissolution profile data (generated using the USP monograph dissolution test for ritonavir tablets) to demonstrate that over-encapsulation of the 100 mg ritonavir tablets for clinical trial blinding purposes did not alter the dissolution

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performance of the commercially/externally sourced ritonavir tablets (manufactured by Hetero Labs, distributed by Camber Pharmaceuticals, Inc). Specifically, the over-encapsulated Hetero ritonavir tablets were still able to meet the dissolution acceptance criterion (i.e., Q = [redacted] % at 90 min) and dissolution method parameters ([redacted]) as approved by FDA for ANDA 204587.

For commercial supply, Norvir® (ritonavir) tablets, 100 mg was initially authorized to be co-packaged with nirmatrelvir 150 mg film-coated tablets in a common foil/foil blister. Per 3.2.P.5.1 and 3.2.P.5.2 of cross-referenced NDA 22417, the dissolution test and acceptance criterion of the externally sourced Norvir® tablets [redacted]

refer to the Biopharmaceutics assessment of EUA-105/SN-95. It was noted that ANDA 204587 was approved based on demonstration of *in vivo* bioequivalence between Hetero Labs Limited's Ritonavir 100 mg Tablets and Abbvie's Norvir® 100 mg Tablets, and satisfactory *in vitro* dissolution profile data using a suitable dissolution method. It was also noted that commercially available Hetero Ritonavir 100 mg tablets (distributed by Camber Pharmaceuticals in the US) were used in the pivotal clinical studies that supported the granting of the EUA of PAXLOVID. Additionally, the externally sourced Hetero ritonavir 100 mg tablets (to be used for co-packaging with nirmatrelvir 150 mg tablets) will continue to use for QC testing the same dissolution specifications as previously approved by FDA for ANDA 204587.

Note that in SN-121, per the Drug Product Reviewer's recommendation, the Applicant included [redacted] Per the Drug Product Reviewer, the Applicant's proposal (in SN-89) to perform release testing of nirmatrelvir bulk tablets only (not the co-packaged tablets) at the nirmatrelvir drug product manufacturing site (prior to shipping the bulk tablets to the packaging site) is acceptable.

B. 13 BIOWAIVER REQUEST

Assessment: *Not Applicable*

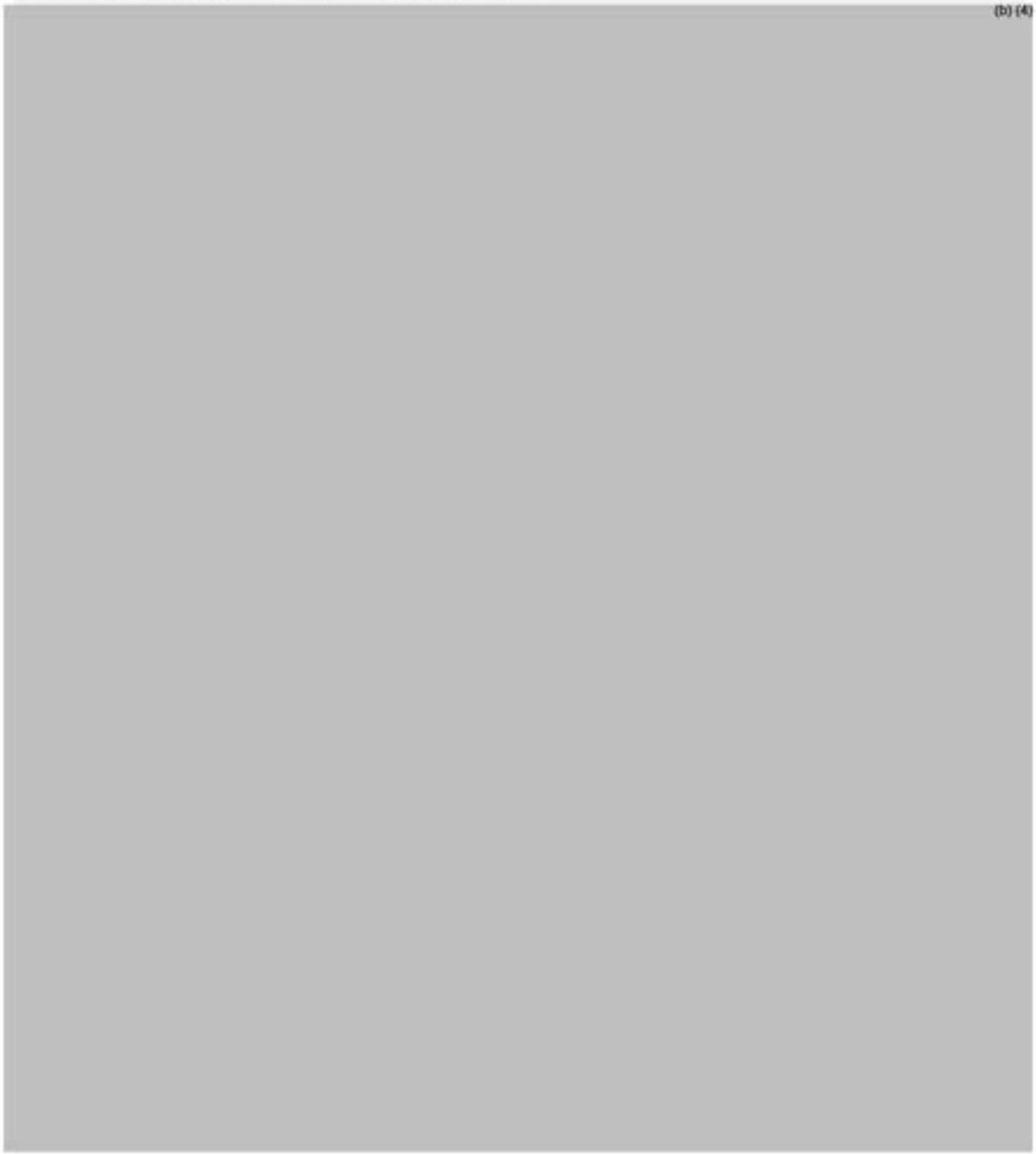
The Applicant did not submit a biowaiver request. There is only one strength (150 mg) of the nirmatrelvir tablet proposed for emergency use authorization and this strength was also used by a majority of the patients (who received 300 mg nirmatrelvir with 100 mg ritonavir twice daily for 5 days) in the pivotal

clinical trial (as well as for primary registration/stability studies). Thus, a biowaiver for additional strengths not studied clinically was not requested nor required.

B. R. REGIONAL INFORMATION

Comparability Protocols – *ADEQUATE*

(b) (4)



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General Note Regarding The Proposed Comparability Protocols:
Also in SN-53, the Applicant agreed to update to the CBE-30 filing category the comparability protocols (b) (4) The Applicant also acknowledged the possibility that the CBE-30 submission may be elevated to a Prior-Approval NDA Supplement based on FDA determination upon submission receipt.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Biopharmaceutics Assessor's Name and Date:
Gerlie Gieser, Ph.D., 02/01/2023

Secondary Assessor Name and Date:
Elsbeth Chikhale, Ph.D., 02/03/2023

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U.S. FDA Center for Drug Evaluation and Research Application number: 217188Orig1s000 Integrated Review

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217188Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	217188
Priority or standard	Priority
Submit date(s)	6/29/2022
Received date(s)	6/29/2022
PDUFA goal date	5/28/2023
Division/office	Division of Antivirals (DAV)
Review completion date	5/24/2023
Established/proper name	nirmatrelvir and ritonavir
(Proposed) proprietary name	PAXLOVID
Pharmacologic class	Nirmatrelvir: SARS-CoV-2 main protease (M^{pro}) inhibitor Ritonavir: HIV-1 protease inhibitor and CYP3A inhibitor
Other product name(s)	PF-07321322 (nirmatrelvir)
Applicant	Pfizer, Inc.
Dosage form(s)/formulation(s)	Co-packaged Tablets
Dosing regimen	300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all 3 tablets taken together twice daily for 5 days
Applicant-proposed indication(s)/ population(s)	Treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults (b) (4) who are at high risk for progression to severe COVID 19, including hospitalization or death.
SNOMED CT code for proposed indication disease term(s)[1]	186747009 | Coronavirus infection (disorder)
Regulatory action	Approval
Approved dosage (if applicable)	300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) with all 3 tablets taken together orally twice daily for 5 days In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), the dosage of PAXLOVID is 150 mg nirmatrelvir (one 150 mg tablet) and 100 mg ritonavir (one 100 mg tablet) with both tablets taken together twice daily for 5 days
Approved indication(s)/ population(s) (if applicable)	PAXLOVID is indicated for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.
SNOMED CT code for approved indication disease term(s)[1]	186747009 | Coronavirus infection (disorder)

[1] For internal tracking purposes only.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; HIV, human immunodeficiency virus; M^{pro}, main protease; NDA, new drug application; PDUFA, Prescription Drug User Fee Act; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BID	twice daily
BLASTN	nucleotide basic local alignment search tool
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CI	confidence interval
CKD	chronic kidney disease
C_{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
COVID	coronavirus disease
COVID-19	coronavirus disease 2019
CS	cleavage site
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug induced liver injury
E-DMC	external data monitoring committee
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
E-R	exposure-response
EUA	emergency use authorization
^{19}F-NMR	fluorine-19 nuclear magnetic resonance
FAS	full analysis set
FDA	Food and Drug Administration
FMQ	FDA medical query
GCP	good clinical practice
GD	gestation day
GLP	good laboratory practice
HIV-1	human immunodeficiency virus
IC_{50}	half maximal inhibitory concentration
ICH	International Council for Harmonisation
ICU	intensive care unit
IND	investigational new drug
ITT	intent-to-treat
LLN	lower limit of normal
LLOQ	lower limit of quantification
MA	mouse adapted
MAD	multiple ascending dose

MedDRA	Medical Dictionary for Regulatory Activities
MHV	mouse hepatitis virus
mITT	modified intent-to-treat
M^{pro}	main protease
NCT	national clinical trial
NDA	new drug application
NGS	next-generation sequencing
NIH	National Institutes of Health
NIR	nirmatrelvir
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NP	nasopharyngeal
OSE	Office of Surveillance and Epidemiology
PD	pharmacodynamic
PI	principal investigator
PIN	personal identification number
PK	pharmacokinetic
PMC	postmarketing commitment
PMR	postmarketing requirement
PO	orally
PP	per-protocol
PT	prothrombin time
QSP	quantitative systems pharmacology
RT-PCR	real-time, reverse transcription-polymerase chain reaction
RWE	real-world evidence
SAE	serious adverse event
SAF	safety analysis set
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TEAE	treatment-emergent adverse event
TES	treatment-emergent substitution
ULN	upper limit of normal
VL	viral load

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I. Executive Summary

1. Summary of Regulatory Action

This new drug application (NDA) for oral nirmatrelvir tablets co-packaged with ritonavir tablets (PAXLOVID) was submitted by Pfizer, Inc and was reviewed by the Food and Drug Administration (FDA) interdisciplinary team. Nirmatrelvir is a first-in-class peptidomimetic inhibitor of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) main protease (M^{pro}). Ritonavir is a human immunodeficiency virus (HIV-1) protease inhibitor but is not active against SARS-CoV-2 M^{pro}. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir. The intended indication for PAXLOVID is for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.

The Applicant submitted an original investigational new drug (IND) in December 2020, for treatment of COVID-19; fast track designation was granted in February 2022. The FDA issued an emergency use authorization (EUA) for PAXLOVID on December 22, 2021, for the treatment of mild-to-moderate COVID-19 in certain adults and pediatric patients 12 years of age and older weighing at least 40 kg who are at high risk for progression to severe COVID-19, including hospitalization and death.

This NDA received a priority review and was presented at the Antimicrobial Drugs Advisory Committee Meeting on March 16, 2023 to discuss whether the available data support a favorable benefit-risk assessment for the use of PAXLOVID for the intended indication. An overwhelming majority of the committee members agreed that the overall benefit-risk assessment is favorable for PAXLOVID when used for the proposed indication.

Each discipline (clinical, clinical virology, clinical pharmacology, pharmacology/toxicology, statistics, chemistry, and regulatory) did not identify any issues that preclude approval. I, the signatory authority for this application, concur with the approval recommendation. Please refer to the Approval Letter for further details.

The Applicant has conducted one pivotal clinical trial in adults who are at high risk for progression to severe COVID-19, EPIC-HR, to support the proposed indication. Additionally, data are available from two supporting clinical trials: EPIC-SR, which evaluated PAXLOVID for the treatment of mild-to-moderate COVID-19 in subjects with no risk factors for progression to severe disease or subjects fully vaccinated against COVID-19 (i.e., completed a primary vaccination series) with at least one of the risk factors for progression to severe disease, and EPIC-PEP, which evaluated PAXLOVID used as post-exposure prophylaxis in adult household contacts of an individual with symptomatic COVID-19.

The PAXLOVID proposed dosage is 300 mg nirmatrelvir with ritonavir 100 mg orally (PO) twice daily for 5 days. The PAXLOVID 300 mg nirmatrelvir with ritonavir 100 mg twice daily for 5 days dosage was studied in the EPIC-HR, EPIC-SR, and EPIC-PEP clinical trials. EPIC-PEP also studied PAXLOVID for 10 days. In patients with moderate renal impairment (defined

as an estimated eGFR ≥30 to <60 mL/min), the proposed PAXLOVID dosage is 150 mg nirmatrelvir with 100 mg ritonavir PO twice daily for 5 days.

Pediatric patients 12 years of age and older weighing at least 40 kg were included in the EUA because the adult dosing regimen was anticipated to be appropriate for this population based on population pharmacokinetic (PK) modeling, and this met the distinct regulatory criteria for an EUA despite the lack of pediatric clinical data. However, to determine the optimal dose in the pediatric population, more data are needed from the ongoing clinical trial EPIC-PEDS, which is evaluating PAXLOVID for the treatment of mild-to-moderate COVID-19 in high-risk pediatric subjects. (b) (4)

The available efficacy data from the clinical trials demonstrate that PAXLOVID is effective for its intended use. In the pivotal trial EPIC-HR in unvaccinated high-risk adults with mild-to-moderate COVID-19, PAXLOVID, when administered within 5 days of symptom onset, demonstrated a 5.6% absolute reduction and an 86% relative reduction, compared to placebo, for the primary endpoint of COVID-19 related hospitalization of or death from any cause through Day 28. Additional nonclinical, clinical, and clinical virology data analyses support that PAXLOVID continues to reduce the risk of COVID-19 related hospitalization or death from any cause through Day 28 in high-risk adults with mild-to-moderate COVID-19 regardless of baseline SARS-CoV-2 immunity or the infecting SARS-CoV-2 variant. The available safety data from the clinical trials demonstrate that PAXLOVID is safe for its intended use. I concur that the risks identified in the review of the clinical trial data can be mitigated through labeling and further evaluated during routine pharmacovigilance. The key safety concern with PAXLOVID is the risk of serious adverse reactions due to drug-drug interactions (DDIs) which will be described appropriately in labeling. A Boxed Warning has been included to ensure that prescribers are aware of this important risk.

Based upon review of all available efficacy and safety data, the benefits of PAXLOVID outweigh the risks for the treatment of mild-to-moderate COVID-19 in adults at high risk for progression to severe disease. The availability of PAXLOVID will provide a new, effective, and convenient outpatient COVID-19 treatment option for this patient population. For detailed information supporting the basis for the benefit-risk assessment please refer to the details in this Integrated Assessment document.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• COVID-19 is the disease caused by infection with SARS-CoV-2. Disease severity ranges widely, from mild to critical illness, and SARS-CoV-2 can also cause asymptomatic infection. • From when SARS-CoV-2 was first identified in late 2019 through April 2023, the CDC estimates there have been over 104 million COVID-19 cases and over 1.1 million COVID-19 deaths in the United States (CDC 2023a). While the weekly incidence of both COVID-19 cases and deaths have decreased substantially from their prior peaks of approximately 5.5 million cases and 23,000 deaths (from January 2022 and January 2021, respectively), there were still an average of 162,000 cases and 2,000 deaths per week in March 2023. • Risk factors for progression to severe COVID-19, including hospitalization and death, include age (with substantially increased risk at ages >65 years) and presence of one or more of certain underlying medical conditions (e.g., obesity, immunosuppressive conditions, chronic lung disease, cardiovascular disease, diabetes, cancer, chronic kidney disease, pregnancy). • COVID-19 vaccination status, and immunity from prior SARS-CoV-2 infection, also impact the risk for progression to severe COVID-19. • Circulating SARS-CoV-2 variants and subvariants have continously evolved, and the specific SARS-CoV-2 variant or subvariant can impact disease severity as well as the protection conferred by prior COVID-19 vaccination and/or prior SARS-CoV-2 infection.	• COVID-19 is a serious and potentially life-threatening illness which can result in pneumonia, respiratory failure, multiorgan failure, and death. While the incidence of COVID-19 cases and COVID-19-associated deaths have decreased substantially since earlier in the pandemic, likely in relation to increased population immunity from COVID-19 vaccination or prior infection, there were still an average of approximately 162,000 COVID-19 cases and 2,000 COVID-19-associated deaths per week in the United States in March 2023.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	• Remdesivir, administered by intravenous infusion daily for 3 days, is the only FDA-approved therapy currently available for the treatment of mild-to-moderate COVID-19 in individuals who are at high risk for progression to severe disease. – It may be logistically challenging for individuals with mild-to-moderate COVID-19 to find an accessible infusion center or other facility that can administer an intravenous infusion daily for 3 days, particularly as remdesivir treatment should be initiated within 7 days of symptom onset. • Two additional products are currently authorized under an EUA for the treatment of mild-to-moderate COVID-19 in certain individuals at high risk for progression to severe disease, though neither of these products are FDA-approved. These two products are the oral drugs PAXLOVID (the product being evaluated in this NDA application) and molnupiravir. The National Institutes of Health guidelines panel currently recommends only using molnupiravir when PAXLOVID and remdesivir are not available, feasible to use, or clinically appropriate (NIH 2022c). • Anti-SARS-CoV-2 therapeutic monoclonal antibodies (mAbs) were previously available under EUA for the treatment of mild-to-moderate COVID-19 in certain individuals at high risk for progression to severe disease. However, no anti-SARS-CoV-2 mAbs are currently authorized for emergency use for COVID-19 treatment because of nonsusceptibility to the currently circulating SARS-CoV-2 Omicron subvariants.	• There is an unmet medical need for safe, effective, and convenient outpatient COVID-19 treatment options, particularly ones with a target that is anticipated to be conserved across the different SARS-CoV-2 variants and subvariants.
Benefit	• The efficacy of PAXLOVID was assessed in three Phase 2/3 clinical trials. – The pivotal trial, EPIC-HR, was a randomized, double-blind, global trial in which non-hospitalized adults who were unvaccinated for COVID-19 and at high risk for progression to severe disease were randomized to receive 5 days of PAXLOVID versus placebo for the treatment of mild-to-moderate COVID-19. ▪ Treatment with PAXLOVID demonstrated a 5.6% (95% CI: -7.3% to -4.0%; p<0.0001) absolute reduction, or 86% (95% CI: 72%, 93%) relative reduction, compared to placebo, for the primary efficacy endpoint of COVID-19 related hospitalization or death from any cause through Day 28 in the mITT1 population (subjects who were dosed within 5 days of symptom onset and who at baseline did not receive nor were expected to receive COVID-19 therapuetic mAb treatment).	• Approval of PAXLOVID would provide an effective oral treatment option for mild-to-moderate COVID-19 in adults at high risk for progression to severe disease. – PAXLOVID demonstrated overwhelming efficacy in EPIC-HR (p<0.0001) in reducing COVID-19 related hospitalization or death from any cause in unvaccinated adults with mild-to-moderate COVID-19. – While pre-existing SARS-CoV-2 immunity, either from vaccination or prior infection, is among the factors that impact the risk of progression to severe COVID-19, EPIC-HR and EPIC-SR clinical trial results support the efficacy of PAXLOVID for

	▪ Similar trends for the COVID-19 related hospitalization and death endpoint were observed across subject subgroups. ▪ Among subjects who were SARS-CoV-2 seropositive at baseline, 1/490 (0.2%) PAXLOVID recipients versus 8/479 (1.7%) placebo recipients met the primary endpoint of COVID-19 related hospitalization or death from any cause through Day 28 [reduction relative to placebo -1.47% (-2.70%, -0.25%)]. – EPIC-SR was a randomized, double-blind, global trial in which non-hospitalized adults who were either vaccinated against COVID-19 and at high risk for progression to severe disease or unvaccinated with no risk factors for progression to severe disease were randomized to receive 5 days of PAXLOVID versus placebo for the treatment of mild-to-moderate COVID-19. ▪ The trial failed to demonstrate any meaningful difference for the primary efficacy endpoint of time to sustained symptom alleviation through Day 28. ▪ However, a numerically lower rate of COVID-19 related hospitalizations or deaths from any cause through Day 28 was observed in all randomized subjects and in the subgroup of vaccinated high-risk subjects. – EPIC-PEP was a randomized, double-blind, global trial in which adult household contacts of individuals with symptomatic COVID-19 were randomized to receive 10 days of PAXLOVID, 5 days of PAXLOVID followed by 5 days of placebo, or 10 days of placebo for the post-exposure prophylaxis of COVID-19. ▪ The trial failed to demonstrate any meaningful difference for the primary efficacy endpoint of symptomatic SARS-CoV-2 infection through Day 14. • COVID-19 has evolved since the beginning of the COVID-19 pandemic and when the PAXLOVID registrational clinical trials were conducted. Currently in the United States: – The vast majority (>90%) of adults have either received one or more COVID-19 vaccine doses or have previously been infected with SARS-CoV-2. ▪ Although EPIC-HR enrolled unvaccinated adults with no prior confirmed SARS-CoV-2 infection, EPIC-HR and EPIC-SR subgroup analyses indicate that the relative risk reduction with PAXLOVID	the treatment of mild-to-moderate COVID-19 in high-risk adults regardless of COVID-19 vaccination status or evidence of prior SARS-CoV-2 infection. – Although clinical trial data to assess clinical efficacy against the SARS-CoV-2 Omicron variant are limited, based on the available virology data, it is reasonable to conclude that PAXLOVID is likely to retain clinical efficacy in adults with COVID-19 caused by currently circulating SARS-CoV-2 Omicron subvariants, and who are at high risk of progression to severe disease. – Comprehensive analyses conducted by FDA and the Applicant did not identify a clear association between PAXLOVID treatment and COVID-19 rebound. • More data are needed to determine if a longer duration of PAXLOVID dosing may be optimal for the treatment of mild-to-moderate COVID-19 in patients who are moderately or severely immunocompromised. • Additional clinical data are needed in pediatric individuals, individuals with severe renal impairment, pregnant individuals, and lactating individuals in order to determine the appropriate dose and to make an assessment of benefit-risk in these individuals.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	versus placebo for COVID-19 related hospitalization or death from any cause is similar (>50%) in high-risk subjects regardless of prior COVID-19 vaccination or baseline SARS-CoV-2 serostatus. – The Omicron variant is responsible for essentially all SARS-CoV-2 infections. ▪ Clinical trial data to directly determine the clinical efficacy of PAXLOVID in high-risk adults infected with the Omicron variant are limited. • In EPIC-HR, ~99% of subjects were infected with the Delta variant and the Omicron variant was not observed. • In the first half of EPIC-SR (2021), 98% of subjects were infected with the SARS-CoV-2 Delta variant. In the second half of EPIC-SR (2022), 100% of subjects were infected with the SARS-CoV-2 Omicron variant (mostly BA.2 and BA.2.12.1), but high-risk subjects were not enrolled during this time period due to the availability of PAXLOVID through the EUA. ▪ Analyses of nonclinical and clinical virology data demonstrate that PAXLOVID retains antiviral activity against the Omicron variant and major subvariants. In addition, bioinformatics analysis demonstrate that the PAXLOVID target (the SARS-CoV-2 main protease) is highly conserved across SARS-CoV-2 variants. – Different clinical presentations of COVID-19 have become more well known, including persistent SARS-CoV-2 infection in severely immunocompromised individuals and COVID-19 rebound, which is characterized by a relapse of symptoms or SARS-CoV-2 detection after initial recovery. ▪ Less than one percent of subjects in EPIC-HR were classified as having immunosuppression. ▪ In comprehensive post hoc analyses of clinical trial data conducted by FDA and the Applicant, viral RNA rebound and symptom rebound were observed in both PAXLOVID and placebo recipients, and at frequencies that were generally similar in both arms across multiple analyses. • Clinical trials are ongoing in pediatric individuals, individuals with severe renal impairment, pregnant individuals, and lactating individuals.	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and risk management	• Clinical trial safety data are available from over 2400 subjects who received the proposed PAXLOVID dosing regimen (nirmatrelvir 300 mg and ritonavir 100 mg both twice daily for 5 days), plus over 900 subjects who received PAXLOVID for 10 days in EPIC-PEP. • In addition, over 11 million patients worldwide have received PAXLOVID for the treatment of COVID-19 since it was first authorized for emergency use in December 2021, and post-authorization safety reports of AEs after PAXLOVID use were reviewed to detect safety signals outside of the clinical trial setting. • PAXLOVID demonstrated an overall favorable safety profile in the clinical trials. The incidences of AEs were generally similar between treatment groups in EPIC-HR, EPIC-SR, and EPIC-PEP. The incidences of severe AEs, serious AEs, and AEs leading to permanent discontinuation of study drug were similar or higher in the placebo group compared to the PAXLOVID group. No deaths occurred in PAXLOVID-treated subjects. • The most common EPIC-HR treatment-emergent AEs (≥2% incidence) in the PAXLOVID group in the clinical trials were dysgeusia and diarrhea, and these occurred at a higher frequency compared to the placebo group (4.6% and 3.0% versus 0.1% and 1.5%, respectively). These AEs were generally mild in severity. • The most common treatment-emergent AEs observed in EPIC-SR and EPIC-PEP were consistent with those observed in EPIC HR. • In the EPIC-PEP trial, similar safety profiles were observed in the PAXLOVID 5-day and 10-day treatment groups. • Prior COVID-19 vaccination and baseline SARS-CoV-2 serostatus had no discernible impact on the safety of PAXLOVID. • Based on post-authorization safety reports, the following additional adverse reactions have been identified with PAXLOVID use: anaphylaxis, serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson Syndrome), and other hypersensitivity reactions; headache; hypertension; abdominal pain; nausea and vomiting; and malaise. • The key safety concern related to PAXLOVID use is the risk of serious adverse reactions due to DDIs, mainly related to the ritonavir component (ritonavir is a potent CYP3A inhibitor).	• PAXLOVID has an acceptable safety profile for the indicated patient population. • The major adverse reactions identified in the clinical trials were dysgeusia and diarrhea. • The key safety concern with PAXLOVID is the risk of serious adverse reactions due to DDIs: prescribers need to review all medications taken by the patient to assess potential drug-drug interactions with a strong CYP3A inhibitor like PAXLOVID and determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring. In addition, prescribers need to consider the benefit of PAXLOVID treatment in reducing hospitalization and death versus the risk of potential DDIs for an individual patient. The risk of DDIs will be described appropriately in labeling, including a Boxed Warning to ensure that prescribers are aware of this important risk.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	– Because EPIC-HR, EPIC-SR, and EPIC-PEP excluded subjects with current or expected use of any medications that have DDIs with PAXLOVID that may lead to serious AEs, this risk cannot be evaluated through analysis of these clinical trial data. – Based on analyses of post-authorization use of PAXLOVID: ▪ Over 50% of PAXLOVID-eligible patients are on medications with DDIs with PAXLOVID (though the most common medications with DDIs could potentially be managed by holding the drug, adjusting the dose of the drug, or increased monitoring). ▪ The majority of PAXLOVID prescribers are adult primary care practitioners (who may not be experienced in managing ritonavir DDIs). ▪ Serious adverse reactions, including death, have been reported in association with DDIs that are included in the current EUA Fact Sheet for Healthcare Providers. The most commonly reported concomitant medications resulting in serious adverse reactions were calcineurin inhibitors (e.g., tacrolimus, cyclosporine) and calcium channel blockers.	

Abbreviations: AE, adverse event; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; CYP3A, cytochrome P450, family 3, subfamily A; DDI, drug-drug interaction; EUA, emergency use authorization; FDA, Food and Drug Administration; mITT, modified intent to treat; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; U.S., United States

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2.2. Conclusions Regarding Benefit-Risk

COVID-19 is a serious and potentially life-threatening illness that has led to over one million deaths in the United States since SARS-CoV-2, the causative virus, was first identified in late 2019. While the weekly incidence of COVID-19 cases as well as of COVID-19 related deaths have decreased substantially from their peaks due to increased population immunity from COVID-19 vaccines and prior SARS-CoV-2 infection, approximately two thousand COVID-19 related deaths were still reported in the United States each week in March 2023. Currently, the only approved treatment option for outpatients with mild-to-moderate COVID-19 who are at high risk for progression to severe disease is remdesivir, which must be administered by IV infusion daily for three days. Additional effective, convenient, outpatient COVID-19 treatment options are needed.

PAXLOVID, an orally administered antiviral product, has clearly demonstrated clinical benefit for high-risk adults with mild-to-moderate COVID-19. In the pivotal trial EPIC-HR in unvaccinated high-risk adults with mild-to-moderate COVID-19, PAXLOVID, when administered within 5 days of symptom onset, demonstrated a 5.6% absolute reduction and an 86% relative reduction, compared to placebo, for the primary endpoint of COVID-19 related hospitalization or death from any cause through Day 28. This risk reduction was highly statistically significant and was consistent across subgroups. While the COVID-19 pandemic has evolved since the conduct of EPIC-HR, with most adults now having some baseline SARS-CoV-2 immunity from vaccination or prior infection and with evolving SARS-CoV-2 variants, available data continue to support that PAXLOVID reduces the risk of COVID-19 related hospitalization or death from any cause through Day 28 in high-risk adults with mild-to-moderate COVID-19 regardless of baseline SARS-CoV-2 immunity or the infecting SARS-CoV-2 variant. Furthermore, comprehensive analyses did not identify an association between PAXLOVID treatment and COVID-19 rebound, a concern that was raised with use of PAXLOVID under emergency authorization.

The safety database for PAXLOVID is adequate for the proposed indication, dosing regimen, and population. Overall, PAXLOVID has a favorable safety profile: adverse reactions associated with PAXLOVID use identified in clinical trials were dysgeusia and diarrhea, which were generally infrequent and mild in severity. The key safety concern with PAXLOVID relates to the risk of serious adverse reactions due to drug-drug interactions (DDIs), mainly related to the ritonavir component (ritonavir is a potent CYP3A inhibitor). The risk of DDIs will be described appropriately in labeling, including a Boxed Warning to ensure that prescribers are aware of this important risk.

The overall benefit-risk profile for PAXLOVID is favorable to support an indication for the treatment of mild-to-moderate COVID-19 in adults at high risk for progression to severe disease. Areas of uncertainty include if a longer duration of PAXLOVID dosing may be optimal for the treatment of mild-to-moderate COVID-19 in patients who are moderately or severely immunocompromised, along with the appropriate dose and data to inform benefit-risk assessment in pediatric individuals, individuals with severe renal impairment, pregnant individuals, and lactating individuals. In our decision to approve PAXLOVID, we considered the available safety and efficacy data, the recommendation for approval by all review disciplines, and the Antimicrobial Drugs Advisory Committee vote where the majority (94%) of the

committee members agreed that the overall benefit-risk assessment is favorable for PAXLOVID when used for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. The availability of PAXLOVID will provide a new, effective, and convenient outpatient COVID-19 treatment option for this patient population.

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II. Interdisciplinary Assessment

3. Introduction

Background of the Condition/Standard of Clinical Care

Coronavirus disease 2019 (COVID-19) is a serious and potentially life-threatening illness which can result in pneumonia, multiorgan failure, respiratory failure, and death. Through April 7, 2023, the Centers for Disease Control and Prevention (CDC) estimates there have been over 104 million COVID-19 cases and over 1.1 million COVID-19 deaths in the United States. While the weekly incidence of both COVID-19 cases and deaths have decreased substantially from their prior peaks of approximately 5.5 million cases and 23,000 deaths (from January 2022 and January 2021, respectively), there were still an average of approximately 162,000 cases and 2,000 deaths per week in March 2023 (CDC 2023a). Patients with COVID-19 can experience a wide range of clinical manifestations. Mild illness is defined by the presence of symptoms without shortness of breath or abnormal chest imaging. Moderate illness is defined as the presence of symptoms and evidence of lower respiratory tract disease by clinical examination or chest imaging accompanied by oxygen saturation ≥94% on room air. Severe illness is defined as an oxygen saturation <94% on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen of <300 mmHg, a respiratory rate >30 breaths/minute, or lung infiltrates >50%. Critical illness is defined as individuals who have respiratory failure, septic shock, and/or multiorgan dysfunction (May 2020; NIH 2022a).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants have emerged over time and continue to emerge. By late January 2022, it was estimated that the Omicron variant was responsible for more than 99% of SARS-CoV-2 infections in the United States (Lambrou et al. 2022). The Omicron variant and its numerous subvariants have been noted to have substantial evasion of neutralizing antibodies (Willett et al. 2022) and may be more transmissible when compared with previous variants of concern (Baker et al. 2022); however, the risk of severe disease or death may be lower (Adjei et al. 2022).

To date, remdesivir is the only Food and Drug Administration (FDA) approved therapy for the treatment of mild-to-moderate COVID-19 in non-hospitalized adults who are at high risk for progression to severe disease (Gilead Sciences 2020). Remdesivir, administered by intravenous infusion for 3 days, is a nucleotide prodrug of an adenosine analog and binds to the viral RNA-dependent RNA polymerase/template complex and inhibits viral replication by terminating RNA transcription prematurely (NIH 2022d). Remdesivir retains antiviral activity in cell-based assays against the Omicron variant and its subvariants (NIH 2022d).

In December 2021, the FDA issued an emergency use authorization (EUA) for molnupiravir for the treatment of adults with mild to moderate COVID-19 who are within 5 days of symptom onset, who are at high risk of progressing to severe disease, and for whom alternative antiviral therapies are not accessible or clinically appropriate. Molnupiravir is the oral prodrug of N4-hydroxycytidine, a ribonucleoside which, after phosphorylation to the active triphosphate, incorporates into viral RNA by viral RNA-dependent RNA-polymerases resulting in an accumulation of errors in the viral genome leading to inhibition of replication (known as viral

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error catastrophe or viral lethal mutagenesis) (NIH 2022c).The National Institutes of Health guidelines panel currently recommends only using molnupiravir when PAXLOVID and remdesivir are not available, feasible to use, or clinically appropriate (NIH 2022c).

Anti-SARS-CoV-2 therapeutic monoclonal antibodies (mAbs) have previously shown clinical benefit in treating COVID-19; however, laboratory studies have found that the activity of anti-SARS-CoV-2 mAbs against specific variants and subvariants can vary dramatically (NIH 2022b). By the end of January 2023, FDA had made determinations, based on the terms and conditions of each respective EUA, that have resulted in all of the mAb therapies not being authorized in the United States until further notice by the Agency. FDA made such determinations based on the variant susceptibility to the particular therapeutic and CDC variant frequency data.

Pertinent Drug Development and Regulatory History

PAXLOVID is oral nirmatrelvir tablets co-packaged with ritonavir tablets. Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (M^{pro}). Inhibition of SARS-CoV-2 M^{pro} renders it incapable of processing polyprotein precursors, preventing viral replication. Ritonavir is a human immunodeficiency virus (HIV-1) protease inhibitor but is not active against SARS-CoV-2 M^{pro}. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir.

The Applicant has submitted a new drug application (NDA) seeking approval of PAXLOVID for the proposed indication of treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. The PAXLOVID proposed dosage is 300 mg nirmatrelvir with ritonavir 100 mg orally (PO) twice daily (BID) for 5 days. In patients with moderate renal impairment (defined as an eGFR ≥30 to <60 mL/min), the proposed PAXLOVID dosage is 150 mg nirmatrelvir with 100 mg ritonavir PO twice daily for 5 days.

To support the proposed indication, the Applicant has conducted one pivotal clinical trial in adults who are at high risk for progression to severe COVID-19, EPIC-HR, to support the proposed indication. Additionally, data are available from two supporting clinical trials: EPIC-SR, which evaluated PAXLOVID for the treatment of mild-to-moderate COVID-19 in subjects who were either fully vaccinated or who had no risk factors for progression to severe COVID-19, and EPIC-PEP, which evaluated PAXLOVID used as post-exposure prophylaxis in adult household contacts of an individual with symptomatic COVID-19.

The Applicant previously submitted an original investigational new drug (IND) in December 2020, for treatment of COVID-19, fast track designation was granted in February 2022. The FDA issued an EUA for PAXLOVID on December 22, 2021, for the treatment of mild-to-moderate COVID-19 in certain adults and pediatric patients 12 years of age and older weighing at least 40 kg who are at high risk for progression to severe COVID-19, including hospitalization and death. The EUA dosing regimen was primarily supported by adult interim data from EPIC-HR, in which PAXLOVID was generally safe and well-tolerated and reduced the risk of COVID-19 related hospitalization or death from any cause through Day 28. Please refer to Section 12 for complete regulatory history.

- Pediatric patients 12 years of age and older weighing at least 40 kg were included in the EUA because the adult dosing regimen was anticipated to be appropriate for this population based

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on population pharmacokinetic (PK) modeling, and this met the distinct regulatory criteria for an EUA despite the lack of pediatric clinical data. However, to determine the optimal dose in the pediatric population, more data are needed from the ongoing clinical trial EPIC-PEDS, which is evaluating PAXLOVID for the treatment of mild-to-moderate COVID-19 in high-risk pediatric subjects.

This NDA was given priority review; the Prescription Drug User Fee Act (PDUFA) goal date was extended by three months due to a major amendment based on submissions received on November 23 and December 5, 2022. These submissions contained extensive key efficacy, safety, and virology reanalyses following removal of select clinical trial sites due to data reliability and good clinical practice (GCP) noncompliance issues (see Section 6.3.1).

An Advisory Committee meeting was held on March 16, 2023 to discuss whether the available data support a favorable benefit-risk assessment for the use of PAXLOVID for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. A majority (94%) of the committee members agreed that the overall benefit-risk assessment is favorable for PAXLOVID when used for the proposed indication. Please refer to Section 11 for further Advisory Committee meeting information.

The review team identified several key review issues that had a significant impact on the overall regulatory assessment of PAXLOVID as outlined in Section 3.1. In-depth analyses of these efficacy and safety review issues can be found in Section 6.3 and Section 7.7 respectively.

3.1. Review Issue List

The review team identified seven key review issues relevant to the evaluation of benefit (Section 6.3) and one key review issue relevant to the evaluation of risk (Section 7.7).

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

3.1.1.1. Data Reliability Issues at Specific Clinical Trial Sites

- The review team identified unusual patterns of viral RNA shedding levels, viral sequencing results, and/or daily clinical symptom reporting times from subjects enrolled at selected study sites in EPIC-HR and EPIC-SR. These observations triggered additional site inspections and in-depth investigations of all study data and sites from EPIC-HR and EPIC-SR to determine if there were data reliability issues.

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3.1.1.2. Efficacy in High-Risk Adults Who Are Vaccinated Against COVID-19 or Previously Infected With SARS-CoV-2

- The pivotal trial, EPIC-HR, only enrolled subjects without prior SARS-CoV-2 vaccination and without prior confirmed SARS-CoV-2 infection.
- Currently, an overwhelming majority of the U.S. population has either received one or more COVID-19 vaccine doses, or previously been infected with SARS-CoV-2.

3.1.1.3. Efficacy of PAXLOVID in the Setting of the SARS-CoV-2 Omicron Variant

- The clinical trial data from EPIC-HR and from EPIC-SR (through the December 19, 2021 data cutoff) were from a time before the emergence of the SARS-CoV-2 Omicron variant, which currently accounts for essentially all SARS-CoV-2 infections in the United States.

3.1.1.4. Efficacy in High-Risk Patients With Mild Disease

- EPIC-HR and EPIC-SR enrolled subjects with mild to moderate COVID-19, but per the protocols subjects were not further classified as to whether their COVID-19 was mild versus moderate.
- Since the EUA of PAXLOVID in December 2021, there have been several articles questioning whether PAXLOVID should be taken by patients who are only mildly ill.

3.1.1.5. Optimal Duration of PAXLOVID Treatment in Immunocompromised Patients

- The Phase 3 treatment trials evaluated a 5-day duration of PAXLOVID treatment, but less than 1 percent of subjects enrolled in EPIC-HR were classified as having immunosuppression.
- Individuals with moderate to severe immunosuppression may take longer than the general population to clear SARS-CoV-2 infection in the absence of treatment, and persistent SARS-CoV-2 infection has been reported in immunocompromised patients.

3.1.1.6. Impact of PAXLOVID on COVID-19 Rebound

- COVID-19 rebound, defined as recurrence of symptoms and/or SARS-CoV-2 RNA detection in upper respiratory tract samples after initial resolution, has been reported in patients after completion of PAXLOVID treatment. Analyses of the EPIC-HR and EPIC-SR data were conducted to assess whether COVID-19 rebound is associated with PAXLOVID use or whether COVID-19 rebound simply reflects the natural history of SARS-CoV-2 infection.

3.1.1.7. Benefit of PAXLOVID for the Prevention of Post-COVID Conditions

- Post- coronavirus disease (COVID) conditions, or long COVID, have been described after resolution of the acute SARS-CoV-2 infection.

3.1.2. Key Review Issues Relevant to Evaluation of Risk

3.1.2.1. Serious Adverse Reactions Due to Drug-Drug Interactions (DDIs)

- PAXLOVID contains ritonavir, a potent CYP3A inhibitor, that can result in significant elevations of concomitant medications that are metabolized by the CYP3A isoenzyme.
- EPIC-HR and EPIC-SR excluded subjects with current or expected use of any medications that have DDIs with PAXLOVID that may lead to serious adverse reactions.
- Data from the use of PAXLOVID under EUA were evaluated to assess the risk of serious adverse reactions due to DDIs.

3.2. Approach to the Clinical Review

Table 3 provides an overview of the clinical trials conducted to support the benefit-risk assessment of PAXLOVID. Data from the Phase 2/3 trial EPIC-HR provide the primary basis of efficacy and safety of PAXLOVID for treatment in patients with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death. Results from the Phase 2/3 trials EPIC-SR (non-hospitalized adults with mild-to-moderate COVID-19 who were either unvaccinated with no risk factors for progression to severe disease or were vaccinated against COVID-19 and at high risk for severe disease) and EPIC-PEP (prevention of symptomatic SARS-CoV-2 infection in adult household contacts of individuals with COVID-19) provide supportive safety and efficacy data.

Phase 1 trials, data from the Safety Update Report, and post-authorization reports of adverse events (AEs) after PAXLOVID use under the EUA were also reviewed to provide additional safety experience.

Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for PAXLOVID

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen[2] (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[3]	Number of Centers and Countries[3]
EPIC-HR (C4671005) [NCT04960202]	Non-hospitalized symptomatic adult subjects with COVID-19 who are at increased risk of progressing to severe illness.	Control type: PC Randomization: Randomized 1:1 Blinding: DB Biomarkers: None Innovative design features: None	Drug: PAXLOVID (300 mg nirmatrelvir/ 100 mg ritonavir) administered orally Dosage: PAXLOVID every 12 hours (N=1038); placebo (N=1053) Number treated: 2091 Duration: 5 days	Primary: • Proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28 in all subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were dosed to receive COVID-19 therapeutic mAb treatment and were treated ≤3 days of COVID-19 symptom onset. Key Secondary: • Proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28 in all subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were dosed to receive COVID-19 therapeutic mAb treatment and were treated ≤5 days of COVID-19 symptom onset. • Time to sustained alleviation of in all targeted signs/symptoms through Day 28 in all subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were dosed to receive COVID-19 therapeutic mAb treatment and were treated ≤3 days of COVID-19 symptom onset.	Planned:3000 Actual: 2113	Centers: 189 Countries: 19

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen[2] (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[3]	Number of Centers and Countries[3]
EPIC-SR (C4671002) [NCT0501151]	Adult outpatients with COVID-19 who are fully vaccinated and have at least one risk factor for progression to severe disease or who are unvaccinated and have no risk factors for progression to severe disease.	Control type: PC Randomization: Randomized 1:1 Blinding: DB Biomarkers: None Innovative design features: None	Drug: PAXLOVID (300 mg nirmatrelvir/ 100 mg ritonavir) administered orally Dosage: PAXLOVID every 12 hours (N=540); placebo (N=528) Number treated: 1068 Duration: 5 days	Primary: • Time to sustained alleviation of all COVID-19 signs/symptoms through Day 28 in all subjects randomly assigned to study intervention, who took at least 1 dose of study intervention and were dosed within ≤3 days of COVID-19 symptom onset. Key Secondary: • Time to sustained alleviation of all COVID-19 signs/symptoms through Day 28 in all subjects randomly assigned to study intervention who took at least 1 dose of study intervention. • Proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28 in all subjects randomly assigned to study intervention who took at least 1 dose of study intervention.	Planned:1140 (extended to 1980 for 2022 enrollment) Actual: 1075 (data cutoff December 19, 2021)	Centers: 171 Countries: 16

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen[2] (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[3]	Number of Centers and Countries[3]
EPIC-PEP (C4671006) [NCT05047601]	Asymptomatic adults with a negative screening SARS-CoV-2 rapid antigen test and who were exposed to household contacts who were symptomatic with confirmed COVID-19	Control type: PC Randomization: Randomized 1:1:1 Blinding: DB Biomarkers: None Innovative design features: None	Drug: PAXLOVID (300 mg nirmatrelvir/ 100 mg ritonavir) administered orally Dosage: PAXLOVID every 12 hours, 5 days (N=912); PAXLOVID every 12 hours, 10 days (N=911); placebo (N=898) Number treated: 2721 Duration: 5 or 10 days	Primary: • Proportion of subjects who develop a symptomatic, RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14 among subjects who have a negative RT-PCR result at baseline. Key Secondary: • The proportion of subjects with symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 in adult subjects who have a negative RT-PCR result at baseline and who are at increased risk of severe COVID-19.	Planned:2880 Actual: 2736	Centers:147 Countries:17

Source: Clinical study report and adsl.xpt for each trial.
[1.] Includes all submitted clinical trials, even if not reviewed in-depth, except for Phase 1 and pharmacokinetic studies.
[2.] Number of subjects treated based on the safety population
[3.] Based on the full analysis set, excluding subjects from sites with data reliability issues
Abbreviations: BID, twice daily; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; DB, double-blind; LTE, long-term extension; MC, multicenter; N, number of subjects in treatment group; NCT, national clinical trial; OL, open-label; PC, placebo-controlled; PG, parallel group; R, randomized; RAT, rapid antigen test; RT-PCR, real-time, reverse transcription-polymerase chain reaction; h, hour; d, day; wk, week(s); mo, month(s); y, year(s)

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4. Patient Experience Data

The protocol included collection of patient-reported outcomes using three instruments to measure the impact of PAXLOVID: Global Impression Questions, Work Productivity and Activity Impairment Questionnaire, and Euroquol Quality of Life 5-Dimension 3-Level Scale. However, these data were not submitted. The Applicant also captured symptom data in the clinical trials.

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical Outcome Assessment Data Submitted in the Application		
☒	Patient-reported outcome	• EPIC-HR: Symptom Diary related efficacy endpoints (Section 6.2.1.3) • EPIC-SR: Primary efficacy endpoint (Section 6.2.2.3) • Review issues: COVID-19 rebound (Section 6.3.6), post-COVID conditions (Section 6.3.7)
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2

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5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

Mechanism of Action

- Nirmatrelvir (NIR) is an oral peptidomimetic inhibitor of the SARS-CoV-2 M^{pro}, also referred to as 3C-like protease ($3CL^{pro}$) or nonstructural protein 5 (nsp5). NIR inhibits M^{pro} by binding directly to the M^{pro} active site, forming a covalent bond with the catalytic residue (C145) and non-covalent interactions with ten other residues. M^{pro} inhibition prevents proteolytic processing of the viral polyproteins pp1a/pp1ab, a critical early step in the viral replication cycle. The mechanism of action of nirmatrelvir as a SARS-CoV-2 M^{pro} inhibitor is supported by data from biochemical, cell culture, and animal studies.

Summary of Data Reviewed for Nonclinical Virology-Related Studies

- Key results and conclusions from nonclinical virology-related studies are summarized in the following text. Additional details are provided in Sections 18 and 20.

Mechanism of Action and Cell Culture Antiviral Activity Studies

- In biochemical assays, nirmatrelvir inhibited the activity of recombinant SARS-CoV-2 (Wuhan-Hu-1) M^{pro} enzyme with an IC_{50} value of 19.2 nM and a K_i value of 3.1 nM. Nirmatrelvir also inhibited recombinant M^{pro} enzymes from other human coronaviruses (SARS-CoV-1, MERS-CoV, HCoV-OC43, HCoV-HKU1, HCoV-229E, and HCoV-NL63), with IC_{50} values ranging from 28.9 to 479 nM.
- Using X-ray crystallography, nirmatrelvir was shown to bind directly to the active site of recombinant SARS-CoV-2 (Wuhan-Hu-1) M^{pro}. In the cocrystal structure, nirmatrelvir was covalently bound to the catalytic amino acid residue C145 and formed non-covalent interactions with ten other residues: H41, M49, F140, G143, H163, H164, M165, E166, L167, and P168. Twelve additional residues were located within 5 Å but did not directly contact nirmatrelvir: Y54, L141, N142, S144, H172, V186, D187, R188, Q189, T190, A191, and Q192.
- The 23 SARS-CoV-2 M^{pro} residues that directly interacted with nirmatrelvir or were located in close proximity (<5 Å) of nirmatrelvir were found to be highly conserved in the GISAID EpiCov sequence database (~12.7 million sequences; accessed November 30, 2022), with polymorphism frequencies ≤0.1%.
- In cell culture, nirmatrelvir had activity against SARS-CoV-2 in differentiated normal human bronchial epithelial (dNHBE, EC_{50} value: 32.6-61.8 nM [16.3-30.9 ng/mL]), A549-ACE2 (EC_{50} value: 77.9 nM), and Vero E6 (EC_{50} value: 4,480 nM) cells. Nirmatrelvir activity was weaker in Vero E6 cells due to high levels of P-glycoprotein (P-gp) expression in this cell line. In the presence of a P-gp inhibitor (CP-100356), nirmatrelvir had a ~60-fold lower EC_{50} value of 74.5 nM in Vero E6 cells, comparable to the EC_{50} values observed in other cell

types. The lower level of P-gp expression in A549-ACE2 and dNHBE cells, which are both of respiratory tissue origin, is considered more relevant and predictive of P-gp expression in key tissue sites of SARS-CoV-2 infection, relative to Vero E6 cells (African green monkey kidney cell line).

- Nirmatrelvir retained activity (≤3-fold change in EC_{50} value relative to WA1/2020) against 15 SARS-CoV-2 variants in cell culture: Alpha/B.1.1.7, Gamma/P.1, Delta/B.1.617.2, Lambda/C.37, Mu/B.1.621, and Omicron BA.1, BA.2, BA.2.12.1, BA.4, BA.4.6, BA.5, BF.7, BQ.1, BQ.1.11, and XBB.1.5. Nirmatrelvir had reduced activity (3.0-4.4-fold change in EC_{50} value) against Beta/B.1.351 in some assays but not in other assays. These experiments were performed in Vero E6 P-gp knockout cells, Vero E6-TMPRSS2 cells treated with a P-gp inhibitor, or HeLa-ACE2 cells.
- Nirmatrelvir also had activity against SARS-CoV-1 in Vero E6 cells (EC_{50} value: 151 nM with a P-gp inhibitor), MERS-CoV in Vero 81 cells (EC_{50} value: 166 nM with a P-gp inhibitor), and HCoV-229E in MRC-5 cells (EC_{50} value: 190 nM). Thus, nirmatrelvir appears to have broad anti-CoV activity. Nirmatrelvir did not have activity against enterovirus 71 or human rhinovirus 1B, which encode 3C proteases structurally related to M^{pro}. These results indicate that the antiviral activity of nirmatrelvir is likely restricted to coronaviruses.
- Ritonavir, an HIV-1 protease inhibitor and pharmacokinetic enhancer, did not have activity against SARS-CoV-2 in cell culture (tested up to 3,000 nM). In addition, ritonavir did not significantly antagonize the activity of nirmatrelvir against SARS-CoV-2 in cell culture.
- Nirmatrelvir was 69%, 57%, or 52% bound to plasma protein from humans, cynomolgus monkeys, or rats, respectively, across a range of drug concentrations, as measured by equilibrium dialysis. The Applicant selected a nirmatrelvir target plasma exposure (C_{min}) of 585 nM (292 ng/mL) for clinical studies, which is equivalent to the unbound EC_{90} value against SARS-CoV-2 in dNHBE cells (181 nM [90 ng/mL]).

Assessments of Cytotoxicity and Off-Target Activity

- Nirmatrelvir had low cytotoxicity in A549-ACE2 (CC_{50} value >3 μM), Vero E6 (CC_{50} value >100 μM with or without a P-gp inhibitor), Vero 81 (CC_{50} value >100 μM with a P-gp inhibitor), and MRC-5 (CC_{50} value >100 μM) cells used in antiviral activity studies, with favorable selectivity indices (CC_{50} values/EC_{50} values) against SARS-CoV-2 of >38.5 to >1,250 across different experiments.
- In biochemical assays, nirmatrelvir did not inhibit 8 mammalian proteases (IC_{50} values >100 μM or >10 μM), including 3 cysteine proteases. In addition, nirmatrelvir did not inhibit HIV-1 protease (IC_{50} value >100 μM). These results indicate that the activity of nirmatrelvir is selective for M^{pro}.

Resistance Development and Cross-Resistance

- In biochemical assays, nirmatrelvir activity against recombinant SARS-CoV-2 M^{pro} was significantly reduced (≥3-fold higher K_i value) by 19/101 of the single substitutions tested: Y54A (25-fold), F140A/L/S (7.6-260-fold), G143S (3.6-fold), S144A/E/T (46-480-fold), H164N (6.7-fold), E166A/G/V (6.2-7,700-fold), H172Y (250-fold), A173S/V (4.1-16-fold), R188G (38-fold), Q192L/P (6.8-29-fold), and V297A (3.0-fold). In addition, nirmatrelvir

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activity was significantly reduced by 15/22 of the substitution combinations tested: T21I+L50F+A193P+S301P (7.3-fold), T21I+S144A (20-fold), T21I+S144A+T304I (51-fold), T21I+C160F+A173V+V186A+ T304I (28-fold), T21I+E166V (11,000-fold), T21I+A173V (15-fold), T21I+A173V+T304I (55-fold), L50F+F140L+L167F+T304I (190-fold), L50F+E166A+L167F (210-fold), L50F+E166V (4,500-fold), E55L+S144A (56-fold), T135I+T304I (5.1-fold), F140L+A173V (95-fold), H172Y+P252L (180-fold), and A173V+T304I (28-fold). In most of these combinations, the primary M^{pro} substitution(s) responsible for the reduced activity of nirmatrelvir appeared to be F140L, S144A, E166A/V, H172Y, and A173V.

- In cell culture, resistance selection experiments were first conducted with mouse hepatitis virus (MHV), a betacoronavirus used as a surrogate for SARS-CoV-2. Nirmatrelvir inhibited MHV replication in L929 cells with EC_{50} values of 847 and 395 nM in the absence and presence of P-gp inhibitor, respectively. The reduced activity of nirmatrelvir against MHV may be due to several amino acid differences near the nirmatrelvir binding site, including N142C, H164Q, M165L, P168S, V186R, R188A, T190V, and A191V. Nirmatrelvir-selected MHV acquired eight distinct M^{pro} substitutions: P15A, T50K, P55L, F126L, T129M, S144A, F213L, and A250V. The equivalent residues in SARS-CoV-2 are G15, L50, E55, Y126, A129, S144, I213, and P252, respectively. The MHV M^{pro} P55L and S144A substitutions were associated with reduced nirmatrelvir activity (4.4-4.9-fold higher EC_{50} values). SARS-CoV-2 M^{pro} substitutions at several of these positions have been associated with nirmatrelvir resistance in cell culture, including L50F, S144A, and P252L.
- In Vero E6 P-gp knockout cells, nirmatrelvir -selected SARS-CoV-2 (WA1/2020) acquired seven distinct M^{pro} substitutions: T21I, L50F, T135I, S144A, A173V, A191V, and T304I. The substitution frequencies indicate that some viruses had multiple M^{pro} substitutions, e.g., A173V+T304I, T21I+T304I, and T21I+S144A+T304I. Nirmatrelvir activity was significantly reduced (≥3-fold higher EC_{50} value) against six plaque-purified viruses with the following M^{pro} substitutions: T304I (3.4-fold), T21I+T304I (7.9-fold), L50F+T304I (5.9-fold), T135I+T304I (3.8-fold), A173V+T304I (20.2-fold), and T21I+S144A+T304I (27.8-fold).
- In A549-ACE2 cells, nirmatrelvir -selected SARS-CoV-2 (WA1/2020) acquired the M^{pro} F140L and A173V substitutions. Nirmatrelvir activity was significantly reduced (≥3-fold higher EC_{50} value) against plaque-purified virus with the F140L+A173V substitutions (10.1-fold) but not the A173V substitution alone (0.9-fold). Virus cultures with only the F140L substitution were not identified.
- In Vero E6 P-gp knockout cells or Vero E6-TMPRSS2 cells (with P-gp inhibitor), nirmatrelvir had reduced activity (EC_{50} value fold-change ≥3) against recombinant SARS-CoV-2 viruses with M^{pro} F140L (4.1), E166A (3.3), A173S (3.2), E55L+S144A (6.5), S144A+T304I (3.1), and T21I+A260V+T304I (3.2) substitutions. Nirmatrelvir retained activity (EC_{50} value fold-change <3) against recombinant viruses with M^{pro} G15S, E55L, L89F, K90R, S144A, H164N, E166G, Q189K, Q192L, T304I, and E166G+L232I substitutions. Recombinant viruses could not be generated with M^{pro} Y54A, F140A/I/S, S144E/L/P/T, E166V, H172Y, A173T, and A191V substitutions.
- Cross-resistance is not expected between nirmatrelvir and remdesivir or any other anti-SARS-CoV-2 agents with different mechanisms of action (i.e., agents that are not M^{pro}

inhibitors). Nirmatrelvir is known to exhibit partial cross-resistance with some other M^{pro} inhibitors under development.

Activity in Animal Models of SARS-CoV-2 Infection

- Nirmatrelvir (±ritonavir) was shown to have antiviral activity against mouse-adapted (MA) SARS-CoV-2 MA10 in 129 and BALB/c mice. SARS-CoV-2 MA10 causes severe, and in some cases lethal, lung disease in mice, with the extent of lethality depending on infectious dose and age of the mice (Leist et al. 2020). SARS-CoV-2 MA10 does not encode any M^{pro} substitutions relative to SARS-CoV-2. These studies had several limitations. Nirmatrelvir dosing was initiated early and modeled post-exposure prophylaxis rather than treatment of symptomatic disease. In addition, the studies were terminated shortly after infection, such that the impact of nirmatrelvir on lethality was not assessed. Lastly, the utility of these animal models for predicting clinical outcomes is uncertain. However, these studies demonstrated a consistent antiviral effect and are further supportive of the antiviral activity of nirmatrelvir.
- In 129 mice, nirmatrelvir was administered PO at 300 or 1,000 mg/kg BID, beginning 4- or 12-hours post-infection on Day 0 and continuing through Day 2. Mice were euthanized on Day 3 for determination of lung virus titers and lung histopathology. At 1,000 mg/kg, nirmatrelvir prevented weight loss, reduced lung virus titers by ~4 $\log_{10}$, and reduced lung histopathology relative to vehicle-treated mice.
- In BALB/c mice, nirmatrelvir was administered PO at 300 or 1,000 mg/kg BID, beginning 4 hours post-infection on Day 0 and continuing through Day 3. Mice were euthanized on Day 4 for determination of lung virus titers, lung histopathology, and immunohistochemistry. Nirmatrelvir prevented weight loss, reduced lung virus titers by ~1.4 $\log_{10}$ (300 mg/kg) or ~1.9 $\log_{10}$ (1,000 mg/kg), reduced lung histopathology, and reduced SARS-CoV-2 nucleocapsid staining in the lungs relative to vehicle-treated mice.
- In BALB/c mice, nirmatrelvir (300 mg/kg BID), ritonavir (50 mg/kg BID), or nirmatrelvir+ritonavir (300+50 mg/kg BID) were administered PO, beginning 4 hours post-infection on Day 0 and continuing through Day 3. Mice were euthanized on Day 4 for determination of lung virus titers and lung histopathology. Nirmatrelvir±ritonavir prevented weight loss and reduced lung virus titers by ~1.2 $\log_{10}$ (nirmatrelvir-ritonavir) or ~1.6 $\log_{10}$ (nirmatrelvir +ritonavir) relative to vehicle-treated mice. Nirmatrelvir+ritonavir also reduced lung histopathology, while nirmatrelvir alone did not have a significant effect. Ritonavir alone did not affect weight loss, lung virus titers, or lung histopathology.

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5.2. Clinical Pharmacology/Pharmacokinetics

The clinical pharmacology properties of nirmatrelvir/ritonavir were comprehensively evaluated (Table 5). The clinical pharmacology review focused on determining dosing recommendations for specific populations including moderate renal and hepatic impairment (Section 8.1.2 and Section 8.1.3) and providing recommendations for clinical management of drug-drug interactions (Section 8.2.2).

Table 5. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
Pharmacologic Activity	
Established pharmacologic class (EPC)	Nirmatrelvir is a SARS-CoV-2 main protease (M^{pro}) inhibitor. Ritonavir is an HIV-1 protease inhibitor and CYP3A inhibitor.
Mechanism of action	Nirmatrelvir inhibits SARS-CoV-2 M^{pro} and renders it incapable of processing polyprotein precursors, preventing viral replication. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir.
Active moieties	Nirmatrelvir, ritonavir
QT prolongation	A clinical and nonclinical integrated risk assessment was submitted in lieu of a thorough QT study. In vitro *hERG* assays and an in vivo QT study in monkeys suggested that nirmatrelvir has a low risk for QT prolongation. In Phase 1 clinical Study 1001, subjects received a supratherapeutic nirmatrelvir dose of 2250 mg (divided into three doses) boosted with ritonavir 100 mg. A concentration-Qtc analysis was conducted using the PK and ECG parameters from Study 1001. The upper bounds of 90% CI for QTcF estimates across the entire concentration range were all well below 10 ms, the threshold for potential clinical and regulatory concern. A small increase in blood pressure cannot be excluded based on a numerical increase in PR which is not expected to be clinically meaningful given the short treatment duration.
General Information	
Bioanalysis	LC-MS/MS methods were validated and were used to determine the concentrations of nirmatrelvir, ritonavir and co-administered drugs in human plasma and urine. The analyses were deemed to be acceptable.
Healthy subjects versus patients	The observed plasma nirmatrelvir concentrations from EPIC-HR subjects with COVID-19 are similar to concentrations observed in the healthy subjects enrolled in study 1014 (C_{max} 3.43 µg/mL versus 2.21 µg/mL and AUC 30.40 µg*hr/mL versus 23.01 µg*hr/mL, respectively).
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	**Table 6. Predicted Day 5 Nirmatrelvir Exposure Parameters for Adult Subjects in EPIC-HR Following Twice-Daily Dosing With 300 mg/100 mg Nirmatrelvir/Ritonavir** **Pharmacokinetic Parameter (units)[a]** / **Nirmatrelvir[b]** C_{max} (µg/mL) — 3.43 (2.59, 4.52) AUC_{tau} (µg*hr/mL)[c] — 30.40 (22.90, 39.80) C_{min} (µg/mL) — 1.57 (1.16, 2.10) Source: Study 1005. [a.] Data presented as geometric mean (10th and 90th percentile). [b.] Based on 1,016 subjects with their post hoc PK parameters. [c.] AUC_{tau}, predicted area under the plasma concentration-time profile from time 0 to 12 hours for twice-daily dosing. Abbreviations: C_{max}, predicted maximal concentration; C_{min}, predicted minimal concentration (C_{trough})

Characteristic	Drug Information
Range of effective dose(s) or exposure	Nirmatrelvir/ritonavir 300/100 mg twice daily was the only dosing regimen evaluated in the pivotal efficacy study.
Maximally tolerated dose or exposure	An MTD was not determined. The evaluated dose that achieved the highest exposure in humans was an oral dose of 2250 mg nirmatrelvir (3 doses of 750 mg each administered at 0 h, 2 h and 4 h) and 3 doses of ritonavir 100 mg administered at -12 h, 0 h, and 12 h post NIR dose.
Dose proportionality	Nirmatrelvir C_{max} and AUC increased in a less than dose proportional manner following administration of an oral suspension formulation at single ascending nirmatrelvir doses of 250 mg to 750 mg, administered with 100 mg ritonavir or multiple ascending nirmatrelvir/ritonavir doses of 75/100 mg BID to 500/100 mg BID for 10 days.
Accumulation	Geometric mean accumulation ratios ranged from 1.8 to 2.1 for AUC_{tau} and C_{max}, respectively, on Day 10 with 75mg to 500 mg nirmatrelvir administered twice daily with 100 mg ritonavir. Values were similar on Day 5 and Day 10.
Time to achieve steady-state	Twice daily dosing of nirmatrelvir with ritonavir over 10 days achieved steady-state on Day 2.
Bridge between to-be-marketed and clinical trial/study formulations	The to-be-marketed 150 mg nirmatrelvir and 100 mg ritonavir tablets were used in the pivotal efficacy study.
Absorption	
Bioavailability	The absolute bioavailability of nirmatrelvir/ritonavir is unknown.
T_{max}	Nirmatrelvir (when given with ritonavir): 3 hours[a] Ritonavir (when given with nirmatrelvir): 3.98 hours[a]
Food effect (fed/fasted) Geometric least square mean and 90% CI	Following a single oral dose of to-be-marketed oral tablet of nirmatrelvir 300 mg boosted with 3 doses of (q12h) ritonavir 100 mg administered with a high fat (approximately 50% of total caloric content of the meal), high-calorie (approximately 800 to 1000 calories) meal versus fasted, the adjusted geometric means (90% CI) for nirmatrelvir AUC_{inf}, and C_{max} were 1.20 (1.09, 1.32) and 1.61 (1.39, 1.86), respectively. The median T_{max} was 2.50 hours for the fed treatment compared to 2.29 hours for the fasted treatment.
Distribution	
Volume of distribution	Nirmatrelvir (when given with ritonavir): 104.7 L[b] Ritonavir: 112.4 L[b]
Plasma protein binding	Nirmatrelvir: 69% Ritonavir: 98-99%
Drug as substrate of transporters	In vitro data indicate that nirmatrelvir is a substrate for human MDR1 (P-gp), but not a substrate for human BCRP, MATE1, MATE2K, NTCP, OAT1, OAT2, OAT3, OCT1, OCT2, PEPT1, OATPs 1B1, 1B3, 2B1, or 4C1.
Elimination	
Mass balance results	The excretory pathways and metabolic profile of unlabeled nirmatrelvir was evaluated in urine and feces in a mass balance trial. Nirmatrelvir concentrations were determined using quantitative LC-MS/MS bioanalysis and quantitative fluorine (^{19}F) NMR. After a single unlabeled dose of 300 mg nirmatrelvir oral suspension co-administered with 100 mg ritonavir tablet (at -12 hours, 0 hours, 12 hours, and 24 hours relative to nirmatrelvir administration), a total of 49.6% and 35.3% of the administered dose of nirmatrelvir 300 mg was recovered in urine and feces, respectively. The percentage of the dose excreted as total (unchanged drug) was 55.0% in urine and 27.5% in feces. After a single radiolabeled dose of 600 mg ^{14}C-ritonavir oral solution, a total of 11.3% and 86.4% of the administered dose of nirmatrelvir 300 mg was recovered in urine and feces, respectively. The percentage of the dose excreted as total (unchanged drug) was 3.5% in urine and 33.8% in feces.
Clearance (CL/F)	Nirmatrelvir (when given with ritonavir): 8.99[b] Ritonavir: 13.92[b]

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Characteristic	Drug Information
Half-life	Nirmatrelvir (when given with ritonavir): 6.05[a] Ritonavir: 6.15[a]
Metabolic pathway(s)	Nirmatrelvir is a CYP3A4 substrate but when dosed with ritonavir, metabolic clearance is minimal. Ritonavir undergoes major metabolism by CYP3A4 with minor contribution by CYP2D6.
Primary excretion pathways (% dose)	Nirmatrelvir (when given with ritonavir): Renal elimination Ritonavir: Fecal elimination
Intrinsic Factors and Specific Populations	
Body weight	No dosage adjustment is required based on body weight.
Age	No dosage adjustment is required based on age.
Renal impairment	A dosage adjustment of 150 mg nirmatrelvir/ 100 mg ritonavir twice daily for 5 days is recommended for patients with moderate renal impairment (eGFR 30 to <60 mL/min). No dose adjustment is required for mild renal impairment (eGFR 60 to <90 mL/min). PAXLOVID is not recommended in patients with severe renal impairment until additional data are available.
Hepatic impairment	No dosage adjustment is required in patients with mild and moderate hepatic impairment (Child-Pugh Score A and B, respectively). PAXLOVID is not recommended for use in patients with severe hepatic impairment due to a lack of pharmacokinetic or safety data in this population.
Drug Interaction Liability (Drug as Perpetrator)	
Inhibition/induction of metabolism	The combination of nirmatrelvir and ritonavir is a strong inhibitor of CYP3A4. Ritonavir is a weak inhibitor of CYP2D6. Ritonavir is an inducer of CYP1A2, CYP2C8, CYP2C9 and CYP2C19.
Inhibition/induction of transporter systems	Ritonavir is an inhibitor of P-gp. Nirmatrelvir is an inhibitor of P-gp and OATP1B1.

Source: Study PF-07321332_04Nov20_113907, Study PF-07321332_09Nov20_122202, Study PF-07321332_18Oct20_102559, Study PF-07321332_18Nov20_020944, NORVIR USPI.
[a.] Represents data after a single dose of 300 mg nirmatrelvir (2 x 150 mg tablet formulation) administered together with 100 mg ritonavir tablet in healthy subjects.
[b.] 300 mg nirmatrelvir (oral suspension formulation) and 100 mg ritonavir (tablet formulation) administered together twice daily for 3 days.
Abbreviations: AUC, area under the curve; AUC_{inf}, area under concentration-time curve to infinity; BID, twice daily; CI, confidence interval; C_{max}, maximum plasma concentration; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; CYP, cytochrome P450; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; hERG, human ether-a-go-go related gene; HIV, human immunodeficiency virus; LC-MS/MS, liquid chromatography tandem mass spectrometry; M^{pro}, main protease; MTD, maximum tolerated dose; NIR, nirmatrelvir; NMR, nuclear magnetic resonance; P-gp, P-glycoprotein; PK, pharmacokinetic; PR, pulse rate; q12h, every 12 hours; QT, interval from beginning of QRS complex to the end of the T wave; QTc, QT interval corrected for heart rate; QTcF, the corrected QT interval by Fridericia; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; T_{max}, time for drug to reach maximum concentration

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

The dosing regimen for the treatment of high-risk symptomatic SARS-CoV-2 is primarily supported by the data from EPIC-HR demonstrating that the dose of nirmatrelvir/ritonavir 300/100 mg BID for 5 days is generally safe and well-tolerated and effective at reducing the risk of hospitalization/death. This dosing regimen was the only regimen evaluated in EPIC-HR and was chosen to achieve a target minimum nirmatrelvir concentration in plasma approximating the protein binding-adjusted EC_{90} value (292 ng/mL, 585 nM) for anti-SARS-CoV-2 activity in cell

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culture, which was supported by antiviral activity data from a SARS-CoV-2 mouse model and simulations with a preliminary population PK model suggesting that >90% of subjects achieve a trough concentration above the nirmatrelvir EC_{90} value after the first dose. The 5-day treatment duration for immunocompetent patients was based on the interplay of viral dynamics of SARS-CoV-2 and immune response in a quantitative systems pharmacology (QSP) model. In addition, the model suggested that a longer treatment duration beyond 5 days may be beneficial for immunocompromised patients. Specifically, a treatment duration of 10 days is supported by the QSP modeling for further clinical trial evaluation (See Sections 6.3.5 and 14).

The exposure (C_{min})-response (E-R) analyses were conducted and verified by the review team using viral load (VL) data from SARS-CoV-2 positive patients who received 300/100 mg BID for 5 days in EPIC-HR. VL over time in study subjects was evaluated using viral RNA levels measured via real-time, reverse transcription-polymerase chain reaction (RT-PCR). Change from baseline (CFB) in VL at Day 5 was used to assess the E-R relationship. No E-R relationship was observed for Day 5 CFB VL and nirmatrelvir concentrations which could be attributed to greater than 95% of subjects having nirmatrelvir concentrations ≥3-5 times the EC_{90} value, with a very limited number of lower concentrations (see Section 14, Table 7, and Figure 1). Few immunocompromised patients were included in the E-R analyses which limited the ability to inform the potential effect of immune function on E-R.

A scatterplot with the associated linear regression line of the VL response versus nirmatrelvir concentrations including all EPIC-HR subjects in the E-R analysis population is shown in Figure 2. In a small subset of subjects from the active treatment group who were hospitalized (n=6, represented by red dots), nirmatrelvir concentrations were within the range of those in non-hospitalized patients and were all below the median predicted Day 5 nirmatrelvir C_{min} and below 5 times the EC_{90} value. However, this trend should be interpreted with caution due to the very low sample size of hospitalized subjects and the high degree of variability in the VL data.

Table 7. Summary of Day 5 Change From Baseline by Day 5 C_{min} of Nirmatrelvir Relative to EC_{90} Multiples

EC_{90}	N	Day 5 CFB in VL- Median (log_{10}copies/mL)
Placebo group	740	-2.13
Missing exposure	8	-2.18
<EC_{90}	1	-2.00
1-3x EC_{90}	31	-1.73
3-5x EC_{90}	332	-3.00
>5x EC_{90}	362	-2.97

Source: EPIC-HR.
Abbreviations: CFB, change from baseline; C_{min}, minimum plasma concentration; EC_{90} 90% maximal effective concentration; log, logarithm; N, total number of subjects; VL, viral load

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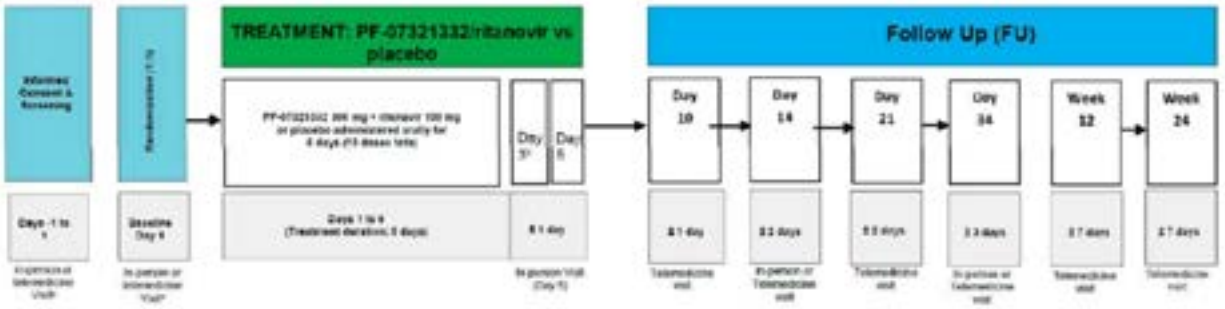
6.2. Clinical Studies/Trials Intended to Demonstrate Efficacy

6.2.1. EPIC-HR C4671005

6.2.1.1. Design, EPIC-HR

EPIC-HR was a randomized, double-blind, placebo-controlled Phase 2/3 global trial for the treatment of adult outpatients with mild-to-moderate COVID-19, who were unvaccinated against COVID-19 and at high risk for progression to severe disease (see Section 6.2.1.2 for protocol-defined risk factors for progression to severe disease). Subjects with a confirmed diagnosis of SARS-CoV-2 infection and with symptom onset within 5 days were randomized 1:1 to receive PAXLOVID or placebo orally q12h for 5 days. Randomization was stratified by geographic region and whether subjects had received or were expected to receive COVID-19 therapeutic mAb treatment (yes/no) at the time of randomization. The total study duration was up to 24 weeks. The study schematic is summarized in Figure 3.

Figure 3. Study Design of EPIC-HR



Source: EPIC-HR Clinical Study Report, Figure 1.2.
[a.] The baseline and screening visits may be a combination of in-person and telemedicine visits.
[b.] The Day 3 visit must be conducted in-person for the first 60 subjects (sentinel cohort) and thereafter only if a PK sample (not using Tasso) is collected by an HCP or if ECG is required.
Abbreviations: ECG, electrocardiogram; FU, follow up; HCP, healthcare provider; PK, pharmacokinetic

The primary analysis population was updated in protocol amendment 2 (August 2, 2021) to include only those with onset of COVID-19 symptoms ≤3 days and the total sample size was increased from 2260 to approximately 3000. Sites in India were terminated (on September 22, 2021) due to a blinded data review of a >90% rate of serology positive subjects at baseline. Site 1470 was terminated for GCP noncompliance.

Enrollment of subjects who had received or were expected to receive COVID-19 therapeutic mAb treatment was to be limited to approximately 25%. Enrollment of subjects who had COVID-19 symptom onset >3 days prior to randomization was expected to be approximately 25% and was to be limited to approximately 1000.

An independent external data monitoring committee (E-DMC) reviewed unblinded safety data on an ongoing basis throughout the trial duration, and for a sentinel cohort of the first 60 subjects after completion through Day 10. In addition, the E-DMC conducted a proof-of-concept assessment using viral RNA shedding data from approximately 200 subjects from the modified

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intent-to-treat (mITT) analysis population through Day 5, and a formal interim analysis for efficacy and futility (with a sample size re-estimation) after approximately 45% of subjects in the mITT analysis population completed the Day 28 assessments. The E-DMC determined that the prespecified criteria for stopping the trial due to overwhelming efficacy had been achieved at the 45% interim efficacy analysis (data cutoff October 26, 2021) and further enrollment in the trial was subsequently stopped on November 5, 2021. The pre-planned second interim analysis at 70% enrollment was cancelled. The final efficacy analysis was conducted as a supportive analysis after all subjects completed the Day 34 visit. The follow-up analysis was performed after all subjects completed the Week 24 visit.

During the NDA review, data anomalies were observed from Site 1274. Data from this site were removed from the review. In addition, data from Site 1470 were also removed from the review due to GCP noncompliance as noted above. Detailed discussion on data anomalies can be found in Section 6.3.1.

6.2.1.2. Eligibility Criteria, EPIC-HR

Key eligibility criteria are summarized in this section and the full criteria are available in Section 15.1.

Inclusion Criteria

1. ≥18 years of age.
2. Confirmed SARS-CoV-2 infection as determined by RT-PCR in any specimen collected within 5 days prior to randomization.
3. Initial onset of signs/symptoms attributable to COVID-19 within 5 days prior to the day of randomization and at least 1 of the specified signs/symptoms attributable to COVID-19 present on the day of randomization. Specified signs/symptoms include: cough, shortness of breath or difficulty breathing, fever or subjective fever, chills or shivering, fatigue, muscle or body aches, diarrhea, nausea, vomiting, headache, sore throat, stuffy or runny nose.
4. Has at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19 including:
   - ≥60 years of age
   - Body mass index (BMI) >25 kg/m2
   - Current smoker and history of at least 100 lifetime cigarettes
   - Immunosuppressive disease OR prolonged use of immune-weakening medications
   - Chronic lung disease
   - Known diagnosis of hypertension
   - Cardiovascular disease
   - Type 1 or Type 2 diabetes mellitus
   - Chronic kidney disease (CKD)
   - Sickle cell disease
   - Neurodevelopmental disorders
   - Active cancer
   - Medical-related technological dependence

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Exclusion Criteria

1. History of hospitalization for the medical treatment of COVID-19.
2. Current need for hospitalization or anticipated need for hospitalization within 48 hours after randomization.
3. Prior to current disease episode, any confirmed SARS-CoV-2 infection.
4. Known medical history of active liver disease.
5. Receiving dialysis or have known moderate to severe renal impairment (i.e., eGFR <45 mL/min).
6. Known HIV infection with viral load > 400 copies/mL or taking prohibited medications for HIV treatment (from known medical history within past 6 months of the screening visit).
7. Received or expected to receive convalescent COVID-19 plasma.
8. Received or expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit.
9. Previous administration with any investigational drug or vaccine within 30 days or 5 half-lives preceding the first dose of study intervention used in this study.
10. Current or expected use of any medications or substances highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations may be associated with serious and/or life-threatening events during treatment and for 4 days after the last PAXLOVID dose.
11. Concomitant use of any medications or substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to first dose of PAXLOVID and during study treatment.
12. Known history of any of the following abnormalities in clinical laboratory tests (within past 6 months of the screening visit):
    - Aspartate aminotransaminase (AST) or alanine aminotransferase (ALT) level ≥2.5 X upper limit of normal (ULN)
    - Total bilirubin ≥2 X ULN (≥3 X ULN for Gilbert's syndrome)
    - eGFR <45 mL/min within 6 months of the screening visit, using the serum creatinine-based CKD-EPI formula
    - Absolute neutrophil count <1000/mm^3
13. Oxygen saturation of <92% on room air obtained at rest within 24 hours prior to randomization.
14. Females who are pregnant or breastfeeding.

6.2.1.3. Statistical Analysis Plan, EPIC-HR

The following analysis populations were included:

- **Full Analysis Set (FAS):** All subjects randomly assigned to study intervention regardless of whether or not study intervention was administered.
- **Modified Intent-To-Treat (mITT):** All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.

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- **Modified Intent-To-Treat 1 (mITT1):** All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were dosed to receive COVID-19 therapeutic mAb treatment and were treated ≤5 days of COVID-19 symptom onset.
- **Modified Intent-To-Treat 2 (mITT2):** All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset. Subjects were analyzed according to the study intervention to which they were randomized.
- **Per-Protocol (PP):** All subjects in the mITT set without important protocol deviations considered to impact the interpretation of the primary efficacy endpoint.
- **Safety Analysis Set (SAF):** All subjects who receive at least 1 dose of study intervention. Subjects were analyzed according to the study intervention they received.

The pre-specified primary efficacy analysis population was the mITT population.

The primary efficacy endpoint was proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28 in the mITT population. The first key secondary efficacy endpoint was proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28 in the mITT1 population. The second key secondary efficacy endpoint was time to sustained alleviation of all targeted signs/symptoms through Day 28 in the mITT population. Following the positive test of the primary endpoint, the first key secondary endpoint, and the second key secondary endpoint, the following secondary endpoints were subsequently tested in the mITT population following the Hochberg procedure:

1. Time to sustained resolution of all targeted signs/symptoms through Day 28.
2. Proportion of subjects with a resting peripheral oxygen saturation ≥95% at Days 1 and 5.
3. Number of COVID-19 related medical visits.

The following additional secondary endpoints were also evaluated:

1. Proportion of subjects with severe signs/symptoms attributed to COVID-19 through Day 28.
2. Duration of each targeted COVID-19 sign/symptom.
3. Progression to a worsening status in 1 or more self-reported COVID-19 associated symptoms through Day 28.
4. Proportion of subjects with death (all cause) through Week 24.
5. Viral titers measured via RT-PCR in nasal swabs over time.
6. Number of days in hospital and intensive care unit (ICU) stay in subjects with COVID-19 related hospitalization.

6.2.1.4. Results of Analyses, EPIC-HR

After excluding Sites 1274 and 1470, 2256 subjects were screened and 2113 were randomized. Conclusion of efficacy was based on interim analysis as pre-specified in the protocol. Results of the complete EPIC-HR trial are summarized in this section. All p-values displayed in this section are nominal p-values. Refer to Section 16.2.1 for interim analyses results.

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Table 8. Subject Disposition, EPIC-HR

Disposition Outcome	PAXLOVID N=1049 n (%)	Placebo N=1064 n (%)
Subjects randomized	1049 (100.0)	1064 (100.0)
FAS population	1049 (100.0)	1064 (100.0)
mITT population	671 (64.0)	647 (60.8)
mITT1 population	977 (93.1)	989 (93.0)
mITT2 population	1038 (99.0)	1053 (99.0)
PP population	646 (61.6)	616 (57.9)
Safety population	1038 (99.0)	1053 (99.0)
Discontinued study drug[a]	63 (6.0)	85 (8.0)
Adverse event (AE)	21 (2.0)	45 (4.2)
Withdrawal by subject	30 (2.9)	27 (2.5)
No longer meets eligibility criteria	3 (0.3)	1 (0.1)
Medication error without associated adverse event	0	1 (0.1)
Other	9 (0.9)	11 (1.0)
Discontinued study[a]	73 (7.0)	85 (8.0)
Withdrawal by subject	41 (3.9)	44 (4.1)
Lost to follow-up	20 (1.9)	16 (1.5)
Death	0	15 (1.4)
Other	12 (1.1)	10 (0.9)

Source: Reviewer's analysis on ADSL dataset, excluding subjects from site 1274 and site 1470.
[a.] Percentages are based on number of randomized subjects.
Abbreviations: FAS, full analysis set, mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects in specified population or group; PP, per-protocol

Baseline demographic and clinical characteristics are listed in Table 9. The two groups had similar distributions in these characteristics. All subjects were between 18 and 88 years of age. Approximately 49% of patients were female and 38% of subjects were from the United States.

Table 9. Baseline Demographic and Clinical Characteristics, Full Analysis Set, EPIC-HR

Characteristic	PAXLOVID N=1049 n (%)	Placebo N=1064 n (%)
Sex		
Female	523 (49.9)	521 (49.0)
Male	526 (50.1)	543 (51.0)
Age, years		
Mean (SD)	44.8 (15.3)	45.9 (15.6)
Median (min, max)	44.0 (18.0, 86.0)	46.0 (18.0, 88.0)
Age group, years		
18 to 44	540 (51.5)	505 (47.5)
45 to 59	310 (29.6)	320 (30.1)
60 to 64	70 (6.7)	105 (9.9)
65 to 74	96 (9.2)	103 (9.7)
≥75	33 (3.1)	31 (2.9)
Race		
American Indian or Alaska Native	96 (9.2)	95 (8.9)
Asian	154 (14.7)	160 (15.0)
Black or African American	53 (5.1)	36 (3.4)
Multiple	1 (0.1)	2 (0.2)
White	736 (70.2)	760 (71.4)
Unknown or Missing	9 (0.9)	11 (1.0)

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Characteristic	PAXLOVID N=1049 n (%)	Placebo N=1064 n (%)
Ethnicity		
Hispanic or Latino	429 (40.9)	443 (41.6)
Not Hispanic or Latino	615 (58.6)	614 (57.7)
Not Reported	5 (0.5)	7 (0.7)
Region		
United States	392 (37.4)	403 (37.9)
Europe	334 (31.8)	335 (31.5)
India	95 (9.1)	98 (9.2)
Rest of the World	228 (21.7)	228 (21.4)
BMI, kg/m^2		
Mean (SD)	29.0 (5.4)	29.2 (5.7)
Median (min, max)	28.1 (16.6, 58.1)	28.3 (16.0, 59.1)
Missing, n (%)	0	1 (0.1)
BMI group, kg/m^2		
<25	210 (20.0)	210 (19.7)
25 to <30	471 (44.9)	466 (43.8)
30 to <35	250 (23.8)	250 (23.5)
35 to <40	71 (6.8)	79 (7.4)
≥40	47 (4.5)	58 (5.5)
Missing	0	1 (0.1)
Duration since first symptom, days		
≤3	722 (68.8)	696 (65.4)
>3	327 (31.2)	368 (34.6)
COVID-19 mAb treatment		
Received / expected to receive	61 (5.8)	65 (6.1)
Not received / not expected to receive	988 (94.2)	999 (93.9)
Baseline serology status		
Negative	505 (48.1)	529 (49.7)
Positive	523 (49.9)	514 (48.3)
Unknown	21 (2.0)	21 (2.0)
Baseline Viral RNA (NP samples, log_{10} copies/mL)		
Mean (SD)	4.76 (2.89)	4.67 (2.88)
Median (min, max)	5.52 (0, 9.16)	5.39 (0, 9.15)
Missing, n (%)	36 (3.4)	37 (3.5)

Source: Reviewer's Analysis on ADSL dataset, excluding subjects from site 1274 and site 1470.
Abbreviations: BMI, body mass index; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; log, logarithm; mAb, monoclonal ant bodies; max, maximum; min, minimum; N, number of subjects in treatment group; n, number of subjects with given characteristic; NP, nasopharyngeal; RNA, ribonucleic acid; SD, standard deviation

Primary Efficacy Endpoint

Table 10 displays analysis results for COVID-19 related hospitalization or death from any cause through Day 28, in the mITT (primary endpoint), mITT1 (first key secondary endpoint), and mITT2 populations. After accounting for premature study discontinuation by using the follow-up time in the Kaplan-Meier calculation, treatment with PAXLOVID demonstrated a 5.6% (95% CI: -7.3% to -4.0%; p<0.0001) absolute reduction, or 86% (95% CI: 72%, 93%) relative reduction compared to placebo, in mITT1 population. All three analyses had p-values <0.0001. The trial was terminated early for efficacy as planned. Interim analyses results for efficacy can be found in Section 16.2.1.

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Table 10. Proportion of Subjects With COVID-19 Related Hospitalization or Death From Any Cause Through Day 28, EPIC-HR

mITT[a] **Analysis**	**PAXLOVID N=671**	**Placebo N=647**
Subjects with event, n (%)	5 (0.7)	44 (6.8)
COVID-19 hospitalization	5 (0.7)	44 (6.8)
Death	0	9 (1.4)
Estimated difference in proportion % (95% CI)[d]	-6.1 (-8.2, -4.1)	
Two-sided nominal p-value	<0.0001	
mITT1[b] **Analysis**	**PAXLOVID N=977**	**Placebo N=989**
Subjects with event, n (%)	9 (0.9)	64 (6.5)
COVID-19 hospitalization	9 (0.9)	63 (6.4)
Death	0	12 (1.2)
Estimated difference in proportion % (95% CI)[d]	-5.6 (-7.3, -4.0)	
Two-sided nominal p-value	<0.0001	
mITT2[c] **Analysis**	**PAXLOVID N=1038**	**Placebo N=1053**
Subjects with event, n (%)	10 (1.0)	66 (6.3)
COVID-19 hospitalization	10 (1.0)	65 (6.2)
Death	0	12 (1.1)
Estimated difference in proportion % (95% CI)[d]	-5.4 (-7.0, -3.8)	
Two-sided nominal p-value	<0.0001	

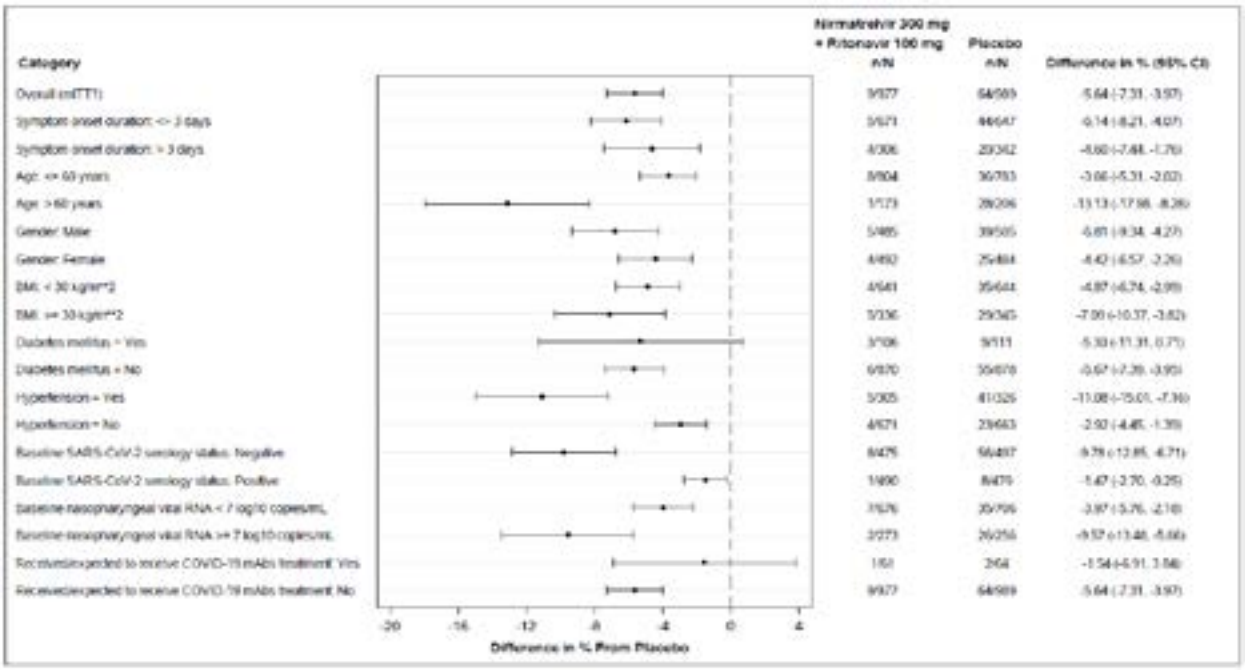
Source: Reviewer's analysis on ADTTE dataset, excluding subjects from site 1274 and site 1470
[a.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset
[d.] The estimated cumulative proportion of subjects hospitalized for the treatment of COVID-19 or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mAb, monoclonal antibody; mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic

The below sensitivity analyses were conducted for the endpoint of COVID-19 related hospitalization or death from any cause through Day 28 in the mITT, mITT1, and mITT2 populations; results were consistent with the above findings in Table 10. Detailed findings of these sensitivity analyses are available in Section 16.2.2.

- For subjects who enrolled more than once in EPIC-HR or enrolled in EPIC-HR and in one or two other Phase 2/3 PAXLOVID trials, data from a duplicate subject's first enrollment within this trial were included and data from a duplicate subject's subsequent enrollments were excluded.
- Sites in India were excluded.
- Subjects who were lost to follow up before Day 21 were hypothetically assumed to have experienced both COVID-19 related hospitalization or death in a worst-case scenario.
- Subjects who did not complete Day 28 follow up and discontinued study treatment due to AE were hypothetically assumed to have experienced both COVID-19 related hospitalization and death in a worst-case scenario.

As shown in Figure 4, similar trends have been observed across subgroups of subjects. Additional subgroup analyses are available in Section 16.2.3.

Figure 4. Subgroup Analysis of Adults With COVID-19 Dosed Within 5 Days of Symptom Onset With COVID-19 Related Hospitalization or Death From Any Cause Through Day 28, EPIC-HR



Source: Figure 84a.67a.3, NDA 217188 SDN 75.
Note: All categories are based on mITT1 population except for COVID-19 mAb treatment which is based on mITT2 population.
Abbreviations: BMI, body mass index; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mAb, monoclonal antibody; mITT, modified intent-to-treat; N, number of subjects in the category of analysis set; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Refer to review issue Section 6.3.1 on discussion of data anomalies; additional sensitivity analyses are available in Section 16.1.

Symptom Diary-Related Efficacy Endpoints

Subjects were provided an electronic handheld device or used their own device to record daily COVID-19 signs and symptoms in the study diary through Day 28. While this subsection summarizes symptom diary related efficacy endpoint data, these results should be interpreted with caution based on the following limitations:

- Approximately 19% subjects in the mITT2 population missed more than 25% symptom diary entries (18% in PAXLOVID group and 19% in placebo group).
- On average, there were 18% missing symptom diary entries in the overall mITT2 population (see Section 16.4.1 for details).
- Approximately 41% subjects in the mITT2 population were enrolled at sites with symptom data collection issues with respect to PIN codes (after excluding site 1274 and site 1470, see Section 16.1 for details).

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The reasons for missing symptom diary data are complicated. Some subjects stopped completing symptom diary after having absence of symptoms, while some subjects did not properly complete the diary when having severe disease progression (e.g., being hospitalized).

Targeted COVID-19 symptoms for analysis included cough, shortness of breath or difficulty breathing, feeling feverish, chills or shivering, muscle or body aches, diarrhea, nausea, vomiting, headache, sore throat, stuffy or runny nose.

Table 11 displays analysis results for the endpoint of time to sustained symptom alleviation, in the mITT (second key secondary endpoint), mITT1 and mITT2 populations. Sustained alleviation was defined as the first of four consecutive days when all symptoms scored as moderate or severe at study entry were scored as mild or absent and all symptoms scored mild or absent at study entry were scored as absent. The first day of the four consecutive-day period will be considered the first event date. Definition of this endpoint was related to baseline symptom severity, making it more difficult to interpret the findings compared to the time to sustained resolution endpoint discussed later in the review.

The PAXLOVID group demonstrated superiority to the placebo group in all three analyses. This result is influenced by the fact that the PAXLOVID group had fewer hospitalization and death events, and those events were considered failures in the sustained symptom alleviation endpoint and censored on Day 25.

Table 11. Time to Sustained Symptom Alleviation Through Day 28, EPIC-HR

Sustained Symptom Alleviation in mITT[a]	**PAXLOVID N=666**	**Placebo N=645**
Subjects with sustained symptom alleviation, n (%)	507 (76.1)	436 (67.6)
Median time to sustained symptom alleviation by Day 28 (95% CI)	12 (12, 13)	15 (13, 16)
Two-sided nominal p-value	<0.0001	
Sustained Symptom Alleviation in mITT1[b]	**PAXLOVID N=970**	**Placebo N=986**
Subjects with sustained symptom alleviation, n (%)	705 (72.7)	640 (64.9)
Median time to sustained symptom alleviation by Day 28 (95% CI)	13 (12, 13)	15 (14, 16)
Two-sided nominal p-value	<0.0001	
Sustained Symptom Alleviation in mITT2[c]	**PAXLOVID N=1031**	**Placebo N=1050**
Subjects with sustained symptom alleviation, n (%)	743 (72.1)	680 (64.8)
Median time to sustained symptom alleviation by Day 28 (95% CI)	13 (12, 13)	16 (15, 17)
Two-sided nominal p-value	<0.0001	

Source: Reviewer's analysis on ADTTESS dataset, excluding subjects from site 1274 and site 1470.
Note: P-values calculated from log rank test.
Note: Subjects with no symptom diary data were not included in the analyses.
[a.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mAb, monoclonal antibody; mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic

Table 12 displays analysis results for the endpoint of time to sustained symptom resolution, in the mITT (secondary endpoint), mITT1 and mITT2 populations. Sustained resolution was

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defined as the time when all targeted symptoms were scored as absent for four consecutive days. The first day of the four consecutive-day period was considered the first event date.

The PAXLOVID group was superior to the placebo group in all three analyses. This result is influenced by the fact that the PAXLOVID group had fewer hospitalization and death events, while those events were considered failures in the sustained symptom resolution endpoint and censored on Day 25.

Table 12. Time to Sustained Symptom Resolution Through Day 28, EPIC-HR

Sustained Symptom Resolution in mITT[a]	PAXLOVID N=666	Placebo N=645
Subjects with sustained symptom resolution, n (%)	445 (66.8)	388 (60.2)
Median time to sustained symptom resolution by Day 28 (95% CI)	16 (14, 17)	18 (17, 20)
Two-sided nominal p-value	0.0026	
Sustained Symptom Resolution in mITT1[b]	**PAXLOVID N=970**	**Placebo N=986**
Subjects with sustained symptom resolution, n (%)	619 (63.8)	566 (57.4)
Median time to sustained symptom resolution by Day 28 (95% CI)	16 (15, 18)	19 (18, 20)
Two-sided nominal p-value	0.0004	
Sustained Symptom Resolution in mITT2[c]	**PAXLOVID N=1031**	**Placebo N=1050**
Subjects with sustained symptom resolution, n (%)	654 (63.4)	603 (57.4)
Median time to sustained symptom resolution by Day 28 (95% CI)	17 (15, 18)	19 (18, 20)
Two-sided nominal p-value	0.0004	

Source: Reviewer's analysis on ADTTESS dataset, excluding subjects from site 1274 and site 1470.
Note: P-values calculated from log rank test.
Note: Subjects with no symptom diary data were not included in the analyses.
[a.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mAb, monoclonal antibody; mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic

In the mITT2 population, approximately 15% of subjects from both arms who reached sustained symptom resolution reported at least one day of having any mild or worse symptom, after reaching sustained resolution. However, it is not clear if those symptoms were relapse of previously resolved symptoms or symptoms from new/other infection. Refer to the review issue section COVID-19 rebound discussion for more analyses on symptom rebound (Section 6.3.6).

It was noted that three placebo subjects reported absence of all targeted symptoms for 4-7 consecutive days (not missing data) immediately preceding COVID-19 related hospitalization. Although these subjects were considered not recovered in the above analyses, this finding suggests that the symptom diary data may not be as robust/interpretable as the COVID-19 related hospitalization/death data.

Time to sustained alleviation and time to sustained resolution for each targeted symptom were evaluated. Details can be found in Section 16.2.4.

Table 13 summarizes analysis results for the endpoint of proportion of any severe targeted signs and symptoms attributed to COVID-19 through Day 28 in the mITT (secondary endpoint), mITT1 and mITT2 populations. The two treatment groups had similar percentages, with

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percentages in the PAXLOVID group being numerically lower. Note that this analysis did not make adjustment on difference in symptom severity at baseline or take into account hospitalization or death events, which limits the interpretability of the results. Only 36 hospitalized subjects in the mITT2 population (out of 76 hospitalized subjects in total) reported any severe targeted symptoms through Day 28.

Table 13. Proportion of Subjects With Any Severe Targeted Signs and Symptoms Attributed to COVID-19 Through Day 28, EPIC-HR

mITT[a] Analysis	PAXLOVID N=666	Placebo N=645
Subjects with event, n (%)	121 (18.2)	134 (20.8)
Two-sided nominal p-value	0.2332	
mITT1[b] Analysis	**PAXLOVID N=970**	**Placebo N=986**
Subjects with event, n (%)	191 (19.7)	210 (21.3)
Two-sided nominal p-value	0.3786	
mITT2[c] Analysis	**PAXLOVID N=1031**	**Placebo N=1050**
Subjects with event, n (%)	213 (20.7)	229 (21.8)
Two-sided nominal p-value	0.5213	

Source: Reviewer's analysis on ADSO dataset, excluding subjects from site 1274 and site 1470.
Note: P-values calculated from Pearson's Chi-squared test.
Note: Subjects with no symptom diary data were not included in the analyses.
[a.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mAb, monoclonal antibody; mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic

Table 14 summarizes analysis results for the endpoint of proportion of subjects with progression to a worsening status in one or more self-reported COVID-19-associated targeted symptoms through Day 28 in the mITT (secondary endpoint), mITT1 and mITT2 populations. The two treatment groups had similar percentages, with percentages in the PAXLOVID group being numerically higher. Note that this analysis did not take hospitalization or death events into account, which limits the interpretability of the results.

Table 14. Proportion of Subjects With Progression to Worsening Status in 1 or More Self-Reported COVID-19 Associated Targeted Symptoms Through Day 28, EPIC-HR

mITT[a] Analysis	PAXLOVID N=666	Placebo N=645
Subjects with event, n (%)	507 (76.1)	483 (74.9)
Two-sided nominal p-value	0.6010	
mITT1[b] Analysis	**PAXLOVID N=970**	**Placebo N=986**
Subjects with event, n (%)	735 (75.8)	737 (74.7)
Two-sided nominal p-value	0.5988	

mITT2[c] Analysis	PAXLOVID N=1031	Placebo N=1050
Subjects with event, n (%)	787 (76.3)	790 (75.2)
Two-sided nominal p-value	0.5597	

Source: Reviewer's analysis on ADSO dataset, excluding subjects from site 1274 and site 1470.
Note: P-values calculated from Pearson's Chi-squared test.
Note: Subjects with no symptom diary data were not included in the analyses.
[a.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mAb, monoclonal antibody; mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic

Secondary Efficacy Endpoint: Proportion of Subjects With a Resting Peripheral Oxygen Saturation ≥95% at Days 1 and 5

Table 15 summarizes analysis results for the endpoint of proportion of subjects with a resting peripheral oxygen saturation ≥95% at Days 1 and 5 in the mITT (secondary endpoint), mITT1 and mITT2 populations. Subjects who had a resting peripheral oxygen saturation ≥95% at baseline (Day 1) were more likely to maintain those levels at Day 5 than those with a resting peripheral oxygen saturation <95% at baseline, but the difference between two treatment groups was not statistically significant, with the PAXLOVID group having a numerically higher odds ratio.

Table 15. Subjects With Resting Peripheral Oxygen Saturation ≥95% at Days 1 and 5, EPIC-HR

mITT[a] Oxygen Saturation	PAXLOVID N=671	Placebo N=647
Subjects with Day 1 <95%, n	44	52
<95% at Day 5	11	13
≥95% at Day 5	30	35
Missing at Day 5	3	4
Subjects with Day 1 ≥ 95%, n	627	595
<95% at Day 5	11	22
≥95% at Day 5	582	530
Missing at Day 5	34	43
Odds ratio for Day 5 vs Day 1 (95% CI)	19.4 (7.8, 48.3)	8.9 (4.2, 19.3)
Two-sided nominal p-value	0.1997	
mITT1[b] Oxygen Saturation	**PAXLOVID N=977**	**Placebo N=989**
Subjects with Day 1 <95%, n	65	77
<95% at Day 5	18	24
≥95% at Day 5	40	44
Missing at Day 5	7	9
Subjects with Day 1 ≥95%, n	912	912
<95% at Day 5	18	35
≥95% at Day 5	835	799
Missing at Day 5	59	78
Odds ratio for Day 5 vs Day 1 (95% CI)	20.9 (10.1, 43.2)	12.5 (6.8, 22.7)
Two-sided nominal p-value	0.2810	

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mITT2[c] Oxygen Saturation	PAXLOVID N=1038	Placebo N=1053
Subjects with Day 1 < 95%, n	69	87
<95% at Day 5	19	27
≥95% at Day 5	42	50
Missing at Day 5	8	10
Subjects with Day 1 ≥95%, n	969	966
<95% at Day 5	19	38
≥95% at Day 5	887	847
Missing at Day 5	63	81
Odds ratio for Day 5 vs Day 1 (95% CI)	21.1 (10.4, 42.8)	12.0 (6.8, 21.3)
Two-sided nominal p-value	0.2226	

Source: Reviewer's analysis on ADVS dataset, excluding subjects from site 1274 and site 1470.
Note: p-values calculated from Breslow-Day test. Subjects with missing Day 5 data were excluded in the analyses.
[a.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mAb, monoclonal antibody; mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic

Secondary Efficacy Endpoint: COVID-19 Related Medical Visits Through Day 28

Table 16 summarizes analysis results for COVID-19 related medical visits in the mITT (secondary endpoint), mITT1 and mITT2 populations. Analyses were conducted to compare the event rates between treatment groups, rather than total number of visits. Comparisons between arms using the total number of medical visits may not be clinically meaningful, given that a hospital visit for more than one day is considered as one visit in this dataset. The PAXLOVID group was superior to the placebo group in all three analyses.

Table 16. Proportion of Subjects With COVID-19 Related Medical Visits, EPIC-HR

Medical Visits in mITT[a]	PAXLOVID N=671	Placebo N=647
Subjects with event, n (%)	10 (1.5)	52 (8.0)
Total number of medical visits across all subjects	22	81
Two-sided nominal p-value	<0.0001	
Medical Visits in mITT1[b]	**PAXLOVID N=977**	**Placebo N=989**
Subjects with event, n (%)	22 (2.3)	83 (8.4)
Total number of medical visits across all subjects	40	128
Two-sided nominal p-value	<0.0001	

Medical Visits in mITT2[c]	PAXLOVID N=1038	Placebo N=1053
Subjects with event, n (%)	25 (2.4)	91 (8.6)
Total number of medical visits across all subjects	45	144
Two-sided nominal p-value	<0.0001	

Source: Reviewer's analysis on ADHOSP dataset, excluding subjects from site 1274 and site 1470.
Note: Medical Visits include emergency room, practitioner's office, home healthcare services, urgent care, telephone consultation, outpatient infusion center, other, COVID-19 Related-Hospitalization (ICU and non-ICU stays). The medical visits and hospitalization events are limited through Day 34 visit.
Note: p-values calculated from Pearson's Chi-squared test with continuity correction.
[a.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; ICU, intensive care unit; mAb, monoclonal antibody; mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic

Other Endpoints

Refer to Section 6.3.2 and Section 6.3.3 for detailed analyses on viral RNA level related endpoints.

Table 17 displays analyses results for death from any cause through Week 24 in the mITT (secondary endpoint), mITT1 and mITT2 populations. No deaths were reported in the PAXLOVID group. The PAXLOVID group was superior to the placebo group in all three analyses.

Table 17. Proportion of Subjects With Death From Any Cause Through Week 24, EPIC-HR

Death in mITT[a]	PAXLOVID N=671	Placebo N=647
Subjects with event, n (%)	0	11 (1.7)
Two-sided nominal p-value	0.0004	
Death in mITT1[b]	**PAXLOVID N=977**	**Placebo N=989**
Subjects with event, n (%)	0	15 (1.5)
Two-sided nominal p-value	<0.0001	
Death in mITT2[c]	**PAXLOVID N=1038**	**Placebo N=1053**
Subjects with event, n (%)	0	15 (1.4)
Two-sided nominal p-value	<0.0001	

Source: Reviewer's analysis on ADSL dataset, excluding subjects from site 1274 and site 1470.
Note: p-values calculated from Fisher's exact test.
[a.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mAb, monoclonal antibody; mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic

Table 18 summarizes analysis results for the duration of hospital and ICU stays in subjects with COVID-19 related hospitalization in the mITT (secondary endpoint), mITT1 and mITT2 populations. No subject in the PAXLOVID group reported any ICU visits.

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Table 18. Duration of COVID-19 Related Hospitalization, EPIC-HR

mITT[a] Outcomes	PAXLOVID N=671	Placebo N=647
Duration of hospitalization visits (Days)		
Subjects with event, n	4	55
Mean (SD)	11.8 (3.4)	12.4 (12.7)
Median (range)	13 (7, 16)	9 (3, 63)
Duration of ICU visits (Days)		
Subjects with event, n	0	8
Mean (SD)		14.5 (17.0)
Median (range)		10 (3, 55)
mITT1[b] Outcomes	**PAXLOVID N=977**	**Placebo N=989**
Duration of hospitalization visits (Days)		
Subjects with event, n	9	63
Mean (SD)	9.4 (3.8)	12.0 (11.2)
Median (range)	8 (5, 16)	9 (2, 63)
Duration of ICU visits (Days)		
Subjects with event, n	0	9
Mean (SD)		14.1 (16.0)
Median (range)		10 (3, 55)
mITT2[c] Outcomes	**PAXLOVID N=1038**	**Placebo N=1053**
Duration of hospitalization visits (Days)		
Subjects with event, n	10	65
Mean (SD)	9.5 (3.6)	11.8 (11.0)
Median (range)	9 (5, 16)	9 (2, 63)
Duration of ICU visits (Days)		
Subjects with event, n	0	9
Mean (SD)		14.1 (16.0)
Median (range)		10 (3, 55)

Source: Reviewer's analysis on ADHOSP dataset, excluding subjects from site 1274 and site 1470.
Note: Hospitalization visits are not limited through Day 28.
[a.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; ICU, intensive care unit; mAb, monoclonal antibody; mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation

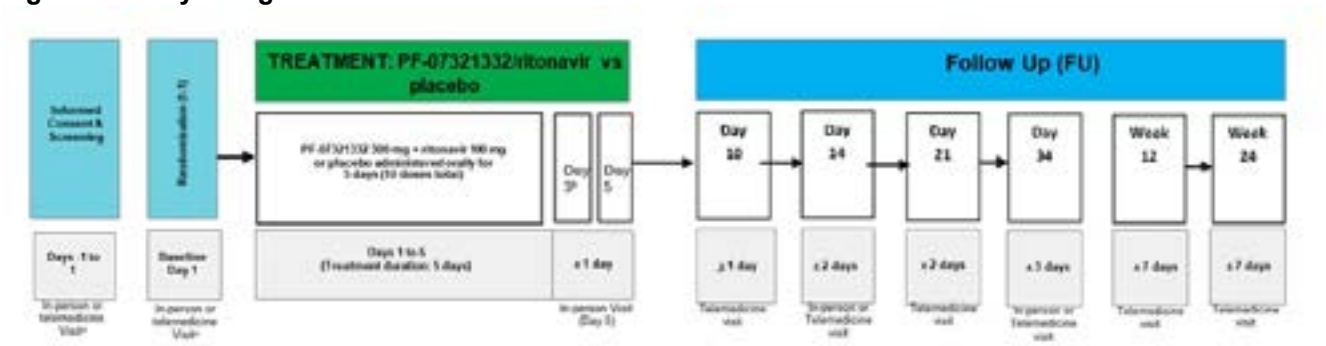
6.2.2. EPIC-SR C4671002

6.2.2.1. Design, EPIC-SR

EPIC-SR was a randomized, double-blind, placebo-controlled Phase 2/3 global trial for the treatment of adult outpatients with mild-to-moderate COVID-19. The trial enrolled COVID-19-vaccinated subjects who were at high risk for progression to severe disease and unvaccinated subjects who had no risk factors for progression to severe disease. Subjects with a confirmed diagnosis of SARS-CoV-2 infection and with symptom onset within 5 days were randomized 1:1 to receive PAXLOVID (nirmatrelvir 300mg co-administered with ritonavir 100mg) or placebo orally q12h for 5 days. Randomization was stratified by geographic region, vaccination status,

and COVID-19 symptom onset (≤3 days versus >3 days). The total study duration was up to 24 weeks. The study schematic is summarized in Figure 5.

Figure 5. Study Design of EPIC-SR



Source: EPIC-SR Interim Clinical Study Report, Figure 1.
[a.] The baseline and screening visits may be a combination of in-person and telemedicine visits.
[b.] The Day 3 visit will only be conducted in-person only if a PK sample (not using Tasso) is collected by an HCP or at the discretion of the investigator.
Abbreviations: FU, follow up; HCP, healthcare provider; PK, pharmacokinetic

The primary analysis population was updated in protocol amendment 3 (August 3, 2021) to include only those with onset of COVID-19 symptoms ≤3 days and the sample size was increased from 800 to 1140. The testing hierarchy of secondary efficacy endpoints was updated in protocol amendment 4 (November 23, 2021), adding COVID-19 related hospitalization or death from any cause through Day 28 in all treated subjects as a key secondary endpoint.

An independent E-DMC reviewed unblinded safety data on an ongoing basis throughout the duration of the trial, and for a sentinel cohort of the first 100 subjects after completion through Day 10. In addition, the E-DMC conducted a proof-of-concept assessment using viral RNA shedding data from approximately 200 subjects in the mITT analysis population through Day 5, and an interim analysis for efficacy and futility (with a sample size re-estimation) after approximately 45% of subjects in the mITT analysis population completed the Day 28 assessments. The originally planned enrollment was completed on November 9, 2021. The third interim analysis utilizing the December 19, 2021, dataset [100% planned enrollment through protocol amendment 4, EPIC-SR (2021/pre-Omicron)] was submitted to support this NDA (results summarized in Section 6.2).

Based on the outcome from this trial's interim analysis and the final results of EPIC-HR, this trial was modified to re-open enrollment in 2022 to collect information on the clinical endpoint of hospitalization or death at a time that the Omicron variant was the dominating circulating variant, with a plan to increase total sample size to 1980 under amendment 5. Enrollment in 2022 was started in March and terminated in June due to no hospitalization or death events reported after reopening. Additional datasets providing information on the 287 subjects enrolled in 2022 [EPIC-SR (2022/Omicron)] were submitted during the NDA review process to support analyses related to review issues described in Section 6.3.

During the NDA review, data anomalies were observed in Site 1281. Data from this site are removed from the review. In addition, data from Site 1488 are removed from the review due to GCP noncompliance. Detailed discussion on data anomalies can be found in Section 6.3.1. In the

EPIC-SR 2022/Omicron datasets, data anomalies were observed in Site 1157 and Site 1197 leading to their removal from specific Omicron-related analyses.

6.2.2.2. Eligibility Criteria, EPIC-SR

Key eligibility criteria are summarized in this section and the full criteria are available in Section 15.2.

Inclusion Criteria

1. ≥18 years of age.
2. Confirmed SARS-CoV-2 infection as determined by RT-PCR in any specimen collected within 5 days prior to randomization.
3. Initial onset of signs/symptoms attributable to COVID-19 within 5 days prior to the day of randomization, and at least 1 of the specified signs/symptoms attributable to COVID-19 present on the day of randomization. Specified signs/symptoms include: cough, shortness of breath or difficulty breathing, fever or subjective fever, chills or shivering, fatigue, muscle or body aches, diarrhea, nausea, vomiting, headache, sore throat, stuffy or runny nose.

Exclusion Criteria

1. Has at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19 including:

Note: Subjects with these conditions who were fully vaccinated (as defined by local regulations and practices) were considered to be at lower risk of developing severe disease and were therefore considered eligible before Amendment 5.

- ≥60 years of age
- BMI >25
- Current smoker (cigarette smoking within the past 30 days) and history of at least 100 lifetime cigarettes
- Chronic lung disease (if asthma, requires daily prescribed therapy)
- Known diagnosis of hypertension
- Cardiovascular disease, defined as history of any of the following: myocardial infarction, stroke, TIA, HF, angina with prescribed nitroglycerin, CABG, PCI, carotid endarterectomy, and aortic bypass
- Type 1 or Type 2 diabetes mellitus
- CKD
- Sickle cell disease
- Neurodevelopmental disorders (e.g., cerebral palsy, Down's syndrome) or other conditions that confer medical complexity (e.g., genetic or metabolic syndromes and severe congenital anomalies)
- Active cancer, other than localized skin cancer, including those requiring treatment as long as the treatment is not among the prohibited medications that must be administered/continued during the trial period
- Medical-related technological dependence (e.g., CPAP [not related to COVID-19])

2. Immunosuppressive disease (e.g., bone marrow or organ transplantation or primary immune deficiencies) OR prolonged use of immune-weakening medications
3. History of hospitalization for the medical treatment of COVID-19
4. Current need for hospitalization or anticipated need for hospitalization within 48 hour after randomization
5. Prior to current disease episode, any confirmed SARS-CoV-2 infection
6. Known medical history of active liver disease
7. Receiving dialysis or have known renal impairment
8. Known HIV infection with viral load >400 copies/mL or taking prohibited medications for HIV treatment
9. Received or expected to receive mAb treatment or convalescent COVID-19 plasma
10. Current or expected use of any medications or substances that are highly dependent on CYP3A4 for clearance, and for which elevated plasma concentrations may be associated with serious and/or life-threatening events during treatment and for 4 days after the last dose of PAXLOVID
11. Concomitant use of any medications or substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to first dose of PAXLOVID and during study treatment
12. Received or expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit, except for subjects with any of the underlying medical conditions specified in Exclusion criterion #1 who are fully vaccinated prior to study entry

Note: Fully vaccinated subjects with underlying medical conditions associated with an increased risk of developing severe illness from COVID-19 must not receive a SARS-CoV-2 vaccine booster between screening and the Day 34 visit.

13. Known history of any of the following abnormalities in clinical laboratory tests (within past 6 months of the screening visit):
    - AST or ALT level ≥2.5 X ULN
    - Total bilirubin ≥2X ULN (≥3X ULN for Gilbert's syndrome)
    - eGFR <45 mL/min within 6 months of the screening visit, using the serum creatinine-based CKD-EPI formula
    - Absolute neutrophil count <1000/mm3
14. Oxygen saturation of <92% on room air obtained at rest within 24 hours prior to randomization.
15. Females who are pregnant or breastfeeding.

6.2.2.3. Statistical Analysis Plan, EPIC-SR

The following analysis populations were included:

- **FAS**: All subjects randomly assigned to study intervention regardless of whether or not study intervention was administered.

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- **mITT**: All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention and were dosed within ≤3 days of COVID-19 symptom onset.
- **mITT1**: All subjects randomly assigned to study intervention who took at least 1 dose of study intervention. Subjects were analyzed according to the study intervention to which they were randomized.
- **PP**: All subjects in the mITT set without important protocol deviations considered to impact the interpretation of the primary efficacy endpoint.
- **SAF**: All randomized subjects who received at least one dose of study intervention. Subjects were analyzed according to the study intervention they received.

The pre-specified primary efficacy endpoint was time to sustained alleviation of all targeted signs/symptoms through Day 28 (see Section 6.2.1.4 for the full definition), evaluated in the mITT population: this primary endpoint was not met. Results of the following secondary efficacy endpoints in the mITT1 population were submitted to support the NDA:

- Time to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28
- Time to sustained resolution of all targeted COVID-19 signs/symptoms through Day 28
- Proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28
- Proportion of subjects with severe signs/symptoms attributed to COVID-19 through Day 28
- Progression to a worsening status in one or more self-reported COVID-19 associated symptoms through Day 28
- Number of COVID-19 related medical visits through Day 28
- Number of days in hospital and ICU stay in subjects with COVID-19 related hospitalization through Day 28
- Proportion of subjects with death (all cause) through Week 24
- Viral titers measured via RT-PCR in nasal swabs over time

6.2.2.4. Results of Analyses, EPIC-SR

After excluding Site 1281 and Site 1488, 1165 subjects were screened and 1075 were randomized in 2021. Results of EPIC-SR (2021/pre-Omicron) analyses are summarized in this section.

Table 19. Subject Disposition, EPIC-SR

Disposition Outcome	PAXLOVID N=544 n (%)	Placebo N=531 n (%)
Subjects randomized	544 (100.0)	531 (100.0)
FAS population	544 (100.0)	531 (100.0)
mITT population	397 (73.0)	388 (73.1)
mITT1 population	540 (99.3)	528 (99.4)
PP population	374 (68.8)	372 (70.1)
Safety population	540 (99.3)	528 (99.4)

Disposition Outcome	PAXLOVID N=544 n (%)	Placebo N=531 n (%)
Discontinued study drug[a]	23 (4.2)	21 (4.0)
Adverse event (AE)	10 (1.8)	5 (0.9)
Withdrawal by subject	7 (1.3)	11 (2.1)
No longer meets eligibility criteria	2 (0.4)	2 (0.4)
Other	4 (0.7)	3 (0.6)
Discontinued study[a]	20 (3.7)	21 (4.0)
Withdrawal by subject	12 (2.2)	17 (3.2)
Lost to follow-up	4 (0.7)	1 (0.2)
Death	0	1 (0.2)
Other	4 (0.7)	2 (0.4)

Source: Reviewer's analysis on ADSL dataset, excluding subjects from site 1281 and site 1488.
[a.] Percentages are based on number of randomized subjects.
Abbreviations: FAS, full analysis set, mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects in specified population or group; PP, per-protocol

Baseline and demographic characteristics are listed in Table 20. The two groups had similar distributions in these characteristics. All subjects were between 18 and 87 years of age. Approximately 52% of patients were female and 39% of subjects were from the United States.

Table 20. Baseline Demographic and Clinical Characteristics, Full Analysis Set, EPIC-SR

Characteristic	PAXLOVID N=544 n (%)	Placebo N=531 n (%)
Sex		
Female	277 (50.9)	285 (53.7)
Male	267 (49.1)	246 (46.3)
Age, years		
Mean (SD)	41.7 (13.8)	42.4 (13.2)
Median (min, max)	40.0 (18.0, 87.0)	42.0 (18.0, 82.0)
Age group, years		
18 to 44	330 (60.7)	311 (58.6)
45 to 59	159 (29.2)	171 (32.2)
60 to 64	19 (3.5)	24 (4.5)
65 to 74	30 (5.5)	15 (2.8)
≥75	6 (1.1)	10 (1.9)
Race		
American Indian or Alaska Native	23 (4.2)	18 (3.4)
Asian	68 (12.5)	70 (13.2)
Black or African American	19 (3.5)	18 (3.4)
White	428 (78.7)	416 (78.3)
Unknown or Missing	6 (1.1)	9 (1.7)
Ethnicity		
Hispanic or Latino	235 (43.2)	225 (42.4)
Not Hispanic or Latino	306 (56.3)	301 (56.7)
Not Reported	3 (0.6)	5 (0.9)
Region		
United States	216 (39.7)	206 (38.8)
Europe	161 (29.6)	157 (29.6)
Rest of the World	167 (30.7)	168 (31.6)

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Characteristic	PAXLOVID N=544 n (%)	Placebo N=531 n (%)
BMI, kg/m^2		
Mean (SD)	26.4 (5.2)	26.6 (5.7)
Median (min, max)	24.9 (17.4, 58.8)	24.9 (14.2, 53.1)
Missing, n (%)	1 (0.2)	2 (0.4)
BMI group, kg/m^2		
<25	280 (51.5)	268 (50.5)
25 to <30	154 (28.3)	139 (26.2)
30 to <35	71 (13.1)	81 (15.3)
35 to <40	28 (5.1)	26 (4.9)
≥40	10 (1.8)	15 (2.8)
Missing	1 (0.2)	2 (0.4)
Duration since first symptom, days		
≤3	400 (73.5)	390 (73.4)
>3	144 (26.5)	141 (26.6)
Baseline serology status		
Negative	133 (24.4)	128 (24.1)
Positive	397 (73.0)	391 (73.6)
Unknown	14 (2.6)	12 (2.3)
Baseline Viral RNA shedding (NP samples, $\log_{10}$ copies/mL)		
Mean (SD)	5.19 (2.88)	4.85 (2.95)
Median (min, max)	6.20 (0, 9.47)	5.82 (0, 9.37)
Missing, n (%)	15 (2.8)	11 (2.1)
Vaccination Status		
Not Vaccinated	212 (39.0)	206 (38.8)
Vaccinated [a]	332 (61.0)	325 (61.2)
Baseline Risk factors		
No risk factor for severe COVID-19	221 (40.6)	211 (39.7)
With risk factor for severe COVID-19	323 (59.4)	320 (60.3)

Source: Reviewer's Analysis on ADSL datasets, excluding subjects from site 1281 and site 1488
[a] Among 657 (61.1%) fully vaccinated subjects, 636 (59.2%) subjects were fully vaccinated and at high risk for severe COVID-19.
Abbreviations: BMI, body mass index; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; log, logarithm; max, maximum; min, minimum; N, number of subjects in treatment group; n, number of subjects with given characteristic; NP, nasopharyngeal; RNA, r bonucleic acid; SD, standard deviation

Primary Efficacy Endpoint

The primary endpoint in this trial, the difference in time to sustained alleviation of all targeted COVID-19 signs and symptoms through Day 28 among PAXLOVID versus placebo recipients, was not met. Table 21 displays analysis results for the time to sustained symptom alleviation endpoint in the mITT and mITT1 populations. No statistically significant difference between the two groups was observed in either analysis. Similar to EPIC-HR, there was high percentage of missing symptom diary data (15% treated subjects missed more than 25% symptom diary entries) in EPIC-SR (2021/pre-Omicron) (see Section 16.4.1 for more details).

Table 21. Time to Sustained Symptom Alleviation Through Day 28, EPIC-SR

Sustained Symptom Alleviation in mITT[a]	PAXLOVID N=397	Placebo N=388
Subjects with sustained symptom alleviation, n (%)	289 (72.8)	286 (73.7)
Median time to sustained symptom alleviation by Day 28 (95% CI)	12 (11, 13)	14 (12, 15)
Two-sided nominal p-value	0.4430	

Sustained Symptom Alleviation in mITT1[b]	PAXLOVID N=540	Placebo N=528
Subjects with sustained symptom alleviation, n (%)	388 (71.9)	382 (72.3)
Median time to sustained symptom alleviation by Day 28 (95% CI)	13 (11, 14)	14 (12, 15)
Two-sided nominal p-value	0.5150	

Source: Reviewer's analysis on ADTTESS dataset, excluding subjects from site 1281 and site 1488
Note: p-values calculated from log rank test
[a.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic

Proportion of Subjects With COVID-19 Related-Hospitalization or Death From Any Cause Through Day 28

Table 22 displays analysis results for the prespecified secondary endpoint of COVID-19 related hospitalization or death from any cause through Day 28. There was no statistically significant difference between the PAXLOVID group and the placebo group. However, a numerically lower hospitalization/death rate was observed in all randomized subjects in the PAXLOVID group. In addition, in an exploratory analysis of the subgroup of fully vaccinated subjects with at least 1 risk factor for progression to severe disease, a non-statistically significant numerical reduction relative to placebo for the secondary endpoint of COVID-19 related hospitalization or death from any cause through Day 28 was observed. None of the five hospitalized PAXLOVID subjects were admitted to the ICU. Three of the ten hospitalized placebo subjects were admitted to the ICU. There was one death reported in the trial, which was from the placebo group.

Table 22. Proportion of Subjects With COVID-19 Related Hospitalization or Death From Any Cause Through Day 28, EPIC-SR

mITT1[a] Analysis	PAXLOVID N=540	Placebo N=528
Subjects with event, n (%)	5 (0.9)	10 (1.9)
COVID-19 hospitalization	5 (0.9)	10 (1.9)
Death	0	1 (0.2)
Estimated difference in proportion % (95% CI)[b]	-1.0 (-2.4, 0.5)	
Two-sided nominal p-value	0.1815	
Vaccinated High Risk Subgroup of mITT1[a] Analysis	**PAXLOVID N=317**	**Placebo N=314**
Subjects with event, n (%)	3 (0.9)	7 (2.2)
COVID-19 hospitalization	3 (0.9)	7 (2.2)
Death	0	1 (0.3)
Estimated difference in proportion % (95% CI)[b]	-1.3 (-3.3, 0.7)	
Two-sided nominal p-value	0.1970	

Source: Reviewer's analysis on ADTTE/ADSL datasets, excluding subjects from site 1281 and site 1488.
[a.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention.
[b.] The estimated cumulative proportion of subjects hospitalized for the treatment of COVID-19 or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic

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Other Efficacy Endpoints

Results of efficacy endpoints including proportion of subjects with COVID-19 related medical visits and symptom diary-related efficacy endpoints in the mITT1 population are provided in Section 16.3. No statistically significant difference was observed between the two arms in any of these endpoints.

Analyses on viral RNA level related endpoints are provided in Section 6.3.2 and Section 6.3.3.

6.2.3. EPIC-PEP C4671006

6.2.3.1. Design, EPIC-PEP

EPIC-PEP was a randomized, double-blind, double-dummy, placebo-controlled Phase 2/3 global trial for post-exposure prophylaxis of symptomatic SARS-CoV-2 infection in adults. Subjects with a negative screening SARS-CoV-2 rapid antigen test (RAT) result and who were asymptomatic household contacts of a symptomatic individual who recently tested positive for SARS-CoV-2 were enrolled. Eligible subjects were randomized 1:1:1 to receive PAXLOVID for 5 days (followed by placebo for 5 days), PAXLOVID for 10 days, or placebo for 10 days. Randomization was stratified by presence of risk factors associated with severe COVID-19 and geographic region. The total study duration was up to 42 days. The study schematic is summarized in Figure 6.

Figure 6. Study Design of EPIC-PEP

Source: EPIC-PEP Final Clinical Study Report, Figure 1.

The planned sample size was increased from 2660 to 2880 under protocol amendment 2 (January 25, 2022), based on external information on estimated relative risk reduction. The timing of planned interim efficacy analysis was changed from 45% subjects completing Day 14 assessments to 70% (with a minimum of 24 subjects having symptomatic infection in the mITT analysis set) to increase information collected on the Omicron variant.

An independent E-DMC reviewed unblinded safety data on an ongoing basis throughout the duration of the trial, and for a sentinel cohort of the first 150 subjects after completion through Day 10. The E-DMC conducted an interim analysis for efficacy and futility (with a sample size re-estimation) after approximately 70% of subjects completed the Day 14 assessments. The interim efficacy analysis concluded no change on sample size was needed. The trial failed the final primary efficacy analysis (see Section 6.2.3.4).

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Due to data reliability concerns from two sites in EPIC-HR/EPIC-SR, data from the corresponding EPIC-PEP sites, Site 1281 and Site 1483, were also excluded from the review. Detailed discussion on data anomalies can be found in Section 6.3.1.

6.2.3.2. Eligibility Criteria, EPIC-PEP

Key eligibility criteria are summarized in this section and the full criteria are available in Section 15.3.

Inclusion Criteria

1. ≥18 years of age
2. Subjects who have a negative screening SARS-CoV-2 rapid antigen test result and who are asymptomatic household contacts (i.e., living in the same residence) of an individual who is symptomatic and recently tested positive for SARS-CoV-2 (i.e., index case: patient with symptomatic COVID-19)

Exclusion Criteria

1. History of SARS-CoV-2 infection as determined by a molecular test from any specimen collected within 6 months before or during the screening visit
2. Experiencing measured fever or other signs or symptoms consistent with COVID-19
3. Known medical history of active liver disease
4. CKD or have known moderate to severe renal impairment
5. Known HIV infection with viral load >400 copies/mL within the last 6 months or taking prohibited medications for HIV treatment
6. Active cancer requiring treatment
7. Has received approved, authorized, or investigational anti-SARS-CoV-2 mAb, convalescent plasma, other drugs for treatment of COVID-19, or other anti-SARS-CoV-2 biologic products within 6 months of screening
8. Has received any SARS-CoV-2 vaccine (includes any level of vaccination) within 6 months prior to screening or is expected to receive a SARS-CoV-2 vaccine or other approved, authorized, or investigational post-exposure prophylaxis treatments through Day 38
9. Current or expected use of any medications or substances that are highly dependent on CYP3A4 for clearance, and for which elevated plasma concentrations may be associated with serious and/or life-threatening events during treatment and for 4 days after the last dose of PAXLOVID
10. Concomitant use of any medications or substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to first dose of PAXLOVID and during study treatment
11. Known history of any of the following abnormalities in clinical laboratory tests (within past 6 months of the screening visit):
    - AST or ALT level ≥2.5 X ULN
    - Total bilirubin ≥2 X ULN (≥3 X ULN for Gilbert's syndrome)

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- eGFR <45 mL/min within 6 months of the screening visit, using the serum creatinine-based CKD-EPI formula
- Absolute neutrophil count <1000/mm3

12. Females who are pregnant or breastfeeding

6.2.3.3. Statistical Analysis Plan, EPIC-PEP

The following analysis populations were included:

- **FAS**: All subjects randomly assigned to study intervention regardless of whether or not study intervention was administered
- **mITT**: All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention and had a negative RT-PCR result at baseline
- **mITT1**: All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and had a positive RT-PCR result at baseline
- **mITT2**: All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, had a negative RT-PCR result at baseline and were at increased risk of severe COVID-19
- **mITT3**: All subjects randomly assigned to study intervention who took at least 1 dose of study intervention
- **PP**: All subjects in the mITT set without important protocol deviations considered to impact the interpretation of the primary efficacy endpoint
- **SAF**: All randomized subjects who received at least 1 dose of study intervention; subjects were analyzed according to the study intervention they received

The primary analysis was conducted using the mITT population.

The primary efficacy endpoint was the proportion of subjects with a negative RT-PCR result at baseline who develop a symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14. A symptomatic infection event through Day 14 was defined as having any reported symptoms consistent with COVID-19 (cough, shortness of breath or difficulty breathing, feeling feverish, chills or shivering, fatigue, muscle or body aches, diarrhea, nausea, vomiting, headache, sore throat, stuffy or runny nose, loss of smell, loss of taste) within 14 days of an RT-PCR or rapid antigen test-confirmed infection through Day 14.

There were two comparisons for the primary endpoint: 5-day regimen of PAXLOVID versus placebo and 10-day regimen of PAXLOVID versus placebo. Multiplicity adjustment for the primary endpoint were planned using Hochberg method. If the primary endpoint was significant for both treatment groups, the key secondary endpoint was to be tested at full alpha level using Hochberg method. If one treatment group was discontinued, sequential testing was to be performed in the remaining treatment groups in the order of the primary endpoint and the key secondary endpoint. The key secondary efficacy endpoint was the proportion of subjects with symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 in adult subjects who had a negative RT-PCR result at baseline and who were at increased risk of severe COVID-19.

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The trial failed the primary efficacy analysis (see Section 6.2.3.4).

6.2.3.4. Results of Analyses, EPIC-PEP

After excluding Site 1281 and Site 1483, 2880 subjects were screened and 2736 were randomized. Results of EPIC-PEP analyses are summarized in this section.

Table 23. Subject Disposition, EPIC-PEP

Disposition Outcome	PAXLOVID 5-Day N=921 n (%)	PAXLOVID 10-Day N=917 n (%)	Placebo N=898 n (%)
Subjects randomized			
FAS population	921 (100.0)	917 (100.0)	898 (100.0)
mITT population	844 (91.6)	830 (90.5)	840 (93.5)
mITT1 population	38 (4.1)	48 (5.2)	29 (3.2)
mITT2 population	627 (68.1)	605 (66.0)	606 (67.5)
mITT3 population	889 (96.5)	887 (96.7)	873 (97.2)
PP population	724 (78.6)	723 (78.8)	720 (80.2)
Safety population[a]	912	911	898
Discontinued study drug[b]	54 (5.9)	58 (6.3)	45 (5.0)
Adverse event (AE)	10 (1.1)	11 (1.2)	14 (1.6)
Withdrawal by subject	19 (2.1)	25 (2.7)	17 (1.9)
No longer meets eligibility criteria	3 (0.3)	2 (0.2)	1 (0.1)
Medication error without associated adverse event	7 (0.8)	10 (1.1)	9 (1.0)
Non-compliance with study drug	0	0	1 (0.1)
Pregnancy	0	0	1 (0.1)
Other	15 (1.6)	10 (1.1)	2 (0.2)
Discontinued study[b]	44 (4.8)	53 (5.8)	35 (3.9)
Withdrawal by subject	25 (2.7)	36 (3.9)	23 (2.6)
Lost to follow-up	9 (1.0)	11 (1.2)	7 (0.8)
Other	10 (1.1)	6 (0.7)	5 (0.6)

Source: Reviewer's analysis on ADSL dataset, excluding subjects from site 1281 and site 1483.
[a.] Based on treatment actually received. One subject randomized to the PAXLOVID 5-day group received placebo.
[b.] Percentages are based on number of randomized subjects.
Abbreviations: FAS, full analysis set, mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects in specified population or group; PP, per-protocol

Baseline and demographic characteristics are listed in Table 24. The two groups had similar distributions in these characteristics. All subjects were between 18 and 91 years of age. Approximately 54% of subjects were female and 72% of subjects were from the United States.

Table 24. Baseline Demographic and Clinical Characteristics, Full Analysis Set, EPIC-PEP

Characteristic	PAXLOVID 5-Day N=921 n (%)	PAXLOVID 10-Day N=917 n (%)	Placebo N=898 n (%)
Sex			
Female	502 (54.5)	479 (52.2)	474 (52.8)
Male	419 (45.5)	438 (47.8)	424 (47.2)
Age, years			
Mean (SD)	43.9 (14.9)	42.8 (15.0)	42.4 (14.4)
Median (min, max)	43.0 (18.0, 89.0)	41.0 (18.0, 91.0)	41.0 (18.0, 87.0)

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Characteristic	PAXLOVID 5-Day N=921 n (%)	PAXLOVID 10-Day N=917 n (%)	Placebo N=898 n (%)
Age group, years			
18 to 44	479 (52.0)	530 (57.8)	509 (56.7)
45 to 59	301 (32.7)	251 (27.4)	279 (31.1)
60 to 64	62 (6.7)	53 (5.8)	44 (4.9)
65 to 74	50 (5.4)	58 (6.3)	49 (5.5)
≥75	29 (3.1)	25 (2.7)	17 (1.9)
Race			
American Indian or Alaska Native	58 (6.3)	52 (5.7)	49 (5.5)
Asian	8 (0.9)	15 (1.6)	11 (1.2)
Black or African American	139 (15.1)	136 (14.8)	132 (14.7)
White	714 (77.5)	711 (77.5)	704 (78.4)
Multiple	1 (0.1)	1 (0.1)	1 (0.1)
Unknown or Missing	1 (0.1)	2 (0.2)	1 (0.1)
Ethnicity			
Hispanic or Latino	664 (72.1)	642 (70.0)	643 (71.6)
Not Hispanic or Latino	257 (27.9)	275 (30.0)	255 (28.4)
Region			
United States	642 (69.7)	639 (69.7)	621 (69.2)
Europe	110 (11.9)	114 (12.4)	112 (12.5)
Rest of the World	169 (18.3)	164 (17.9)	165 (18.4)
BMI, kg/m^2			
Mean (SD)	28.0 (5.8)	27.7 (5.5)	28.0 (5.9)
Median (min, max)	27.2 (15.7, 60.1)	27.1 (17.8, 65.0)	27.1 (16.0, 69.1)
BMI group, kg/m^2			
<25	339 (36.8)	356 (38.8)	335 (37.3)
25 to <30	291 (31.6)	276 (30.1)	289 (32.2)
30 to <35	196 (21.3)	212 (23.1)	183 (20.4)
35 to <40	66 (7.2)	49 (5.3)	57 (6.3)
≥40	29 (3.1)	24 (2.6)	34 (3.8)
Baseline serology status			
Negative	75 (8.1)	86 (9.4)	69 (7.7)
Positive	838 (91.0)	820 (89.4)	823 (91.6)
Unknown	8 (0.9)	11 (1.2)	6 (0.7)
Baseline RT-PCR status			
Negative	872 (94.7)	855 (93.2)	864 (96.2)
Positive	38 (4.1)	48 (5.2)	29 (3.2)
Missing	11 (1.2)	14 (1.5)	5 (0.6)
Vaccination Status			
Subjects DID receive at least one dose of COVID-19 vaccine	118 (12.8)	116 (12.6)	121 (13.5)
Subjects DID NOT receive at least one dose of COVID-19 vaccine	803 (87.2)	801 (87.4)	777 (86.5)
Baseline Risk factor			
No risk factor for severe COVID-19	246 (26.7)	253 (27.6)	251 (28.0)
With risk factor for severe COVID-19	675 (73.3)	664 (72.4)	647 (72.0)

Source: Reviewer's Analysis on ADSL dataset, excluding subjects from site 1281 and site 1483
Abbreviations: BMI, body mass index; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; max, maximum; min, minimum; N, number of subjects in treatment group; n, number of subjects with given characteristic; RT-PCR, real-time, reverse transcription-polymerase chain reaction; SD, standard deviation

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Efficacy Analyses

The study failed the primary efficacy analysis. Table 25 displays analysis results for the endpoint of proportion of subjects with symptomatic infection through Day 14 in the mITT (primary endpoint), mITT1, mITT2 (key secondary endpoint) and mITT3 populations. There was no statistically significant difference in any analysis. Numerically lower infection rates were observed in both PAXLOVID groups compared to placebo in the mITT, mITT2 and mITT3 populations.

Table 25. Proportion of Subjects With Symptomatic, RT-PCR or RAT Confirmed SARS-CoV-2 Infection Through Day 14, EPIC-PEP

Symptomatic Infection in mITT[a]	**PAXLOVID5-Day N=844**	**PAXLOVID 10-Day N=830**	**Placebo N=840**
Subjects with event, n (%)	22 (2.6)	20 (2.4)	33 (3.9)
Estimated risk ratio vs. placebo	0.70	0.65	
Two-sided nominal p-value	0.1722	0.1163	
Symptomatic Infection in mITT2[b]	**PAXLOVID 5-Day N=627**	**PAXLOVID 10-Day N=605**	**Placebo N=606**
Subjects with event, n (%)	18 (2.9)	16 (2.6)	21 (3.5)
Estimated risk ratio vs. placebo	0.88	0.81	
Two-sided nominal p-value	0.6766	0.5070	
Symptomatic Infection in mITT1[c]	**PAXLOVID 5-Day N=38**	**PAXLOVID 10-Day N=48**	**Placebo N=29**
Subjects with event, n (%)	11 (28.9)	22 (45.8)	11 (37.9)
Estimated risk ratio vs. placebo	0.75	1.24	
Two-sided nominal p-value	0.4126	0.4273	
Symptomatic Infection in mITT3[d]	**PAXLOVID 5-Day N=889**	**PAXLOVID 10-Day N=887**	**Placebo N=873**
Subjects with event, n (%)	33 (3.7)	43 (4.8)	46 (5.3)
Estimated risk ratio vs. placebo	0.73	0.95	
Two-sided nominal p-value	0.1333	0.8088	

Source: Reviewer's analysis on ADSL dataset, excluding subjects from site 1281 and site 1483
Note: Estimated risk ratios and p-values are calculated from GEE model with a log link function and fixed effects of treatment, geographic regions and presence of risk factors associated with severe COVID-19 (except mITT2). The compound symmetry variance-covariance structure was used to account for the correlation among the subjects associated with the same index case.
[a.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and had a negative RT-PCR result at baseline.
[b.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and had a negative RT-PCR result at baseline and were at increased risk of severe COVID-19.
[c.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and had a positive RT-PCR result at baseline.
[d.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and had a negative, positive, or missing RT-PCR result at baseline.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic; RAT, rapid antigen test; RT-PCR, real-time, reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Table 26 displays analysis results for the endpoint of proportion of subjects with asymptomatic infection through Day 14 in the mITT population. There was no statistically significant difference in either analysis. Numerically lower asymptomatic infection rates were observed in both PAXLOVID groups compared to placebo.

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Table 26. Proportion of Subjects With Asymptomatic, RT-PCR or RAT Confirmed SARS-CoV-2 Infection Through Day 14, EPIC-PEP

Asymptomatic Infection in mITT[a]	PAXLOVID 5-Day N=844	PAXLOVID 10-Day N=830	Placebo N=840
Subjects with event, n (%)	17 (2.0)	16 (1.9)	26 (3.1)
Estimated risk ratio vs. placebo	0.67	0.63	
Two-sided nominal p-value	0.1869	0.1221	

Source: Reviewer's analysis on ADSL dataset, excluding subjects from site 1281 and site 1483.
Note: Estimated risk rations and p-values are calculated from GEE model with fixed effects of treatment, geographic regions and presence of risk factors associated with severe COVID-19. The compound symmetry variance-covariance structure was used to account for the correlation among the subjects associated with the same index case.
[a.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and had a negative RT-PCR result at baseline.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; GEE, generalized estimating equations; mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic; RAT, rapid antigen test; RT-PCR, real-time, reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Among subjects who had a negative RT-PCR result at baseline (mITT population), RT-PCR or rapid antigen test (RAT) confirmed SARS-CoV-2 infection through Day 14, regardless of the presence or absence of symptoms, was reported for 39 (4.6%) and 36 (4.3%) subjects in the PAXLOVID 5-day and 10-day groups, respectively, fewer than the 59 (7.0%) subjects in the placebo group.

Each treatment group had one COVID-19 related hospitalization event. The two subjects from PAXLOVID groups with hospitalization events had positive RT-PCR results at baseline (not in the mITT population). The subject from the placebo group with a hospitalization event had a negative RT-PCR result at baseline (in the mITT population). No deaths were reported in this trial.

6.3. Key Efficacy Review Issues

6.3.1. Data Reliability Issues at Specific Clinical Trial Sites

Issue

Are the clinical EPIC-HR and EPIC-SR data reliable for regulatory decision-making in the context of viral RNA and symptom data anomalies identified at certain clinical trial sites?

Background

Both EPIC-HR and EPIC-SR were global trials that enrolled subjects across numerous clinical study sites in up to 19 countries across 5 continents, with subjects enrolled at 191 sites in EPIC-HR and 195 sites in EPIC-SR.

During the conduct of the NDA review, the review team identified unusual patterns of viral RNA shedding levels, viral sequencing results, and/or daily clinical symptom reporting times from subjects at selected study sites in EPIC-HR and EPIC-SR [EPIC-HR 1274/EPIC-SR 1281 (Principal investigator [PI]: Martinez), EPIC-SR 1157 (PI: Medzhidiev, Bulgaria) and EPIC-SR 1197 (2022 enrollment period; PI: Haytova, Bulgaria)]. These observations triggered additional site inspections and in-depth investigations of all study data and sites from EPIC-HR and EPIC-

SR in order to determine if there were data reliability issues and, if so, if these were limited to specific study sites or were due to a central issue.

In addition, one study site (PI: Hernandez, Sunrise, FL, United States) that enrolled subjects for EPIC-HR (Site 1470), EPIC-SR (Site 1488), and EPIC-PEP (Site 1483), did not have the unusual data patterns noted above but was selected for a site inspection for cause based on reports of GCP noncompliance[1].

Assessment

EPIC-HR 1274 and EPIC-SR 1281 (PI: Martinez, Cutler Bay, FL, United States)

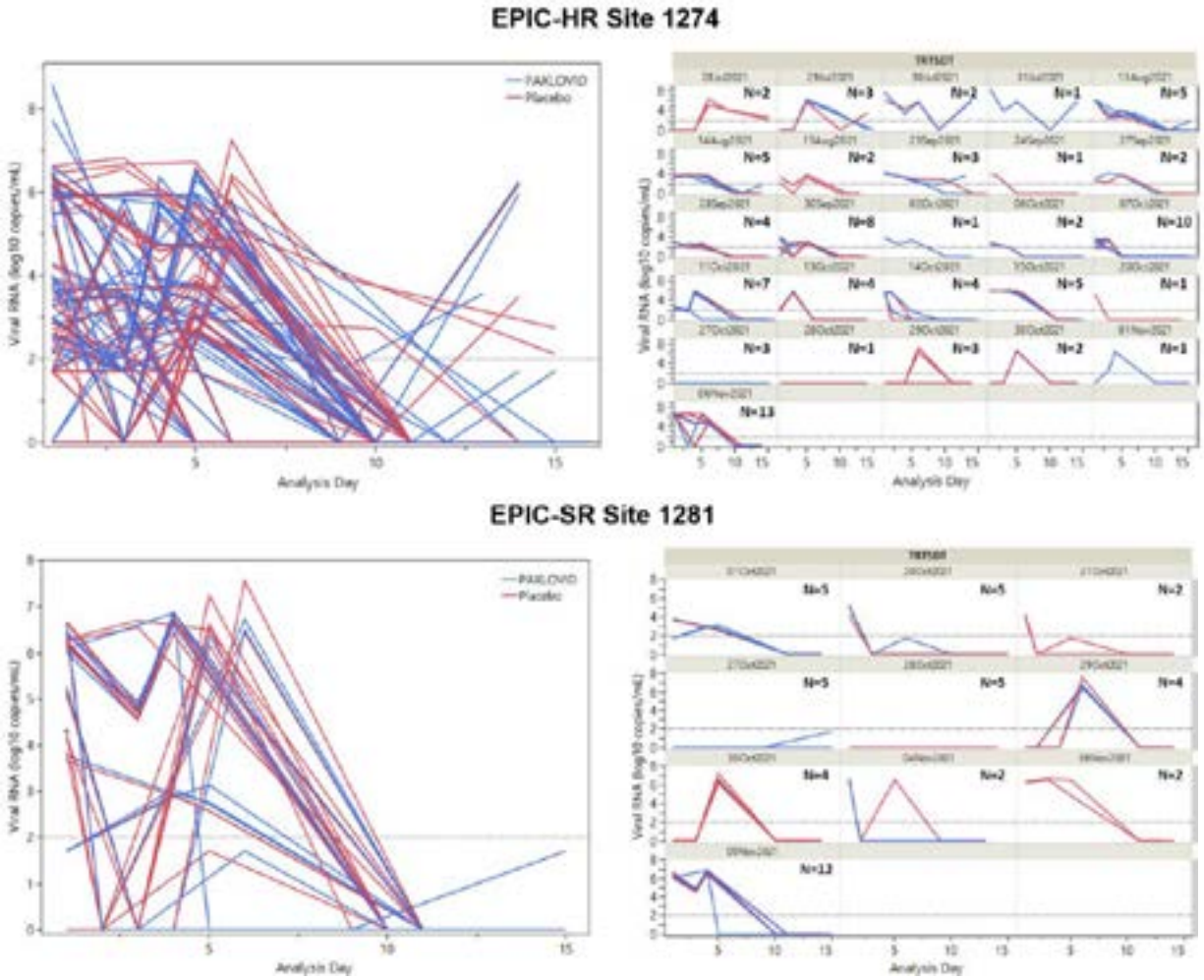
Viral RNA and Sequencing Data Anomalies

EPIC-HR 1274 was the only study site in EPIC-HR from which markedly unusual patterns of viral RNA levels and viral sequences in nasopharyngeal (NP) samples among subjects were observed, with similar unusual patterns observed from subjects enrolled at this same location in EPIC-SR (EPIC-SR 1281). The unusual viral RNA patterns were characterized by a high degree of overlapping and often implausible trends in viral RNA levels over time in different subjects at the same site, which in many cases were associated with similar timing of treatment initiation (Figure 7). For example, in EPIC-HR 1274, four different subjects who all started treatment on October 13, 2021, (2 received PAXLOVID, 2 received placebo) had a similar major spike in viral RNA levels between the Baseline and the Day 3 visits, and in all subjects viral RNA declined to undetected levels at all subsequent visits. As another example from EPIC-HR 1274, five subjects who started treatment on October 15, 2021, (3 received PAXLOVID, 2 received placebo) all had highly similar viral RNA levels which had a relatively delayed decline over time.

The overlapping viral RNA patterns within this site extended between both trials. For example, 12 different subjects across both trials who initiated treatment on October 29, 2021, or October 30, 2021, had highly similar patterns of viral RNA over time, with viral RNA levels of 6.2-7.6 $\log_{10}$ copies in the Day 5 visit window, and viral RNA levels reported as undetected at all other study visits, including baseline. These and other viral RNA patterns from this site are highly implausible and raised concerns about virology data quality or data integrity.

[1] The Applicant investigated this site due to an October 1, 2021, report (b) (6) which stated that study procedures were conducted at a facility which was not identified on the FDA form 1572 for a subset of study subjects in EPIC-HR and EPIC-SR and that the principal investigator was not always on site to see study subjects during their visits. The Applicant conducted an on-site audit from October 6 to 8, 2021, and found that the allegation regarding the use of another facility could not be ruled out, that the principal investigator provided inadequate oversight, and that there were additional instances of GCP non-compliance. Consequently, the Applicant closed this site, censored the data from subjects who had completed the trial at this site, and transferred active subjects enrolled at this site to nearby study sites to complete the trial.

Figure 7. Viral RNA Levels in NP Swab Samples From Subjects Who Enrolled at EPIC-HR 1274/EPIC-SR 1281 Sites (PI: Martinez)



Source: FDA analysis of ADSL and ADMC datasets.
Note: Each line represents viral RNA levels from an individual subject. Dashed lines indicate qRT-PCR assay LLOQ.
Abbreviations: log, logarithm; LLOQ, lower limit of quantitation; N, number of subjects in treatment group; NP, nasopharyngeal; PI, principal investigator; qRT-PCR, quantitative, real-time, reverse transcription-polymerase chain reaction; RNA, r bonucleic acid; TRTSDT, treatment start date

The same viral RNA samples used for qRT-PCR analyses were subjected to next-generation sequencing (NGS) analyses to support resistance analyses and identification of SARS-CoV-2 variants. Following the observations of overlapping viral RNA patterns noted above, extensive analyses of viral sequences were conducted by the Applicant and FDA to assess for unusual patterns of genetic clustering, which could indicate flawed or improper sample handling or processing. These analyses were conducted on consensus nucleotide sequences spanning the entire ~30 kb SARS-CoV-2 genome.

As shown in Figure 8, phylogenetic analyses of viral consensus nucleotide sequences indicated extensive genetic clustering of numerous viral sequences from different subjects from the EPIC-HR 1274/EPIC-SR 1281 site, with many sequences having minimal to nonexistent branch lengths indicating nearly or completely identical viral nucleotide sequences. These results contrast with data from other sites, for example EPIC-HR site 1276 (Figure 8), which typically show longer branch lengths and minimal clustering of highly similar viral sequences other than

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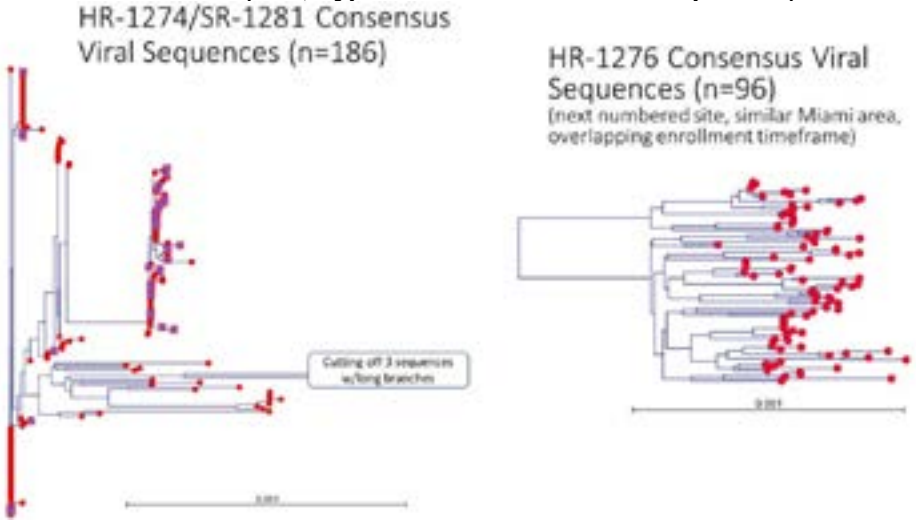
those representing different visits from the same subject. These analyses confirmed similar observations from phylogenetic analyses conducted by the Applicant. This extent of viral genetic conservation across different subjects is implausible and strongly indicates flawed NP swab sample collection, handling, or processing from this site.

Figure 8. Phylogenetic Analysis of Viral Sequences From Site EPIC-HR 1274 (Red)/EPIC-SR 1281 (Purple), and Site EPIC-HR 1276 (Red, Typical EPIC-HR Site for Comparison)

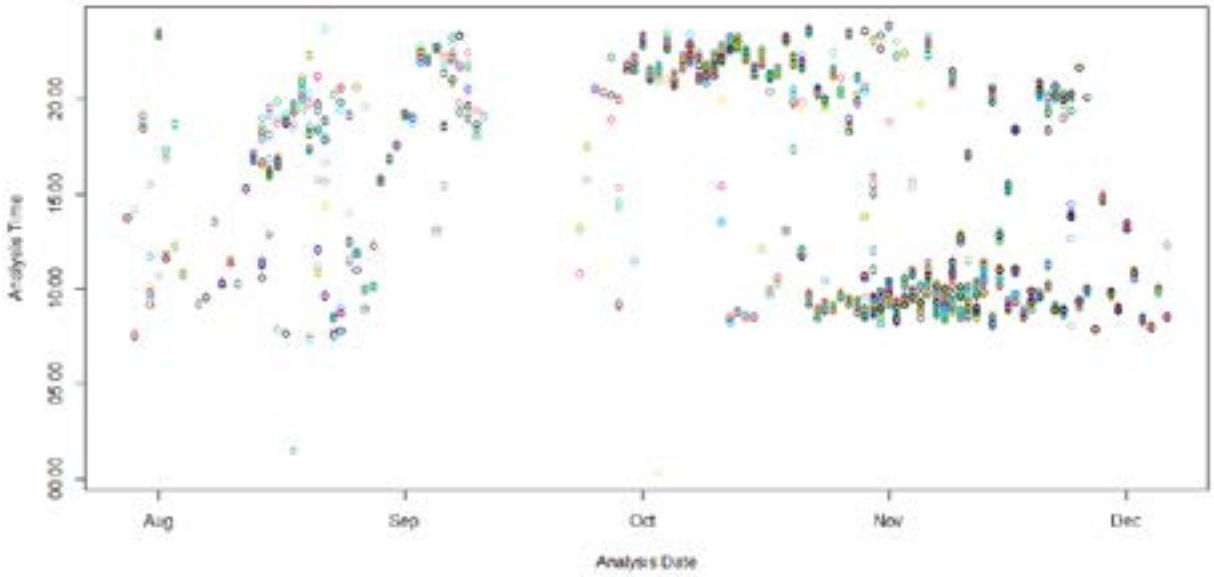


Source: FDA analysis of viral fasta consensus sequences and ADSL dataset.
Abbreviations: n, number of sequences in specified group

Symptom Data Reporting Time Anomalies

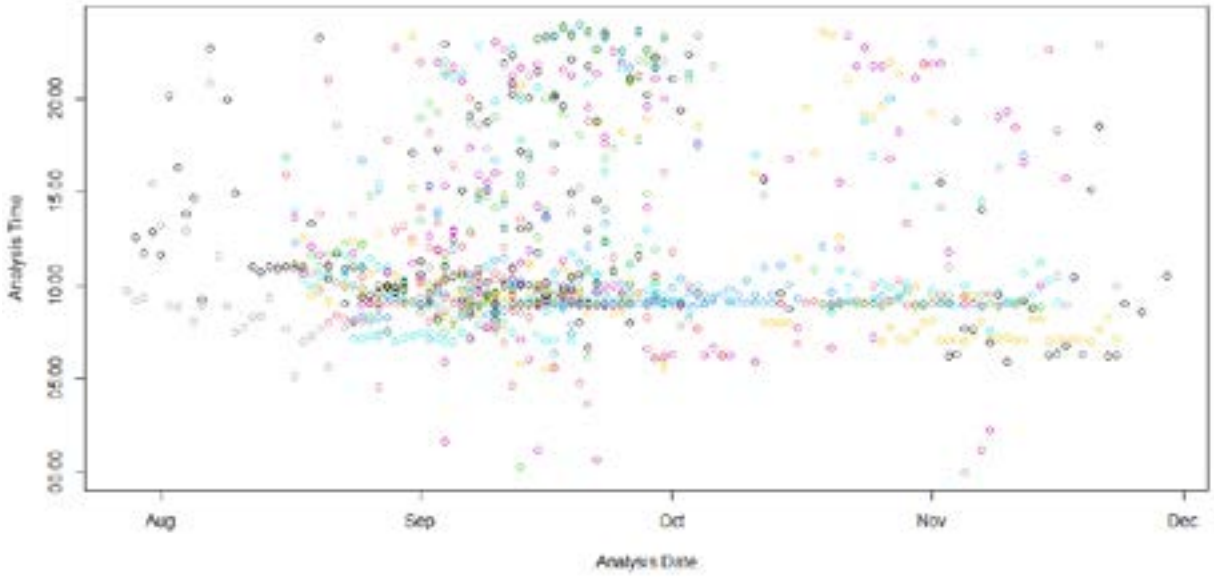
Unusual symptom data reporting time clusters were also observed at site EPIC-HR 1274/EPIC-SR 1281. As shown in Figure 9 for site EPIC-HR 1274/EPIC-SR 1281, many groups of subjects were observed to have similar daily symptom reporting time stamps, and the average time of those similar time stamps changed daily. Those groups of subjects with similar symptom reporting time stamps coincide with the groups of subjects sharing overlapping viral RNA patterns. For comparison, Figure 10 shows symptom reporting time from site EPIC-HR 1276/EPIC-SR 1282, which is similar in location and enrollment timeframe to site EPIC-HR 1274/EPIC-SR 1281. At site EPIC-HR 1276/EPIC-SR 1282, randomness was observed in symptom reporting time stamps, which reflects between-subject differences in symptom reporting time. The majority of symptom reporting time centered around 10:00, which is consistent with the recommendation of completing symptom eDiary at approximately the same time each day.

Figure 9. Symptom Data Reporting Time at Site HR1274/SR1281



Source: Reviewer's Analysis on EPIC-HR and EPIC-SR ADSO datasets.

Figure 10. Symptom Data Reporting Time at Site HR1276/SR1282

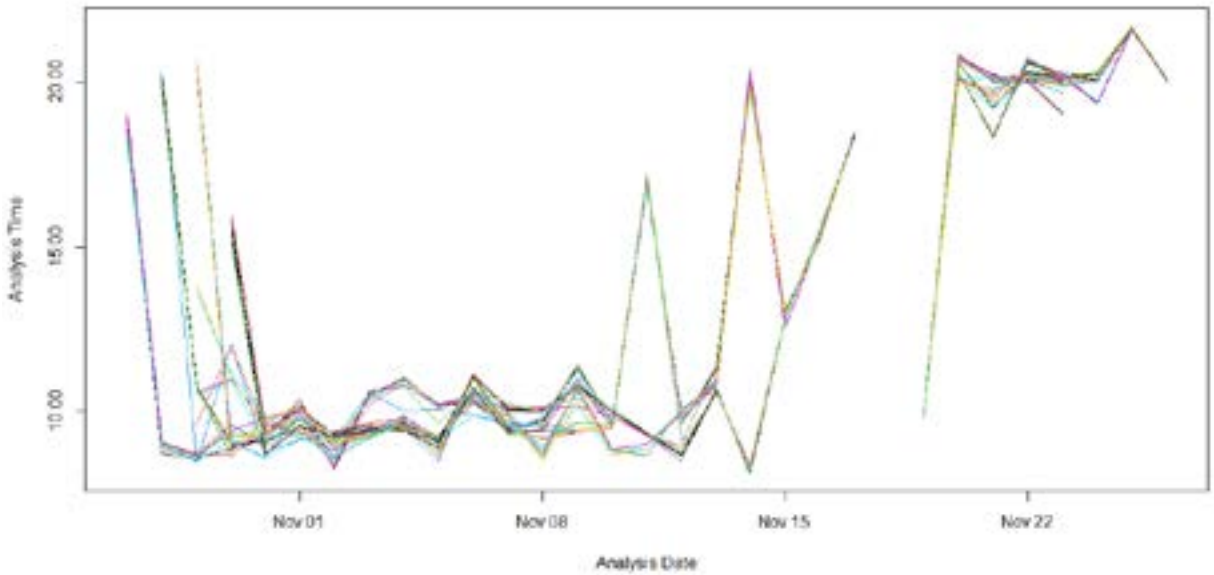


Source: Reviewer's Analysis on EPIC-HR and EPIC-SR ADSO datasets.

Figure 11 and Figure 12 show symptom data reporting time of subjects from EPIC-HR 1274/EPIC-SR 1281 and EPIC-HR 1276/EPIC-SR 1282 within specific treatment initiation time periods. EPIC-HR 1274/EPIC-SR 1281 subjects in Figure 11 initiated treatment between October 27, 2021, and October 30, 2021. Two notable patterns were identified: (1) all subjects (n=9) from EPIC-HR 1274 and all subjects (n=18) from EPIC-SR 1281 did not report symptom data on November 18, 2021, and (2) on the preceding and following days, all 27 subjects had symptom data reported within a narrow timeframe (between 18:17 and 18:29 on November 17, 2021, and between 9:49 and 9:59 on November 19, 2021). For comparison, Figure 12 shows

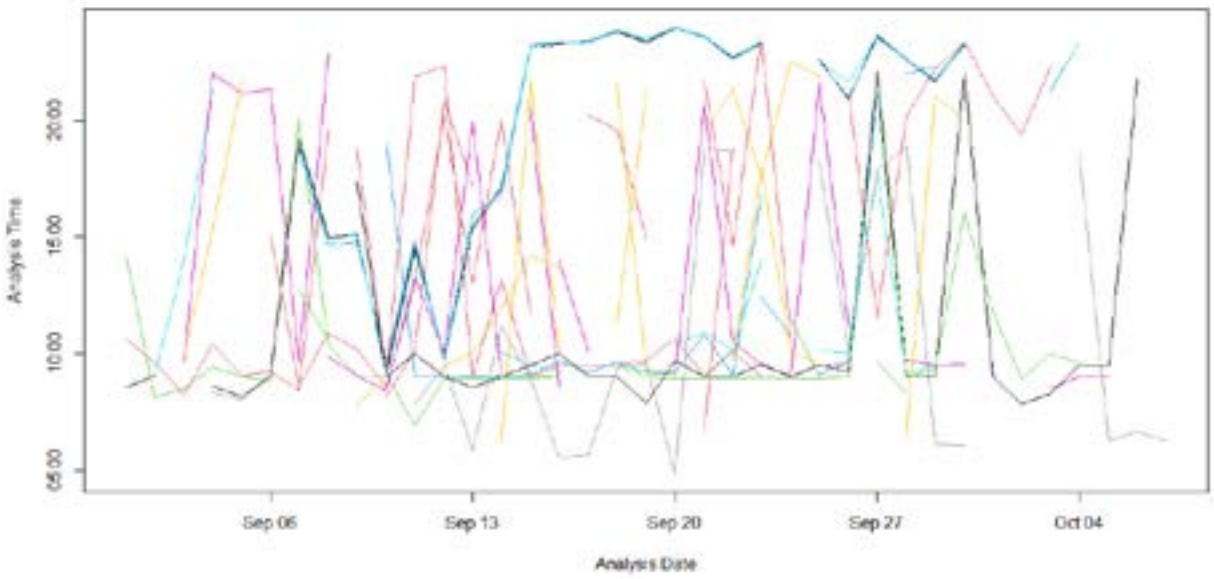
reporting time of subjects from EPIC-HR 1276/EPIC-SR 1282 who initiated treatment between September 1, 2021, and September 10, 2021 (20 subjects in total). Randomness was observed in symptom reporting time stamps in this example.

Figure 11. Symptom Data Reporting Time at Site HR1274/SR1281 for Subjects With Treatment Start Date Between October 27, 2021, and October 30, 2021



Source: Reviewer's Analysis on EPIC-HR and EPIC-SR ADSO datasets.

Figure 12. Symptom Data Reporting Time at Site HR1276/SR1282 for Subjects With Treatment Start Date Between September 1, 2021, and September 10, 2021



Source: Reviewer's Analysis on EPIC-HR and EPIC-SR ADSO datasets.

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The Applicant conducted analyses on the following two key risk indicators (KRIs) using the software application, CluePoints, to assess potential data entry anomalies:

- Time between subsequent data entry times for subjects entering eDiary data on the same date within the same site (Symptom eDiary Data Entry to Subsequent Data Entry Gap [SDOOG]).
- Time between the data save time of the previous entry and data entry time for the next entry for subjects entering eDiary data on the same date within the same site (Symptom eDiary Data Saved to Subsequent Data Entry Gap [SDOSG]).

In the CluePoints analyses combining EPIC-HR and EPIC-SR 2021 data, grouped by investigator, site HR 1274/SR 1281 was identified as high risk for SDOOG and medium risk for SDOSG, which further supports the FDA analysis findings.

The Applicant also reported that all subjects from site EPIC-HR 1274/EPIC-SR 1281 were using the same PIN code, 1274, for eDiary reporting. Note that subjects were supposed to have independent PIN codes for confidentiality and site staff should not be able to have access to eDiary data entries.

Inspection Findings

EPIC-HR 1274 had already been chosen as one of four clinical sites for routine inspection based on the regional distribution of subjects, the numbers of enrolled subjects, and site-specific efficacy results. After the above data anomalies were noted in the viral RNA levels, viral sequencing results, and daily clinical symptom reporting times from EPIC-HR 1274/EPIC-SR 1281, the planned inspection was expanded to include EPIC-SR 1281 (Martinez, Cutler Bay, FL, United States). The Office of Scientific Investigations noted the following key findings from the inspection of EPIC-HR 1274/EPIC-SR 1281:

- (b) (7)(A)
- An FDA Form 483 was issued stating that during the conduct of EPIC-HR and EPIC-SR, multiple subjects were instructed to change their eDiary PIN code to one provided by the study staff. Nevertheless, the inspections found no evidence that anyone other than the subject entered data into the eDiaries.
- There were no hospitalizations or deaths reported for either EPIC-HR 1274 or EPIC-SR 1281.

Site EPIC-SR 1157 (PI: Medzhidiev, Sofia, Bulgaria) and EPIC-SR 1197 (PI: Haytova, Vratsa, Bulgaria, 2022 Enrollment Period)

Viral RNA and Sequencing Data Anomalies

Unusual patterns of overlapping viral RNA levels over time, similar to what was observed for EPIC-HR 1274/ EPIC-SR 1281, were also observed in data from EPIC-SR 1157 (PI:

Medzhidiev, Bulgaria) and EPIC-SR 1197 (PI: Haytova, Bulgaria) specifically during the 2022 (Omicron) enrollment period.

Analyses conducted by the Applicant and FDA also found extensive clustering of viral sequences from EPIC-SR 1157, much like the observations from EPIC-HR 1274/EPIC-SR 1281. Clustering of viral sequences from EPIC-SR 1197 was not as obvious as observed for the other sites, but for subjects who enrolled in the 2022 period (among whom anomalous viral RNA patterns were observed) there was evidence of clustering of viral sequences with short or no branch lengths.

The viral RNA and sequencing data anomalies from these sites are described in detail in review Section 18.5.

Symptom Data Reporting Time Anomalies

All five subjects from EPIC-SR 1197 with treatment start date of April 18, 2022, had no symptom data on 03May 2022. No other abnormal symptom data entry time pattern was identified.

Inspection Findings

Though not initially planned for routine clinical site inspections, both EPIC-SR 1157 (PI: Medzhidiev, Sofia, Bulgaria) and EPIC-SR 1197 (PI: Haytova, Vratsa, Bulgaria) were added as inspection sites based on the unusual patterns of viral RNA levels and viral sequencing results along with eDiary symptom data collection anomalies. In addition, EPIC-HR 1193 was added for inspection because it had the same principal investigator as EPIC-SR 1197 (Haytova, Vratsa, Bulgaria). The Office of Scientific Investigations noted key findings from the inspections listed below.

EPIC-SR 1157 (PI: Medzhidiev, Sofia, Bulgaria)

- An FDA Form 483 was issued stating that during the conduct of EPIC-SR, the clinical investigator did not ensure that each subject created a new device PIN code that remained confidential to the subject only. Instead, subjects were instructed to use PIN codes that were easy to remember, such as their birth dates, which were readily available to the site. Records revealed that 48 of 49 enrolled subjects used their birth year as their new PIN code.
- Nevertheless, the inspections found no evidence that anyone other than the subject entered data into the eDiaries.
- There were no hospitalizations or deaths reported.

EPIC-HR 1193/EPIC-SR 1197 (PI: Haytova, Vratsa, Bulgaria)

- An FDA Form 483 was issued stating that during the conduct of EPIC-SR and EPIC-HR, the clinical investigator did not follow the Site User Guide. Specifically, the Site User Guide for the electronic patient reported outcome (ePRO) application used in the study to collect electronic diaries states “The participant should not share their PIN code with anyone, not even with study staff. The new PIN code must remain confidential, with only the participant knowing the PIN code.” However, when assisting subjects to download and activate the application, the investigator’s site staff provided suggestions in a manner that caused the

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subjects in the studies to create nonconfidential PIN codes. The investigator's site staff gave examples of easily memorable numbers to use for a PIN code, including birth year and specific numbers such as "2323."

- Nevertheless, the inspections found no evidence that anyone other than the subject entered data into the eDiaries.
- For EPIC-HR 1193, the occurrence of COVID-19 related hospitalizations and death from any cause were verified against the data line listings provided by the Applicant for all 59 randomized subjects (there were no hospitalizations or deaths in EPIC-SR 1197).

EPIC-HR 1470 (PI: Hernandez, Sunrise, FL, United States)

Viral RNA and Sequencing Data Anomalies

None identified.

Symptom Reporting Data Anomalies

None identified.

Inspection Findings

EPIC-HR 1470 was selected for inspection due to a complaint and subsequent site closure by the Applicant for GCP noncompliance, as described in the background above; this investigator (Hernandez, Sunrise, FL, United States) also had a site for EPIC-SR (1488) that was not included in the inspection. The Office of Scientific Investigations noted the following key findings from this inspection:

- An FDA Form 483 was issued stating that five of 23 subjects did not meet an inclusion criterion, or met an exclusion criterion, but were screened, enrolled, randomized, and received investigational product.
- The Applicant's previous investigation had found GCP non-compliance at this site (please see the background section for more details), and consequently this site and the corresponding EPIC-SR site (1488) were closed during the trial conduct period.
- Based on the totality of findings from the FDA inspection and the Applicant's inspection of this site, the review team had concerns about the reliability of the clinical data generated at this site. The Applicant had already censored data from the subjects who were enrolled and completed all study assessments (n=2 for EPIC-HR 1470, n=1 for EPIC-SR 1488). However, it was noted by the Office of Scientific Investigations that subjects who were enrolled and who completed Day 28 visits at this site were not censored and were listed in the datasets with the site they were later transferred to for long-term follow-up (n=36 for EPIC-HR 1470, n=30 for EPIC-SR 1488). Notably, most data for the efficacy and safety endpoints were collected by Day 28.

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Other EPIC-HR and EPIC-SR Clinical Sites

Viral RNA and Sequencing Data Anomalies

Numerous additional analyses were conducted by the Applicant and FDA to assess for viral RNA or sequencing anomalies across all study sites in EPIC-HR and EPIC-SR, and ultimately to ensure reliability of these data from other study sites. These included systematic analyses of viral RNA levels for evidence of concordant patterns over time for different subjects at the same site, and both phylogenetic and BLAST (Basic Local Alignment Search Tool) analyses of viral sequences to identify any additional sites with unusually high frequencies of highly similar or identical viral nucleotide sequences. Also, analyses were conducted to identify sites with high frequencies of subjects with low or undetected viral RNA levels.

Overall, these systematic analyses confirmed the observations of overlapping viral RNA patterns and clustering of viral sequences noted above for sites EPIC-HR 1274/EPIC-SR 1281 (PI: Gonzalez/Martinez), EPIC-SR 1157 (PI: Medzhidiev, Bulgaria) and EPIC-SR 1197 (2022 enrollment period; PI: Haytova, Bulgaria). No other sites with similar patterns were identified. Additional sites were identified with high frequencies of subjects with low or undetected viral RNA at baseline, which could be explained by the immunologic characteristics of the population or characteristics of the virus circulating at the time, as these sites were clustered geographically, and most subjects were seropositive for SARS-CoV-2 at baseline.

See Section 18.5, for additional details, investigations, and discussion regarding the viral RNA and sequencing data anomalies observed at certain study sites in EPIC-HR and EPIC-SR.

Symptom Data Reporting Time Anomalies

Additional analyses were conducted to evaluate EPIC-HR and EPIC-SR sites with observable time stamp clusters, sites identified as medium risk in the Applicant's CluePoints analyses, and sites with high percentage of common PIN codes. These sites did not have similar viral RNA data issues as observed in EPIC-HR 1274/EPIC-SR 1281. Additional sensitivity analyses were conducted on the EPIC-HR primary efficacy endpoint of COVID-19 related hospitalization or death from any cause through Day 28, to evaluate the potential impact of removing those sites. The sensitivity analyses showed consistent results with the results in Section 6.2.1. See Section 16.1 for details on the additional analyses. To evaluate the potential impact of these sites on symptom rebound analyses, additional analyses were conducted in Section 16.4, with consistent conclusions as those in Section 6.3.6.

Inspection Findings

Three additional sites were chosen for routine inspection based on the regional distribution of subjects, the numbers of enrolled subjects, and site-specific efficacy results: EPIC-HR 1108 (PI: Igbinadolor, Monroe, NC, United States); EPIC-HR 1158 (PI: Mitreva, Samokov, Bulgaria); and EPIC-HR 1097 (PI: Simova, Pleven, Bulgaria). No issues were identified at these sites. The occurrence of COVID-19 related hospitalizations and death from any cause at Day 28 were verifiable at all three sites.

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Assessments for Anomalies in Other Types of Data

Other EPIC-HR and EPIC-SR data (AEs, vital signs, safety laboratory findings, electrocardiograms (ECGs), and pharmacokinetic data) were analyzed to look for unusual site-specific patterns. No overtly suspicious site-specific patterns were detected from these other data sources. Furthermore, CluePoints analyses done by FDA looking at multiple data elements including laboratory values did not uncover any site-specific atypical results that could not be explained by geographic differences and normal variation.

Conclusion

The extensive analyses summarized above indicate that viral RNA shedding data, viral sequencing data, and certain symptom reporting data from sites EPIC-HR 1274/EPIC-SR 1281 (PI: Martinez), EPIC-SR 1157 (PI: Medzhidiev, Bulgaria) and EPIC-SR 1197 (2022 enrollment period; PI: Haytova, Bulgaria) are highly unusual and implausible, raising concerns about data quality or reliability from these sites. Given the concerning data patterns, the review team determined that these sites should be excluded from all key efficacy, safety, and virology analyses. Note that data from EPIC-SR collected during the 2022/Omicron period were not used for primary efficacy and safety analyses; these data contributed to analyses of viral RNA shedding, drug resistance, and COVID-19 rebound.

Likewise, given that the reliability of data from site EPIC-HR 1470/EPIC-SR 1488 was in question due to the identified GCP noncompliance, and because data for the main efficacy and safety analyses were collected by Day 28, the review team determined that data from all subjects enrolled at this site should also be excluded from the key analyses.

There is no indication that any of the data anomalies or clinical trial oversight concerns were in any manner related to specific treatment assignment, and therefore, data from these sites do not contribute towards any potentially flawed efficacy or safety conclusions regarding PAXLOVID versus placebo. All conclusions on overall efficacy and safety, viral RNA shedding and resistance, and viral and symptomatic rebound remain unchanged regardless of whether these study sites are censored.

In conclusion, the following sites/subjects were excluded from all key efficacy, safety, and virology analyses of the EPIC-HR and EPIC-SR trials that are included in this review:

- EPIC-HR: Sites 1274 (PI: Martinez, N=95 treated) and 1470 (including subjects [IDs that start with 1470] who transferred to 1276, N=38 treated)
- EPIC-SR Pre-Omicron, data through December 19, 2021 cut-off: Sites 1281 (PI: Martinez, N=46 treated), and 1488 (including subjects [IDs which start with 1488] who transferred to site 1282, N=31 treated)
- EPIC-SR Post-Omicron, 2022 data: Sites 1157 (PI: Medzhidiev, N=47 treated) and 1197 (PI: Haytova, 2022 enrollees only, N=18 treated)
- Total N excluded: 275 treated (133 in EPIC-HR, 142 in EPIC-SR; 137 PAXLOVID-treated, 138 placebo-treated)

The exclusion of these sites required resubmission of key analyses by the Applicant, and confirmatory analyses by the FDA, which constituted a major amendment and extended the Prescription Drug User Fee Act (PDUFA) review clock.

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Given the concerns on data reliability of sites EPIC-HR 1274/EPIC-SR 1281 and EPIC-HR 1470/EPIC-SR 1488, data of the corresponding sites in EPIC-PEP, EPIC-PEP 1281 (EPIC-HR 1274/EPIC-SR 1281) and EPIC-PEP 1483 (EPIC-HR 1470/EPIC-SR 1488), were also excluded from the review of EPIC-PEP.

6.3.2. Efficacy in High-Risk Adults Who Are Vaccinated Against COVID-19 or Previously Infected With SARS-CoV-2

Issue

Is the benefit-risk assessment favorable for PAXLOVID for the treatment of mild-to-moderate COVID-19 in high-risk individuals who were previously vaccinated against COVID-19 or previously infected with SARS-CoV-2?

Background

The proposed PAXLOVID indication is for the treatment of mild-to-moderate COVID-19 in high-risk adults regardless of COVID-19 vaccination status or prior SARS-CoV-2 infection. However, EPIC-HR, the pivotal trial which demonstrated an 86% relative risk reduction (RRR) for PAXLOVID in the endpoint of COVID-19 related hospitalization or death from any cause through Day 28 (mITT1 population), enrolled high-risk adults who had not received any dose of a COVID-19 vaccine and who had not had a prior confirmed SARS-CoV-2 infection. Because COVID-19 vaccination is known to reduce the risk of severe disease (CDC 2023b), the relevance of the benefit with PAXLOVID observed in EPIC-HR to high-risk adults with pre-existing SARS-CoV-2 immunity was an important review issue.

Currently, the overwhelming majority of adults in the United States have either received one or more COVID-19 vaccine doses or previously been infected with SARS-CoV-2. As of March 1, 2023, 92% of the total U.S. population ≥18 years of age, and 95% of the U.S. population ≥65 years of age, had received at least one COVID-19 vaccine dose (CDC 2023b). In addition, 79% of the total U.S. population ≥18 years of age, and 94% of the population ≥65 years of age, had completed a COVID-19 primary vaccination series. Furthermore, the results from EPIC-PEP, which enrolled from September 9, 2021, to March 1, 2022 (a later enrollment period than for EPIC-HR), indicate that even unvaccinated adults were likely to be SARS-CoV-2 seropositive by 2022, presumably from prior infection. In EPIC-PEP, which enrolled adults with negative screening SARS-CoV-2 rapid antigen test results and who were asymptomatic household contacts of individuals with COVID-19, only 12% of subjects reported receiving at least one COVID-19 vaccine dose, but 91% were SARS-CoV-2 seropositive at baseline.

Assessment

Methods

In order to assess the benefit and risk of PAXLOVID treatment in high-risk adults who were previously vaccinated against COVID-19 or previously infected with SARS-CoV-2, EPIC-HR and EPIC-SR efficacy and safety data were analyzed as described in the sections below. Unless otherwise noted, in both trials the mITT1 population (treated within 5 days of symptom onset

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and not expected to receive a COVID-19 mAb treatment) was used as this population is most consistent with the indication proposed by the Applicant for PAXLOVID labeling.

Three different populations were identified from EPIC-HR and EPIC-SR, the two trials evaluating PAXLOVID versus placebo for the treatment of mild-to-moderate COVID-19. All subjects in these three populations had at least one risk factor that put them at high risk for progression to severe disease:

(1) The Vaccinated High-Risk Subgroup in EPIC-SR

EPIC-SR was not powered to detect a treatment effect in this subgroup. Once PAXLOVID received an EUA in December 2021 for the treatment of mild-to-moderate COVID-19 in high-risk individuals regardless of vaccination status, there was a lack of clinical equipoise to continue enrolling these subjects into a placebo-controlled trial, as vaccinated high-risk individuals could obtain PAXLOVID outside of a trial setting. Consequently, this analysis is limited to 631 vaccinated high-risk subjects who were enrolled prior to PAXLOVID receiving an EUA.

(2) The Seropositive Subgroup in EPIC-HR, to represent high-risk individuals who may have previously been infected with SARS-CoV-2 and as a surrogate for vaccinated adults.

- Baseline SARS-CoV-2 seropositivity may indicate some pre-existing SARS-CoV-2 immunity due to prior undiagnosed infection or may represent an early immune response to the current infection. Although immunity from prior infection is not identical to immunity from prior vaccination, the seropositive subgroup could be considered the EPIC-HR subgroup most representative of COVID-19 vaccinated adults. Analyses in this subgroup were considered supportive of the PAXLOVID EUA for the treatment of mild-to-moderate COVID-19 in high-risk individuals regardless of COVID-19 vaccination status.

(3) The Seronegative Subgroup in EPIC-HR, for comparison.

<u>Reduction in the Endpoint of COVID-19 Related Hospitalization or Death From Any Cause Through Day 28</u>

The RRR for PAXLOVID for the endpoint of COVID-19 related hospitalization or death from any cause through Day 28 was similar (>50%) in all three subgroups, noting the EPIC-SR vaccinated high-risk subgroup analysis was underpowered and did not reach statistical significance:

- In the EPIC-SR vaccinated high-risk subgroup, 3/317 (<1%) PAXLOVID recipients versus 7/314 (2%) placebo recipients met the composite endpoint, for a RRR of 58% (nominal p-value=0.2).

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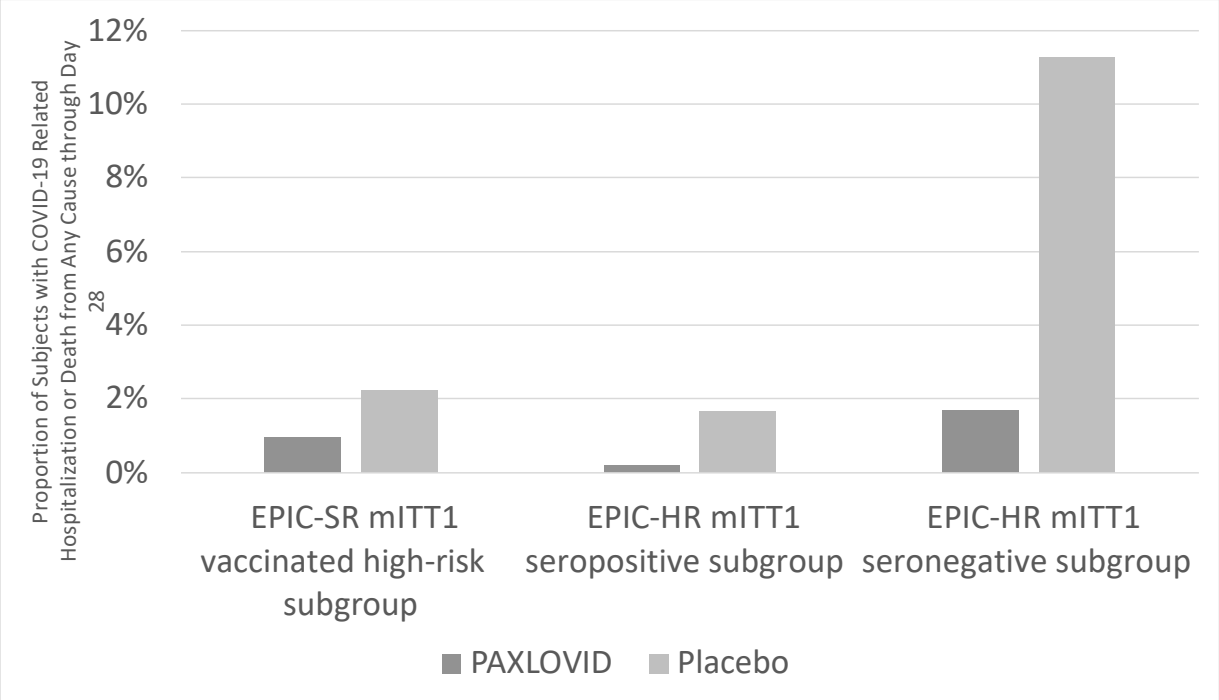
- In the EPIC-HR seropositive subgroup, 1/490 (<1%) PAXLOVID recipients versus 8/479 (2%) placebo recipients met the composite endpoint, for a RRR of 88% (nominal p-value=0.02).
- In the EPIC-HR seronegative subgroup, 8/475 (2%) PAXLOVID recipients versus 56/497 (11%) placebo recipients met the composite endpoint, for a RRR of 85% (nominal p-value<0.0001).

Source: Applicant's Table 84b.2.4.6.1.f from their December 5, 2022, submission and Applicant's Figure 841.2.1.24 from their November 23, 2022, response to an FDA information request. P-values were based on difference in estimated proportions using the Kaplan-Meier method.

Please see Figure 13. While the RRR with PAXLOVID versus placebo was similar in all three subgroups, the absolute risk reduction was lower in the EPIC-SR vaccinated high-risk and the EPIC-HR seropositive subgroups. This is because pre-existing SARS-CoV-2 immunity either from prior infection or prior COVID-19 vaccination reduces the risk of severe COVID-19 outcomes. The absolute risk for COVID-19 related hospitalization or death from any cause through Day 28 in the placebo group was ~2% in the EPIC-HR seropositive and the EPIC-SR vaccinated high-risk subgroups versus 11% in the EPIC-HR seronegative subgroup. Notably, the impact of SARS-CoV-2 seropositivity in reducing the risk of severe outcomes is illustrated further by the following: in the vaccinated high-risk subgroup in EPIC-SR, 2/15 (13%) of the subjects who were baseline SARS-CoV-2 seronegative despite vaccination met the hospitalization/death endpoint versus 8/611 (1%) of the subjects who were baseline SARS-CoV-2 seropositive.

Figure 13. Proportion of High-Risk Subjects With COVID-19 Related Hospitalization or Death From Any Cause Through Day 28



Sources: EPIC-SR Table 84b.2.4.6.1.f from the Applicant's December 5, 2022, submission, verified by the ADSL and ADHosp datasets, and EPIC-HR Figure 841.2.1.24 from the Applicant's November 23, 2022 submission.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent-to-treat

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Other Clinical Efficacy Endpoints

In the EPIC-SR vaccinated high-risk and the EPIC-HR seropositive subgroups, benefit or trends toward benefit with PAXLOVID were observed for other clinical efficacy endpoints for which benefit was seen with PAXLOVID in the EPIC-HR seronegative subgroup as outlined below. However, as with the endpoint of COVID-19 related hospitalization or death from any cause through Day 28 discussed above, outcomes were more favorable overall regardless of treatment in the EPIC-SR vaccinated high-risk and the EPIC-HR seropositive subgroups versus the seronegative subgroup in EPIC-HR.

Time to Sustained Alleviation of All Targeted Signs/Symptoms Through Day 28: median (95% CI) days for PAXLOVID versus placebo recipients, p-value

- EPIC-SR vaccinated high-risk subgroup: 12 (10, 14) versus 13 (11, 14), nominal p-value=0.9749
- EPIC-HR seropositive subgroup: 12 (11, 13) versus 14 (13, 15), nominal p-value=0.0095
- EPIC-HR seronegative subgroup: 13 (12, 15) versus 17 (16, 19), nominal p-value<0.0001

Source: Reviewer's analyses on EPIC-HR and EPIC-SR ADSO/ADSL datasets using log rank test.

Time to Sustained Resolution of All Targeted Signs/Symptoms Through Day 28: median (95% CI) days for PAXLOVID versus placebo recipients, p-value

- EPIC-SR vaccinated high-risk subgroup: 15 (13, 16) versus 15 (14, 17), nominal p-value=0.9523
- EPIC-HR seropositive subgroup: 15 (13, 16) versus 16 (15, 19), nominal p-value=0.0479
- EPIC-HR seronegative subgroup: 19 (17, 20) versus 23 (19, 25), nominal p-value=0.0026

Source: Reviewer's analyses on EPIC-HR and EPIC-SR ADSO/ADSL datasets using log rank test.

Note: The time to sustained symptom alleviation and time to sustained symptom resolution endpoints should be interpreted with caution given the large amount of missing data, potential data anomalies, symptom relapse after achieving the defined alleviation/resolution, and the lower symptom alleviation/resolution rates on Day 28 in the PAXLOVID group in the EPIC-SR vaccinated high-risk subgroup analyses (see Section 6.2.1.4 for more details).

All-Cause Mortality Through Week 24

- EPIC-SR vaccinated high-risk subgroup: 0/317 PAXLOVID recipients versus 1/314 (<1%) placebo recipients died (nominal p-value=0.498 by Fisher's exact test)
- EPIC-HR seropositive subgroup: 0/490 PAXLOVID recipients versus 3/479 (<1%) placebo recipients died (nominal p-value=0.1204 by Fisher's exact test)
- EPIC-HR seronegative subgroup: 0/475 PAXLOVID recipients versus 12/497 (2%) placebo recipients died (nominal p-value=0.0005 by Fisher's exact test)

Source: Applicant's Tables 84b.69b.5 and 84a.69a.5 from their December 5, 2022, response to an FDA information request.

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COVID-19 Related Medical Visits Through Day 34

- EPIC-SR vaccinated high-risk subgroup: 7/317 (2%) PAXLOVID recipients versus 17/314 (5%) placebo recipients, nominal p-value=0.0579
- EPIC-HR seropositive subgroup: 8/490 (2%) PAXLOVID recipients versus 15/479 (3%) placebo recipients, nominal p-value=0.1864
- EPIC-HR seronegative subgroup: 14/475 (3%) PAXLOVID recipients versus 67/497 (14%) placebo recipients, nominal p-value<0.0001

Source: Reviewer's analyses on EPIC-HR and EPIC-SR ADHOSP/ADSL datasets using Pearson's Chi-squared test with continuity correction.

Nasopharyngeal Viral RNA Changes Over Time

In exploratory analyses, PAXLOVID treatment led to significantly greater reductions in NP SARS-CoV-2 viral RNA shedding levels compared to placebo from baseline to Day 5 in all three subgroups, although baseline viral RNA levels were numerically higher overall in the EPIC-HR seronegative subgroup. The Applicant conducted a statistical analysis of change from baseline to Day 5 in $\log_{10}$ transformed viral RNA levels (copies/mL) from NP samples. The analysis of covariance model included treatment, geographic region, symptom onset duration (≤3, >3 days), and baseline viral RNA level as covariates. Baseline SARS-CoV-2 serology status was also a covariate in the EPIC-SR vaccinated high-risk subgroup analysis. PAXLOVID conferred an additional mean reduction (SE) of -0.84 (0.14) $\log_{10}$ copies/mL in the EPIC-SR vaccinated high-risk subgroup ($p \leq 0.0001$), -0.47 (0.12) $\log_{10}$ copies/mL in the EPIC-HR seropositive subgroup ($p \leq 0.0001$), and -1.01 (0.11) $\log_{10}$ copies/mL in the EPIC-HR seronegative subgroup ($p \leq 0.0001$). Please see Table 27 below.

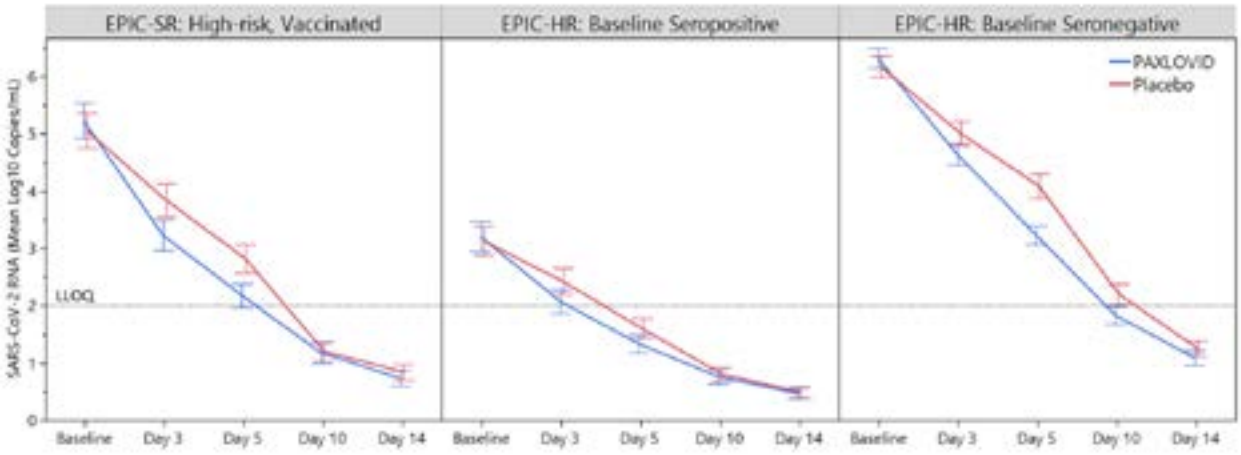
Table 27. Change From Baseline to Day 5 in SARS-CoV-2 RNA Levels in Nasopharyngeal Samples ($\log_{10}$ Transformed Copies/mL)

SARS-COV-2 RNA Measure	EPIC-SR Vaccinated HR PAXLOVID	EPIC-SR Vaccinated HR PBO	EPIC-HR Seropositive PAXLOVID	EPIC-HR Seropositive PBO	EPIC-HR Seronegative PAXLOVID	EPIC-HR Seronegative PBO
Baseline, n	256	257	320	330	436	444
Baseline mean (SD)	6.21 (1.86)	6.00 (1.87)	4.75 (2.23)	4.45 (2.22)	6.54 (1.59)	6.50 (1.60)
Day 5, n	246	238	280	296	396	387
Day 5 mean (SD)	2.58 (1.76)	3.32 (2.02)	1.88 (1.70)	2.22 (1.98)	3.32 (1.65)	4.31 (2.06)
Change* from BL, n	245	236	280	296	396	387
Change from BL mean (SE)*	-3.35 (0.23)	-2.51 (0.23)	-2.72 (0.09)	-2.26 (0.09)	-3.31 (0.17)	-2.30 (0.17)

Source: Information taken from the Applicant's Tables 84b.2.2.16.f and 84a.2.2.12 submitted on December 5, 2022.
* Least squares mean difference
Abbreviations: BL, baseline; HR, high risk; log, logarithm; n, number of subjects in specified population or group; PBO, placebo; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SE, standard error; SD, standard deviation

FDA independent analyses, shown in Figure 14 below, were generally consistent with the Applicant's findings.

Figure 14. SARS-CoV-2 RNA Levels Over Time



Source: FDA analysis of EPIC-HR and EPIC-SR ADSL and ADMC datasets
Abbreviations: log, logarithm; LLOQ, lower limit of quantitation; RNA, r bonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Real-*World Evidence*

Since PAXLOVID was authorized for emergency use in December 2021, FDA has monitored the published literature on real-world evidence (RWE) studies that evaluated PAXLOVID effectiveness in outpatient COVID-19 populations. Most of the data sources used in these published RWE studies had insufficient longitudinal data and/or inappropriate study design to account for potential bias.

Among the identified studies, five are based on appropriate source data and implemented design features that can account for the potential bias introduced by "index time" selection. These five retrospective cohort studies estimated the effectiveness of PAXLOVID by COVID-19 vaccination status, or in a vaccinated population only. In general, these studies had similar findings to the clinical trials (i.e., PAXLOVID was effective or trended towards effectiveness regardless of COVID-19 vaccination status). However, while the source data and certain design elements of these cohort studies were appropriate, there were insufficient details on the data source, methods, or analytical approach for a complete review to determine the quality of the results of the studies. Please see Section 16.5 for more details.

Safety Data

Safety findings did not differ in the clinical trials by vaccination status or by baseline serology. Based on EPIC-HR safety data combined with the interim data from EPIC-SR (December 19, 2021, data cutoff), incidence of treatment-emergent adverse events (TEAEs) was 25% and 27% in the vaccinated subgroup, versus 22% and 24% in the unvaccinated subgroup, for PAXLOVID and placebo recipients, respectively. Likewise, incidence of TEAEs among PAXLOVID recipients was similar in the seropositive versus seronegative subgroups (24% versus 22%). In all subgroups, the most common TEAE among PAXLOVID recipients was dysgeusia followed by diarrhea. Please see Section 17.3 for more details.

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Conclusion

The EPIC-HR and EPIC-SR clinical trial results support the efficacy of PAXLOVID for the treatment of mild-to-moderate COVID-19 in high-risk adults regardless of COVID-19 vaccination status or evidence of prior SARS-CoV-2 infection. While pre-existing SARS-CoV-2 immunity, either from vaccination or prior infection, is among the factors that impact the risk of progression to severe COVID-19, the RRR with PAXLOVID versus placebo for COVID-19 related hospitalization or death from any cause appears to be similar in high-risk subjects regardless of prior COVID-19 vaccination or baseline SARS-CoV-2 serostatus. Similar patterns were seen with other efficacy endpoints. In addition, PAXLOVID led to significant additional reductions in SARS-CoV-2 viral RNA shedding levels in NP swabs through Day 5 versus placebo in high-risk subjects regardless of COVID-19 vaccination status or evidence of prior SARS-CoV-2 infection. In terms of risk, prior vaccination and baseline seropositivity had no discernible impact on the safety of PAXLOVID.

Healthcare providers should consider the benefit-risk for individual patients, including those who have received prior COVID-19 vaccination or been previously infected with SARS-CoV-2. Factors that impact the risk of progression to severe COVID-19, such as vaccination status, age, and cardiovascular disease, should be considered when making individual treatment decisions along with factors that may impact the risk of PAXLOVID use, such as drug interactions with concomitant medications that may result in significant adverse reactions.

6.3.3. Efficacy of PAXLOVID in the Setting of the SARS-CoV-2 Omicron Variant

Issue

Is PAXLOVID likely to retain efficacy against the SARS-CoV-2 Omicron variant?

Background

The pivotal trial EPIC-HR, which showed efficacy of PAXLOVID based on the primary endpoint of COVID-19 related hospitalization or death from any cause through Day 28, enrolled subjects in the timeframe of July to November 2021. During this period, the SARS-CoV-2 Delta variant was predominant in the United States and throughout most of the world, and this preceded the emergence and global spread of the SARS-CoV-2 Omicron variant and sub-variants. As expected, the study population in EPIC-HR was primarily (~99%) infected with the SARS-CoV-2 Delta variant, and the Omicron variant was not observed.

Soon after the completion of EPIC-HR, the Omicron variant (and in particular the Omicron sub-variant BA.1) quickly became predominant and replaced the SARS-CoV-2 Delta variant in the United States and worldwide. Currently, Omicron sub-variants are responsible for essentially all SARS-CoV-2 infections in the United States, with the Omicron sub-variants XBB.1.5 and XBB.1.9.1 most commonly detected (CDC 2023c).

While the second half of the EPIC-SR trial was conducted from March to June 2022, in a study population infected with the SARS-CoV-2 Omicron variant (based on 89% of subjects with available variant data, 100% had an Omicron variant, mostly BA.2-related), data from this trial were insufficient to directly determine the clinical efficacy of PAXLOVID in patients infected

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with the Omicron variant and at high risk for progression to severe COVID-19. Enrollment during this period was restricted to subjects at low risk for severe disease given high-risk subjects could obtain PAXLOVID under EUA, and no subjects during this period reached the secondary efficacy endpoint of COVID-19 related hospitalization or death from any cause through Day 28.

Assessment

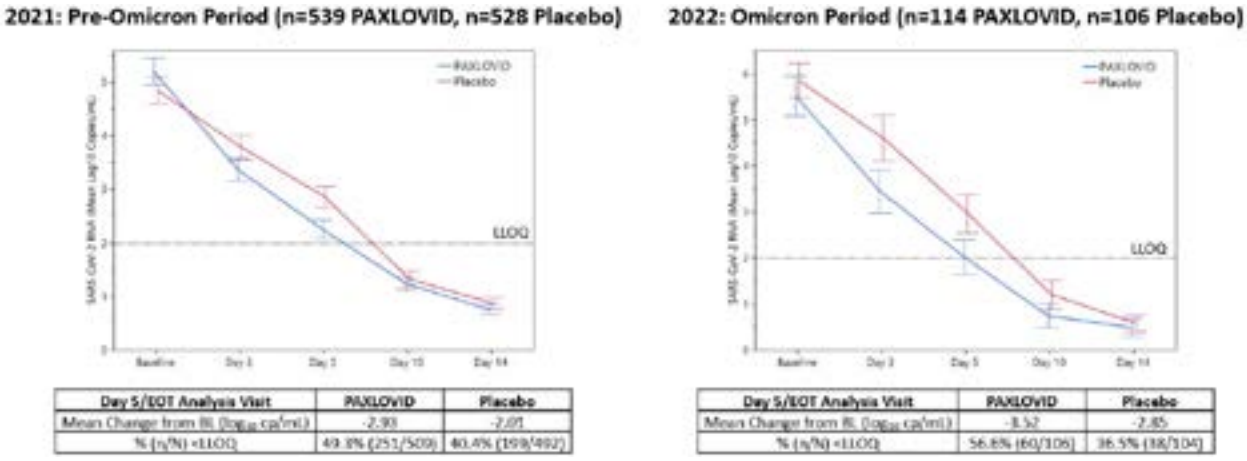
Despite the lack of clinical trial data to directly determine the clinical efficacy of PAXLOVID in high-risk adults infected with the SARS-CoV-2 Omicron variant, nonclinical and clinical data demonstrate that PAXLOVID retains antiviral activity against the SARS-CoV-2 Omicron variant. Using biochemical assays, the activity of nirmatrelvir was determined against recombinant SARS-CoV-2 M^{pro} enzymes containing naturally occurring amino acid polymorphisms, including P132H, a common polymorphism in the Omicron variant and subvariants. Nirmatrelvir retained activity (K_i fold-change <3) against SARS-CoV-2 M^{pro} enzymes with naturally occurring polymorphisms (e.g., G15S, T21I, L75F, K88R, L89F, K90R, P108S, P132H, T169S, and A260V). In cell culture, nirmatrelvir retained activity (EC_{50} value fold-change <3) against different SARS-CoV-2 variants, including Alpha, Gamma, Delta, Lambda, Mu, and Omicron subvariants BA.1, BA.2, BA.2.12.1, BA.4, BA.4.6, BA.5, BF.7, BQ.1, and XBB.1.5 (see Section 20). Literature reports have also indicated that nirmatrelvir retains activity against several SARS-CoV-2 variants in cell culture, including Omicron subvariants BA.1, BA.1.1, BA.2, BA.2.12.1, BA.2.75, BA.4, BA.5, BQ.1.1, and XBB (Abdelnabi et al. 2022; Bojkova et al. 2022a; Bojkova et al. 2022b; Li et al. 2022; Ohashi et al. 2022; Saito et al. 2022; Takashita et al. 2022a; Takashita et al. 2022b; Takashita et al. 2022c; Vangeel et al. 2022; Imai et al. 2023). Nirmatrelvir was also demonstrated to have antiviral activity against other human coronaviruses in cell culture, including SARS-CoV-1, MERS-CoV, and HCoV-229E.

In addition, bioinformatic analyses of M^{pro} and M^{pro} cleavage site amino acid sequence conservation were provided based on the GISAID EpiCoV sequence database (n=12.7 million sequences, accessed November 30, 2022). Note that these analyses are affected by global disparities in SARS-CoV-2 genomic surveillance. Only 10 M^{pro} polymorphisms and 5 M^{pro} cleavage site polymorphisms were found to have a cumulative frequency ≥0.1%. None of the 10 M^{pro} polymorphisms significantly affected nirmatrelvir activity in biochemical assays (K_i fold-change <3). The effects of the M^{pro} cleavage site polymorphisms have not been determined, but M^{pro} cleavage site substitutions outside of M^{pro} have not been associated with nirmatrelvir resistance in cell culture studies. Overall, these analyses demonstrate that SARS-CoV-2 M^{pro} and M^{pro} cleavage sites are highly conserved and that nirmatrelvir is likely to retain activity against circulating and emerging variants of SARS-CoV-2. More recent analyses of sequences through January 31, 2023 are consistent with these findings.

Lastly, analysis of viral RNA shedding data from EPIC-SR subjects who enrolled in the 2022/Omicron enrollment period (March to June 2022) found that PAXLOVID retained antiviral activity against the SARS-CoV-2 Omicron variant in treated subjects (Figure 15). Compared to placebo, PAXLOVID treatment was associated with a more rapid decline in viral RNA levels in NP samples in both the 2021/pre-Omicron enrollment period and in the 2022/Omicron enrollment period. In the 2021/pre-Omicron period, ~98% of subjects with available viral sequence data were infected with the SARS-CoV-2 Delta variant, similar to EPIC-HR, while in

the 2022/Omicron period, all subjects with available data were infected with the SARS-CoV-2 Omicron variant (mostly BA.2-related subvariants).

Figure 15. EPIC-SR: Analysis of SARS-CoV-2 RNA Levels (Log_{10} Copies/mL) in NP Samples (mITT1 Analysis Set), According to Enrollment Year



Day 5/EOT Analysis Visit	PAXLOVID	Placebo
Mean Change from BL (log_{10} cp/mL)	-2.90	-2.05
% (n/N) <LLOQ	49.8% (251/509)	40.4% (199/492)

Day 5/EOT Analysis Visit	PAXLOVID	Placebo
Mean Change from BL (log_{10} cp/mL)	-3.52	-2.85
% (n/N) <LLOQ	56.8% (60/106)	36.5% (38/104)

Source: FDA analysis of ADMC and ADSL datasets.
Note: Charts show mean values and 95% confidence intervals.
Abbreviations: EOT, end-of-treatment; BL, baseline; cp/mL, copies per milliliter; LLOQ, lower limit of quantification; N number of subjects with available data; n in table, number of subjects with viral RNA <LLOQ; n in graph title, number of subjects in treatment group

Conclusion

Based on nonclinical and clinical virology data, PAXLOVID was found to retain antiviral activity against the SARS-CoV-2 Omicron variant and major subvariants, and PAXLOVID is considered likely to retain activity against circulating and emerging variants given the high conservation (based on amino acid identity) of M^{pro} and M^{pro} cleavage site amino acid sequences. Although clinical trial data to assess clinical efficacy against the SARS-CoV-2 Omicron variant are limited, based on the available virology data it is reasonable to conclude that PAXLOVID is likely to retain clinical efficacy in adults with COVID-19 caused by the SARS-CoV-2 Omicron variant, and who are at high risk of progression to severe disease.

Through our monitoring of the RWE publications, we identified five retrospective cohort RWE studies that used appropriate source data and with acceptable design to estimate the effectiveness of PAXLOVID in reducing hospitalization and death from COVID-19 during periods when the SARS-CoV-2 Omicron variant was predominant. While these reports also indicate that PAXLOVID is likely to retain clinical efficacy against COVID-19 caused by the SARS-CoV-2 Omicron variant, these published studies do not provide sufficient information for a complete review to determine their quality (see Section 16.5 for additional details).

6.3.4. Efficacy in High-Risk Patients With Mild Disease

Issue

Is the benefit-risk assessment favorable for PAXLOVID for the treatment of both mild COVID-19 and moderate COVID-19 in high-risk individuals?

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Background

EPIC-HR, the pivotal trial which demonstrated an 86% relative risk reduction for PAXLOVID in the composite endpoint of COVID-19 related hospitalization or death from any cause through Day 28, enrolled adults at high risk for progression to severe disease with either mild or moderate COVID-19 at study entry. Per the protocol, enrolled subjects had to have confirmed SARS-CoV-2 infection, at least one of the prespecified signs/symptoms attributable to COVID-19 on the day of randomization, oxygen saturation ≥92%, and no current need or anticipated need within 48 hours for hospitalization. While these criteria ensured that enrollment was limited to patients with mild or moderate COVID-19, per the protocol subjects were not further classified as to whether their COVID-19 was mild versus moderate.

Mild versus moderate COVID-19 is defined as follows:

- Per National Institutes of Health (NIH) COVID-19 Treatment Guidelines (NIH 2022a):
  - Mild illness: Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging.
  - Moderate illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation measured by pulse oximetry (SpO2) ≥94% on room air at sea level.
- Per the FDA Guidance for Industry, COVID-19: Developing Drugs and Biological Products for Treatment or Prevention (May 2020):
  - Mild COVID-19:
    - Positive testing by standard RT-PCR assay or equivalent test
    - Symptoms of mild illness with COVID-19 that include fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnea
    - No clinical signs indicative of moderate, severe, or critical severity
  - Moderate COVID-19:
    - Positive testing by standard RT-PCR assay or equivalent test
    - Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or shortness of breath with exertion
    - Clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate ≥ 20 breaths per minute, saturation of oxygen (SpO_2) >93% on room air at sea level, heart rate ≥ 90 beats per minute
    - No clinical signs indicative of severe or critical illness severity

Since the EUA of PAXLOVID in December 2021, there have been articles questioning whether PAXLOVID should be taken by patients who are only mildly ill (Morgan M 2022; Sheikh 2023). In order to further inform on the benefit of PAXLOVID in patients with mild illness, a post hoc analysis was performed to determine the benefit of PAXLOVID in preventing COVID-19 related hospitalization or death from any cause through Day 28 by subgroup of baseline COVID-19 disease severity.

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Assessment

Methods

The mITT1 EPIC-HR analysis population (N=977 PAXLOVID recipients and N=989 placebo recipients) was used for this post hoc analysis. "Baseline" was defined as any analysis visit designated as "baseline" in the datasets, which could include both screening and Day 1 study visits, and the maximum analysis value was used in situations where there was more than one entry for a baseline analysis visit.

Two different definitions of moderate illness (which included symptom data and vital signs but not imaging results) were used. The first definition was based on the description of moderate COVID-19 in NIH COVID-19 Treatment Guidelines and in the FDA Guidance. The second definition was based on the maximum severity of overall symptoms, because illness severity is often defined in the general population based on the severity of any symptom rather than the presence of lower respiratory disease. In both cases, mild illness was defined as the absence of any criteria necessary for moderate illness by that specific definition. The definitions for moderate illness were as follows:

- **Moderate COVID-19**: at baseline, any shortness of breath, heart rate ≥ 90 beats per minute, or respiratory rate ≥ 20 breaths per minute.
- **Moderate COVID-19 symptoms**: at baseline, any symptom with greater than mild severity among all the reported COVID-19 symptoms. COVID-19 symptoms included chills or shivering, cough, diarrhea, feeling hot or feverish, headache, low energy or tiredness, muscle or body aches, nausea, loss of sense of smell, loss of sense of taste, shortness of breath or difficulty breathing, sore throat, stuffy or runny nose, and vomiting.
  - Symptoms were not reported at baseline for 57 PAXLOVID recipients and 34 placebo recipients, these subjects were not included in this particular analysis.

Results

While a higher proportion of subjects with moderate versus mild illness met the primary endpoint of COVID-19 related hospitalization or death from any cause through Day 28, PAXLOVID significantly reduced the rate of primary endpoint events in both the moderate and mild illness subgroups. Please see Table 28 below.

Table 28. Proportion of Subjects Who Met the Primary Endpoint of COVID-19 Related Hospitalization or Death From Any Cause Through Day 28 by Baseline Illness Severity (mITT1 Analysis Population)

Primary Endpoint in Subjects With Mild COVID-19 at BL[a]	PAXLOVID N=355	Placebo N=324
Subjects with event, n (%)	0	16 (4.9%)
Difference in proportion	4.9%	
Nominal p-value	<0.0001	
Primary Endpoint in Subjects With Moderate COVID-19 at BL[b]	**PAXLOVID N=622**	**Placebo N=665**
Subjects with event, n (%)	9 (1.4%)	48 (7.2%)
Difference in proportion	5.8%	
Nominal p-value	<0.0001	

Primary Endpoint in Subjects With Mild COVID-19 Symptoms at BL[c]	PAXLOVID N=173	Placebo N=184
Subjects with event, n (%)	0	6 (3.2%)
Difference in proportion	3.2%	
Nominal p-value	0.0304	
Primary Endpoint in Subjects With Moderate COVID-19 Symptoms at BL[d]	**PAXLOVID N=747**	**Placebo N=771**
Subjects with event, n (%)	8 (1.1%)	57 (7.4%)
Difference in proportion	6.3%	
Nominal p-value	<0.0001	

Source: EPIC-HR ADSL, ADSO, and ADVS datasets.
Note: P-values are based on Fisher's exact test.
[a.] Mild COVID-19 at Baseline": no shortness of breath, no heart rate ≥90 beats per minute, and no respiratory rate ≥20 breaths per minute.
[b.] Moderate COVID-19 at Baseline: either shortness of breath, heart rate ≥ 90 beats per minute, and/or respiratory rate ≥ 20 breaths per minute).
[c.] Mild COVID-19 Symptoms at Baseline: no symptom with greater than mild severity at baseline among all the reported COVID-19 symptoms).
[d.] Moderate COVID-19 Symptoms at Baseline: any symptom with greater than mild severity at baseline among all the reported COVID-19 symptoms).
Abbreviations: BL, baseline; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent-to-treat; N, number of subjects in treatment arm; n, number of subjects with specified characteristic

Conclusion

Post hoc analyses of EPIC-HR data support the efficacy of PAXLOVID for the treatment of mild to moderate COVID-19 in high-risk adults regardless of whether the baseline illness severity is mild or moderate.

6.3.5. Optimal Duration of PAXLOVID Treatment in Immunocompromised Patients

Issue

What is the optimal duration of PAXLOVID treatment for mild to moderate COVID-19 in patients who are moderately or severely immunocompromised?

Background

The two Phase 2/3 COVID-19 treatment trials supporting the NDA, the pivotal trial, EPIC-HR, and the supportive trial, EPIC-SR, evaluated 5 days of treatment with PAXLOVID versus placebo. EPIC-HR demonstrated an 86% relative risk reduction with 5 days of PAXLOVID treatment for the endpoint of COVID-19 related hospitalization or death from any cause through Day 28 among adults with laboratory-confirmed, symptomatic SARS-CoV-2 infection who had at least one risk factor that put them at high risk for progression to severe disease, who had not received any dose of a COVID-19 vaccine, and who began treatment within 5 days of symptom onset. However, only 13/2246 subjects (<1%) in the full analysis set in EPIC-HR were classified as having immunosuppression.

Patients with moderate to severe immunocompromise might benefit from a longer treatment course of PAXLOVID based on the clinical course of COVID-19 in this population. While most people with mild-to-moderate COVID-19 are expected to clear their infection within 10 days of symptom onset, individuals with moderate to severe immunocompromise can remain infectious beyond 20 days (CDC 2022a). Persistent SARS-CoV-2 infection, defined as SARS-CoV-2 RNA

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detection ≥30 days after initial positivity, was reported in 14% (51/368) of patients with hematologic malignancies who were diagnosed with COVID-19 from March 10, 2020, to February 28, 2021, at one center and were alive 30 days after their COVID-19 diagnosis; receipt of anti-CD20 therapy within the prior year, cellular therapy including hematopoietic stem cell transplantation within 1 year, and chronic lymphopenia were associated with persistent SARS-CoV-2 infection on multivariate analysis in this study (Lee et al. 2022). Risks of persistent SARS-CoV-2 infection include morbidity and mortality from COVID-19, interruption in treatment for cancer and other medical conditions, SARS-CoV-2 transmission to contacts, and the potential evolution of the SARS-CoV-2 virus.

Assessment

Clinical Trial Data

Currently available clinical trial data are limited on use of PAXLOVID for the treatment of mild-to-moderate COVID-19 in patients with moderate to severe immunocompromise. As noted above, <1% (13/2246) of enrolled subjects in EPIC-HR were classified as having immunosuppression, six of whom were randomized to PAXLOVID versus seven to placebo. Of these 13 subjects, five were on immunosuppressive medications for rheumatoid arthritis, two were on immunosuppressive medications for systemic lupus erythematosus (SLE), three were on immunosuppressive medications for other conditions (ankylosing spondylitis, psoriatic arthritis, and ulcerative colitis), one had SLE, one had acute myeloid leukemia (AML) and was taking immunosuppressive medications, and one had breast cancer and was taking chemotherapy and other immunosuppressive medications. None of these 13 subjects experienced the primary outcome of COVID-19 related hospitalization or death from any cause through Day 28, although one of the subjects who received placebo died on Day 97 due to sepsis with underlying relapsed AML. SARS-CoV-2 viral RNA levels through Day 14 from these 13 immunosuppressed subjects were within the range observed in the overall population, with no evidence of increased levels after treatment ended on Day 5 among the PAXLOVID recipients.

Emergency IND Data

Some (>20) severely immunosuppressed patients with prolonged persistent SARS-CoV-2 infection (up to 6 months) have received longer courses of PAXLOVID of 10 to 28 days duration under emergency INDs. Of the 15 patients with outcome data, 2 died: 1 was hospitalized in the intensive care unit at baseline and died on Day 2 of PAXLOVID treatment, 1 had decreasing SARS-CoV-2 RNA levels at the time of death and other complications such as cavitary pulmonary aspergillosis. The remaining 13 patients with outcome data improved in terms of symptoms, SARS-CoV-2 viral testing, or both. Clinical improvement or complete resolution of symptoms was reported in 11 patients; viral clearance was also reported for 5 of these patients (no SARS-CoV-2 viral level information after PAXLOVID initiation was reported for the other 6 patients). For the remaining 2 patients, viral clearance was reported; persistent symptoms were reported for 1 of these patients, and no information on symptoms was provided for the other patient. The clinical courses of 2 of the 15 patients have been published as case reports (Ford et al. 2022; Trottier et al. 2022). The small number of patients, combined with their variable use of other concurrent antiviral medications like remdesivir or anti-SARS-CoV-2 therapeutic mAb therapy and their variable health status at treatment initiation, as well as the lack of a control group, precludes drawing any conclusions from these cases.

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Quantitative Systems Pharmacology Modeling

Quantitative systems pharmacology (QSP) modeling suggests a potential benefit for longer duration PAXLOVID treatment (e.g., 10 days) in viral RNA reduction in immunocompromised patients (see Section 14.5). The Applicant used QSP models and virtual populations to predict the optimal duration of treatment in both the overall PAXLOVID-eligible population and the immunocompromised population. This QSP modeling attempted to account for the effects of the immune system on SARS-CoV-2 replication in infected patients and was developed using longitudinal data from observational studies in SARS-CoV-2 infected subjects who measured immune markers in the blood (e.g., serum cytokine levels) and SARS-CoV-2 RNA levels in NP samples. Clinical trial data from studies of SARS-CoV-2 antiviral products (i.e., bamlanivimab/etesevimab, casirivimab/imdevimab, and molnupiravir) also informed the QSP model. The virtual immunocompromised patients were generated by two approaches: a mechanistic approach that attenuates Type I IFN and $CD8^+$ T cell-mediated killing of infected cells which induces a prolonged viral shedding profile, and a phenotypic approach that selects PAXLOVID-eligible virtual patients who exhibit a long viral RNA shedding. QSP modeling of 5, 10, or 15 days of PAXLOVID treatment indicated the following: while extending treatment beyond 5 days in the overall PAXLOVID-eligible population under the EUA was not predicted to offer additional benefit for SARS-CoV-2 viral RNA suppression, this strategy could aid in reducing viral RNA to undetectable levels in the immunocompromised population, whose viral RNA shedding (in $\log_{10}$ scale) was predicted to be approximately twice that of the overall PAXLOVID-eligible population by Day 5 of treatment. In the immunocompromised population model, 10 days of PAXLOVID treatment was predicted to be sufficient for optimal viral RNA suppression (although 5 days of PAXLOVID treatment was still predicted to decrease viral RNA more quickly than placebo). The QSP modeling data support investigating longer durations of PAXLOVID treatment in the immunocompromised population in a clinical trial setting, where the impact of longer treatment duration on DDI management can also be evaluated in this population.

Conclusion

More data, including clinical trial data, are needed to determine if a longer duration of PAXLOVID dosing may be optimal for treatment of mild-to-moderate COVID-19 in patients who are moderately or severely immunocompromised. The PAXLOVID EUA was modified on August 05, 2022, to add the following condition of authorization: “Pfizer will conduct a randomized controlled trial to evaluate different durations of PAXLOVID treatment in immunocompromised patients with mild-to-moderate COVID-19. Pfizer will provide topline results by September 30, 2023.” This trial, EPIC-IC (or C4671034, NCT05438602), is a double-blind study in which immunocompromised subjects with mild to moderate COVID-19 are randomized to 5, 10, or 15 days of PAXLOVID treatment; EPIC-IC began enrollment in September 2022 (ClinicalTrials.gov: NCT05438602 2023). The ongoing trial is recommended as postmarketing commitment (PMC) for inclusion in the Approval Letter to inform if there is a need for longer PAXLOVID treatment duration (e.g., 10 days or 15 days versus 5 days) in patients who are immunocompromised.

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6.3.6. Impact of PAXLOVID on COVID-19 Rebound

Issue

What is the rate and clinical significance of virologic and symptomatic COVID-19 rebound, and is it affected by PAXLOVID treatment?

Background

Following the EUA with resulting widespread use of PAXLOVID for the treatment of outpatients with COVID-19, several publications, case reports, and stories in the press described patients with COVID-19 who experienced symptomatic recovery during PAXLOVID treatment, but experienced "relapses" in COVID-19 symptoms after stopping the 5-day course of treatment, which in some cases coincided with rebounds in qualitative or quantitative viral RNA, antigen, or virus detection in upper respiratory tract samples (Antonelli et al. 2022; Boucau et al. 2022; Carlin et al. 2022; Charness et al. 2022; Epling et al. 2022; Ranganath et al. 2022). Likewise, through August 29, 2022, 2143 cases were reported through the FDA Adverse Events Reporting System (FAERS) that described a rebound of COVID-19 symptoms after PAXLOVID use, which occurred on average 6 days after treatment completion (DARRTS ID: 5077785 2022).[2] These cases have occurred in patients with varying demographics including immunocompetent, vaccinated individuals. Symptoms during COVID-19 rebound have generally been reported to be mild. These reports have raised speculation that PAXLOVID treatment may incompletely suppress virus replication or delay the development of a functional host immune response that is ultimately responsible for clearing the infection, resulting in a rebound in viral replication and COVID-19 symptoms following the 5-day treatment course (Rubin 2022; Focosi et al. 2023). Some researchers have also speculated that symptomatic or virologic rebound may be associated with the SARS-CoV-2 Omicron variant or subvariants (Rubin 2022). Others have reported widely varying rates of symptomatic or virologic rebound following treatment with PAXLOVID or molnupiravir, or even in the absence of any antiviral treatment (Deo et al. 2022; Pandit et al. 2022; Wang et al. 2022; Wong et al. 2022).

Despite the publications and widespread reporting in the press of COVID-19 rebound following PAXLOVID treatment, it has been challenging to determine the direct contribution of PAXLOVID treatment to virologic or symptomatic rebound from published reports. Other than analyses from the Applicant based on data from the EPIC-HR trial, published reports and analyses of COVID-19 rebound are based on case reports and non-randomized, observational cohort studies (Anderson et al. 2022).

The systematically collected virology and symptom data from the randomized, placebo-controlled EPIC-HR and EPIC-SR trials allowed for in-depth analyses to investigate the rates of virologic and symptomatic rebound, to assess whether PAXLOVID treatment (compared to placebo) is specifically associated with this phenomenon, and to compare rebound rates in the 2021 (pre-Omicron) and 2022 (Omicron) periods.

[2] This document contains proprietary data obtained by FDA under contract and cannot be released to the public. The information contained within is the result of an OSE review as part of PAXLOVID, NDA 217188 and EUA 105. The source can only be accessed by authorized individuals.

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Assessment

Analyses of SARS-CoV-2 RNA Rebound in EPIC-HR and EPIC-SR

The likelihood of detecting viral RNA rebound is impacted substantially by the analysis definition, frequency of testing, and number of test results considered. FDA analyses used the following analysis parameters to detect and characterize post-treatment viral RNA rebound in NP samples from Day 5 (end-of-treatment) through either Day 10 or Day 14, which were the post-treatment visits with available virology data:

- **Day 10 (lower limit of quantification [LLOQ]/0.5 Combined)**: Day 5 RNA <LLOQ AND at Day 10 RNA ≥LLOQ, OR, Day 5 RNA ≥LLOQ AND Day 10 RNA ≥0.5 $\log_{10}$ copies/mL increase from Day 5.
- **Day 14 (LLOQ/0.5 Combined)**: Day 5 RNA <LLOQ AND at Day 14 RNA ≥LLOQ, OR, Day 5 RNA ≥LLOQ AND Day 14 RNA ≥0.5 $\log_{10}$ copies/mL increase from Day 5.
- **Day 10/14 (LLOQ/0.5 Combined)**: Met either definition of Day 10 (LLOQ/0.5 Combined) OR Day 14 (LLOQ/0.5 Combined).

Additional subgroup analyses were conducted among subjects with evidence of a virologic response through Day 5/end-of-treatment, defined as:

- **Day 5/EOT Virologic Responders**: Day 5 RNA <LLOQ, OR, ≥1 $\log_{10}$ copy/mL decline from BL to Day 5.
- **Day 5/EOT <LLOQ**: Day 5 RNA <LLOQ (i.e., subgroup of Day 5/EOT Virologic Responders).

The Day 10/14 definition was considered the primary definition of viral RNA rebound given it identified subjects with any evidence of viral RNA rebound from Day 5 to either Day 10 or Day 14. These analysis parameters were intended to provide a sensitive means to detect occurrences of post-treatment increases in viral RNA shedding levels, regardless of magnitude. The clinical relevance of any specific quantitative magnitude of viral RNA rebound is unknown. Viral RNA levels over time in individual subjects were also characterized to assess for different patterns between PAXLOVID- and placebo-treated subjects, for example whether the magnitude of post-treatment viral RNA increases clearly differ between PAXLOVID- and placebo-treated subjects. These analyses were conducted for the mITT2 population for EPIC-HR, and the mITT1 population for EPIC-SR, both of which include all subjects randomly assigned to study intervention who took at least 1 dose of study intervention.

Rates of post-treatment viral RNA rebound in EPIC-HR are summarized in Table 29. Based on the Day 10/14 (LLOQ/0.5 Combined) definition, post-treatment viral RNA rebound was observed in 8.3% of PAXLOVID recipients and 5.7% of placebo recipients (p=0.04, Fisher's Exact Test, not adjusted for multiplicity). In both treatment groups, higher rates of viral RNA rebound relative to Day 5/EOT were observed at Day 10 compared to Day 14, indicating most observations of rebound occurred by Day 10. Viral RNA levels for individual subjects who met the definitions of viral RNA rebound showed substantial heterogeneity in the viral RNA patterns, with no clear or consistent differences between PAXLOVID and placebo recipients in the RNA rebound patterns or magnitude of rebound.

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While the Day 10/14 (LLOQ/0.5 Combined) definition showed a modest yet nominally significant higher rate of rebound overall in PAXLOVID recipients compared to placebo recipients, post-treatment (i.e., post-Day 5) viral RNA rebound was clearly not restricted to PAXLOVID recipients. Furthermore, calculated rates of viral RNA rebound could be biased by the greater impact of PAXLOVID on early viral RNA declines through Day 5. This definition would not capture subjects with viral RNA levels that declined slowly or remained relatively high through the treatment period (i.e., did not yet achieve a nadir level by Day 5). Post-Day 5 viral RNA rebound occurred almost exclusively among subjects with a virologic response through Day 5; 94% (119/126) of subjects with Day 10/14 viral RNA rebound had evidence of a virologic response through Day 5 (Day 5/EOT Virologic Responders), defined as Day 5 <LLOQ, or a ≥1 $\log_{10}$ copies/mL decline from baseline to Day 5.

Therefore, to compare post-treatment viral RNA rebound rates more directly between subjects with comparable on-treatment virologic responses, the Day 10/14 (LLOQ/0.5 Combined) analysis was restricted to PAXLOVID and placebo recipients who were considered Day 5/EOT Virologic Responders. In this subgroup of subjects, or in the smaller subset of subjects with viral RNA <LLOQ at Day 5, rates of viral RNA rebound after Day 5 remained modestly higher in PAXLOVID recipients, but the differences were no longer statistically significant (Table 29).

Table 29. EPIC-HR: Rates of Post-Treatment Viral RNA Rebound

Viral RNA Rebound Analysis	PAXLOVID Total N=1035	Placebo Total N=1048	p-Value[a]
Day 10 (LLOQ/0.5 combined)	6.6% (57/865)	4.7% (40/856)	0.09
Day 14 (LLOQ/0.5 combined)	2.6% (23/884)	1.9% (17/893)	0.34
Day 10/14 (LLOQ/0.5 combined)	8.3% (77/925)	5.7% (53/922)	0.04
Day 5/EOT Virologic responders: Day 10/14 (LLOQ/0.5 combined)	8.1% (69/849)	6.5% (50/772)	0.22
Day 5 <LLOQ: Day 10/14 (LLOQ/0.5 combined)	8.2% (36/440)	5.1% (21/410)	0.10

Source: FDA analysis of the ADMC and ADSL datasets; NDA 217188.
[a.] Fisher's exact test, two-sided.
Abbreviations: EOT, end-of-treatment; LLOQ, lower limit of quantification; N, number of subjects in treatment group; RNA, r bonucleic acid

Regardless of any numeric differences in rates of post-treatment viral RNA rebound, PAXLOVID treatment ultimately did not result in delayed declines in viral RNA to unquantifiable levels. At all analysis visits, a similar or greater percentage of PAXLOVID recipients compared to placebo recipients had viral RNA <LLOQ (Table 30). Based on these results, there is no indication that a positive SARS-CoV-2 RNA test result would be more likely for a PAXLOVID-treated patient, compared to an untreated patient, at any single cross-sectional timepoint through Day 14 (i.e., 9 days post-treatment).

Table 30. EPIC-HR: Proportions of PAXLOVID or Placebo Subjects With Viral RNA <LLOQ at Each Analysis Visit

Day	PAXLOVID	Placebo
Day 3	35.1% (340/970)	32.8% (321/980)
Day 5/EOT	47.8% (447/936)	44.1% (415/942)
Day 10	76.1% (702/922)	68.9% (622/903)
Day 14	88.6% (835/942)	86.0% (815/948)

Source: FDA analysis of the ADMC and ADSL datasets; NDA 217188.
Abbreviations: EOT, end-of-treatment; LLOQ, lower limit of quantification; RNA, ribonucleic acid

Post-treatment viral RNA rebound in EPIC-HR was not associated with the primary clinical outcome of COVID-19 related hospitalization or death from any cause through Day 28. Among the 130 subjects who experienced Day 10/14 viral RNA rebound, only 4 subjects (3%) reached the hospitalization or death endpoint (0 deaths), including 1 PAXLOVID recipient and 3 placebo recipients. The hospitalization in the PAXLOVID recipient (Subject (b) (6)) occurred early during treatment and the subject was discharged from the hospital prior to the post-treatment viral RNA rebound.

Post-treatment viral RNA rebound in EPIC-HR was not associated with baseline immunosuppression risk, although this was a small subgroup of subjects in the trial (n=6 PAXLOVID, n=7 placebo). Only one of these subjects experienced post-treatment viral RNA rebound, and the subject received placebo.

Post-treatment viral RNA rebound in EPIC-HR generally was not associated with the emergence of potential nirmatrelvir drug resistance, although there were 2 subjects (3% of the 59 PAXLOVID treated subjects with viral RNA rebound and available viral sequence data) who had a treatment-emergent amino acid substitution detected in M^{pro} that is potentially associated with nirmatrelvir resistance, including E166V in one subject, and T304I in the second subject.

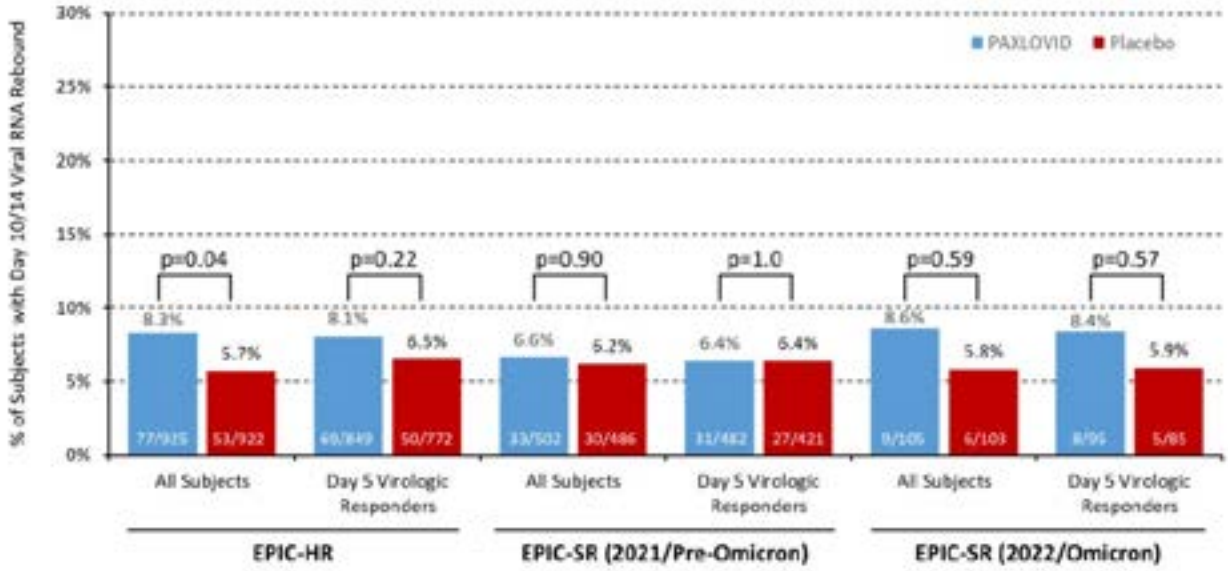
The Applicant also conducted analyses assessing for cell culture infectious virus in a subset of NP samples from subjects in EPIC-HR using two types of infectivity assays: a viral recovery assay and a viral titration immunoassay (i.e., median tissue culture infectious dose [$TCID_{50}$] assay). Considering either the viral recovery assay or the viral titration assay, among those who experienced Applicant-defined post-treatment viral RNA rebound, qualitatively positive test results for virus infectivity for Day 10 or Day 14 samples were observed in a small number of subjects, including subjects treated with PAXLOVID or placebo: 29% (18/62) and 39% (15/38) of PAXLOVID and placebo recipients, respectively.

In EPIC-SR, comparable rates of post-treatment viral RNA rebound were observed between PAXLOVID and placebo recipients, with no analyses indicating statistically significant differences in rebound rates between the two groups. Furthermore, although the numbers of subjects who had Omicron variants detected or who enrolled in the Omicron period were relatively small, there were no significant differences in rebound rates between PAXLOVID and placebo recipients regardless of whether they were determined to be infected with a SARS-CoV-2 Delta or Omicron variant, or more broadly were enrolled in the pre-Omicron or Omicron periods. As observed in EPIC-HR, viral RNA levels for individual subjects with post-treatment viral RNA rebound in EPIC-SR showed no obvious differences in the patterns or magnitude of viral RNA rebound between PAXLOVID and placebo recipients, either overall or within the 2021/pre-Omicron or 2022/Omicron enrollment periods. PAXLOVID treatment also did not result in delayed declines in viral RNA to unquantifiable levels; at all analysis visits through Day

14, and in both the 2021/pre-Omicron and 2022/Omicron periods, a similar or greater percentage of PAXLOVID recipients compared to placebo recipients had viral RNA <LLOQ.

Figure 16 summarizes the rates of post-treatment viral RNA rebound observed in EPIC-HR (conducted during the 2021/pre-Omicron period), EPIC-SR (2021/pre-Omicron period), and EPIC-SR (2022/Omicron period). While there are some modest numeric differences in some comparisons, in general, overall similar rates of post-treatment viral RNA rebound were observed between both trials, between the 2021/pre-Omicron and 2022/Omicron periods, and between PAXLOVID and placebo recipients.

Figure 16. Rates of Post-Treatment Viral RNA Rebound (Day 10/14 [LLOQ/0.5 Combined]) Observed in EPIC-HR and EPIC-SR



Source: FDA analysis of the ADMC and ADSL datasets; NDA 217188.
Note: p-values based on Fisher's exact test, two-sided.
Abbreviation: LLOQ, lower limit of quantification; RNA, ribonucleic acid

See Section 18.1 of the integrated review document for additional details from these analyses.

Analyses of Symptom Rebound and Combined Symptom/Viral RNA Rebound in EPIC-HR and EPIC-SR

As with viral RNA rebound, calculated rates of symptom rebound can vary widely depending on the analysis parameters and available data timepoints. In EPIC-HR and EPIC-SR, multiple targeted symptoms were evaluated and there were differences between subjects in baseline symptom duration/severity.

Analyses of symptom rebound focused on symptom rebound after achieving at least a short-term symptom recovery, using the patient eDiary symptom data. Refer to Section 6.2.1.4 for a complete list of all 11 targeted symptoms.

The definitions listed below were used in the symptom rebound analyses.

- **Short Symptom Recovery:** The first day of at least two consecutive diary entries (regardless of missing entries in between) where all targeted symptoms are absent. If a hospitalization event occurs prior to the short symptom recovery day or during the first two short symptom

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recovery entries, this subject is considered as not having short symptom recovery through Day 28.

- **Symptom Rebound:** After achieving short symptom recovery, the first day of at least two consecutive diary entries (regardless of missing entries in between) where there is any targeted symptom (regardless of severity), or if a patient is hospitalized or died by Day 28 after short symptom recovery. If a symptom rebound occurred on or before Day 5, the subject is considered not recovered on the day of the symptom rebound and reanalyzed for short symptom recovery and symptom rebound in the following days.
- **Moderate Symptom Rebound:** For those with symptom rebound, having (a) at least one rebound symptom being moderate or severe, (b) at least two symptoms of any severity during a day of rebound, or (c) a hospitalization/death event, observed on a day between the first day of symptom relapse to Day 28.

The analyses were conducted in the mITT2 population for EPIC-HR and the mITT1 population for EPIC-SR (separated by pre-Omicron and Omicron period), including all subjects randomly assigned to study intervention who took at least one dose of study intervention. Subjects with no symptom data are not included. Rates of short symptom recovery, symptom rebound, and moderate symptom rebound are summarized separately for EPIC-HR, EPIC-SR 2021 (pre-Omicron period) and EPIC-SR 2022 (Omicron period) trials in Table 31 below.

Table 31. Symptom Rebound Analysis

Symptom Rebound Analysis	PAXLOVID n (%)	Placebo n (%)
EPIC-HR, N	1031	1050
Short symptom recovery	768 (74.5)	706 (67.2)
Short symptom recovery day ≤ Day 14[a]	546 (53.0)	472 (45.0)
Symptom rebound	90 (11.7)	98 (13.9)
Moderate symptom rebound	54 (7.0)	59 (8.4)
EPIC-SR 2021 (Pre-Omicron), N	534	527
Short symptom recovery [a]	411 (77.0)	404 (76.7)
Short symptom recovery day ≤ Day 14[a]	316 (59.2)	280 (53.1)
Symptom rebound, n[b,c]	65 (15.8)	57 (14.1)
Moderate symptom rebound[b]	40 (9.7)	41 (10.1)
EPIC-SR 2022 (Omicron), N	114	106
Short symptom recovery[a]	96 (84.2)	88 (83.0)
Short symptom recovery day ≤ Day 14[a]	70 (61.4)	68 (64.2)
Symptom rebound, n (%)[b]	10 (10.4)	12 (13.6)
Moderate symptom rebound, n (%)[b]	4 (4.2)	9 (10.2)

Source: Reviewer's analysis on EPIC-HR and EPIC-SR ADSL/ADSO datasets, excluding subjects from site HR1274/SR1281, site HR1470/SR1488, site SR1157 (2022), and site SR1197 (2022). Subjects with no symptom data were not included in the analyses.
[a.] Percentage over total subjects.
[b.] Percentage over those who achieved short symptom recovery.
[c.] Difference between two arms is not statistically significant: p-value=0.5589 by Pearson chi-squared test with continuity correction.
Abbreviations: N, number of subjects in treatment group; n, number of subjects in specified population or group

These analyses demonstrated that the rates of symptom rebound (regardless of severity) and moderate symptom rebound were similar between PAXLOVID and placebo recipients. Overall symptom rebound rates ranged from 10 percent to 16 percent, with no evidence of a higher rate of symptom rebound or moderate symptom rebound in PAXLOVID recipients relative to placebo recipients in EPIC-HR, the pre-Omicron period of EPIC-SR, or the Omicron period of EPIC-SR. In addition, for either treatment group, there was also no indication of a higher rate of

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symptom rebound between the pre-Omicron and Omicron periods of EPIC-SR. Additional subgroup analyses on symptom rebound can be found in Section 16.4.2, with results similar to the above general analysis.

The relationship between viral RNA rebound and symptom rebound could not be fully investigated. The majority of symptom rebounds occurred after Day 14, while viral RNA shedding data were only available through Day 14. Furthermore, viral RNA data were not captured daily, while subject-reported symptoms could vary substantially from day to day. Given these limitations in the combined virology and symptom data, cases of symptomatic viral rebound in EPIC-HR and EPIC-SR were identified based on the following definitions:

- **Combined Recovery**: Those who are virologic responders on Day 5 (<LLOQ at Day 5 or ≥1 $\log_{10}$ copies/mL decline from baseline to Day 5) and have short symptom recovery by Day 14.
- **Symptomatic Viral RNA Rebound**: Among those who have combined recovery, any evidence of viral RNA rebound through Day 14, and have symptom rebound at any time after achieving short symptom recovery.

The analyses were conducted in the mITT2 population for EPIC-HR and the mITT1 population for EPIC-SR (separated by pre-Omicron and Omicron period). Subjects with no symptom data or no viral RNA data are not included. As shown in Table 32, cases of symptomatic viral RNA rebound were infrequent (<2% across both arms) with no consistent trend of a difference in rates between PAXLOVID and placebo recipients in EPIC-HR, and both the pre-Omicron and Omicron periods of EPIC-SR.

Table 32. Symptomatic Viral RNA Rebound Analysis

Symptomatic Viral Rebound Analysis	PAXLOVID n (%)	Placebo n (%)
EPIC-HR, N	1029	1045
Combined recovery [a]	470 (45.7)	385 (36.8)
Symptomatic viral RNA rebound[b]	4 (0.9)	3 (0.8)
EPIC-SR 2021 (Pre-Omicron), N	533	527
Combined recovery[a]	292 (54.8)	232 (44.0)
Symptomatic viral RNA rebound[b]	3 (1.0)	4 (1.7)
EPIC-SR 2022 (Omicron), N	114	106
Combined recovery[a]	62 (54.4)	55 (51.9)
Symptomatic viral RNA rebound[b]	1 (1.6)	0

Source: Reviewer's analysis on EPIC-HR and EPIC-SR ADSL/ADMC/ADSO datasets, excluding subjects from site HR1274/SR1281, site HR1470/SR1488, site SR1157 (2022), and site SR1197 (2022). Subjects with no symptom data or no viral RNA data were not included in the analyses.
[a.] Percentage over total subjects.
[b.] Percentage over those who achieved combined recovery.
Abbreviations: N, number of subjects in treatment group; n, number of subjects in specified population or group; RNA, ribonucleic acid

Conclusion

Comprehensive analyses conducted by FDA and the Applicant did not identify a clear association between PAXLOVID treatment and COVID-19 rebound. Viral RNA rebound and symptom rebound were observed in both PAXLOVID and placebo recipients, and at frequencies that were generally similar in both arms across multiple analyses, and with no clear differences from analyses of EPIC-HR and the pre-Omicron and Omicron periods of EPIC-SR.

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While one analysis from EPIC-HR showed a statistically significantly higher rate of post-treatment viral RNA rebound among PAXLOVID recipients, the review team interprets this difference as minor and not clinically significant. In EPIC-HR, viral RNA rebound was not associated with the primary clinical endpoint of hospitalization or death. There was also no evidence that PAXLOVID treatment was associated with a higher rate of symptom rebound in EPIC-HR; rather, a slightly higher rate of symptom rebound was observed among placebo recipients. Furthermore, regardless of any modest differences in rates of viral RNA rebound, there was no indication of prolonged viral RNA shedding among PAXLOVID recipients. In both EPIC-HR and EPIC-SR (including the pre-Omicron and Omicron periods), a similar or greater percentage of PAXLOVID recipients compared to placebo recipients had viral RNA <LLOQ at all analysis visits.

Overall, these findings indicate that in a subset of SARS-CoV-2 infections, virologic and/or symptomatic rebound may occur as part of the natural progression and resolution of COVID-19 disease, irrespective of PAXLOVID treatment. Two ongoing clinical trials of PAXLOVID will further characterize the frequency of COVID-19 rebound following different durations of PAXLOVID treatment in immunocompromised subjects (EPIC-IC, NCT05438602) and the potential benefit of PAXLOVID retreatment in subjects with evidence of post-treatment COVID-19 rebound (C4671042, NCT05567952) (ClinicalTrials.gov: NCT05438602 2023; ClinicalTrials.gov: NCT05567952 2023). Both trials are recommended PMCs for inclusion in the Approval Letter, the latter trial to collect efficacy and safety data on a repeat course of PAXLOVID treatment in patients with COVID-19 rebound.

6.3.7. Benefit of PAXLOVID for the Prevention of Post-COVID Conditions

Issue

Does PAXLOVID used to treat acute COVID-19 prevent the development of post-COVID conditions?

Background

Some people infected with SARS-CoV-2 develop new or persistent long-term symptoms after the acute infection resolves. This syndrome is referred to by many names, including post-COVID conditions, long COVID, post-acute sequelae of COVID-19 (PASC), and long haul COVID; we refer to it as post-COVID conditions here. Post-COVID conditions are defined differently by different organizations:

- Per the CDC, post-COVID conditions are an umbrella term for the wide range of health consequences that can be present four or more weeks after infection with SARS-CoV-2, the virus that causes COVID-19 (CDC 2022b).
- Per the World Health Organization (WHO), post-COVID conditions occur in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday

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functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time (WHO 2021).

- The WHO clinical case definition was based on a global consensus process whereby patients, patient-researchers, external experts, and WHO staff were asked questions about the definition. For the symptoms, in addition to fatigue, shortness of breath, and cognitive dysfunction, at least 50% of survey respondents thought the following symptoms were important to include: memory issues, post-exertional malaise, sleep disorders, muscle pain/spasms, altered smell or taste, tachycardia/palpitations, cough, chest pain, headache, and joint pain.

The estimated prevalence of post-COVID conditions ranges based on the specific definition used. According to a CDC analysis, 18-19% of American adults who reported ever having had COVID-19 currently have symptoms of post-COVID conditions, defined as symptoms lasting 3 or more months that were not present prior to having COVID-19 (CDC 2022b).

There are many different theories about the etiology behind post-COVID conditions. Proposed contributing mechanisms include persistent inflammation, induced autoimmunity, microvascular dysfunction, dysbiosis, reactivation of latent viruses like human herpes viruses, and persistent SARS-CoV-2 infection (possibly limited to specific anatomic reservoirs) (Mehandru and Merad 2022; Peluso and Deeks 2022). Because treatment of the acute infection could theoretically impact all of the proposed contributing mechanisms for post-COVID conditions, one outstanding question is whether PAXLOVID (or other antiviral) treatment of acute SARS-CoV-2 infection can prevent the development of post-COVID conditions. In addition, the possibility that persistent SARS-CoV-2 infection may contribute to post-COVID conditions has raised interest in studying PAXLOVID for the treatment of individuals diagnosed with post-COVID conditions. However, the role of PAXLOVID in the treatment of post-COVID conditions is beyond the scope of this NDA review as data to assess this were not included in the NDA submission; several clinical trials to evaluate PAXLOVID for the treatment of post-COVID conditions are currently planned or ongoing.

Assessment

While the PAXLOVID clinical trials submitted in support of this NDA were not designed to assess for the development of post-COVID conditions, subjects were queried about the presence of certain symptoms at Week 12 and Week 24, and these data from EPIC-HR were submitted. A comparison of these symptoms in PAXLOVID versus placebo recipients was not a prespecified analysis and was not included as part of the statistical testing hierarchy; however, descriptive analyses of these Week 12 and Week 24 symptom data are presented in Table 33.

The symptoms included in the Week 12 and Week 24 assessments were: cough, shortness of breath, difficulty breathing, fever, chills, fatigue, malaise, muscle pain, diarrhea, nausea, vomiting, headache, sore throat, rhinorrhea, loss of taste/smell, difficulty with concentration, sleep disturbances, and heart palpitations. FDA analysis was limited to the symptoms from the post-COVID conditions WHO clinical case definition that ≥50% of survey respondents thought were important to include (see "Background" at the top of Section 6.3.7), and like terms were grouped. Chest pain and joint pain, which were among the symptoms for the WHO definition

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that ≥50% of survey respondents thought were important to include, were not assessed in EPIC-HR at Week 12 and Week 24 and so were not included among the assessed symptoms.

Overall, symptoms associated with post-COVID conditions were infrequent and reported at similar rates among both PAXLOVID and placebo recipients at Week 12 and Week 24 (see Table 33 below).

Table 33. Presence of Symptoms Associated With Post-COVID Conditions at Week 12 and Week 24 Among PAXLOVID and Placebo Recipients in EPIC-HR, mITT1 Analysis Set

	Week 12		Week 24	
Symptoms of Post-COVID-Associated Condition – n (%)	**PAXLOVID (N=929)**	**Placebo (N=919)**	**PAXLOVID (N=918)**	**Placebo (N=916)**
Any of the below symptoms	59 (6%)	69 (8%)	35 (4%)	34 (4%)
Fatigue/malaise	20 (2%)	36 (4%)	17 (2%)	17 (2%)
Shortness of Breath/ Difficulty Breathing	7 (1%)	10 (1%)	4 (<1%)	3 (<1%)
Difficulty with concentration[a]	8 (1%)	11 (1%)	4 (<1%)	4 (<1%)
Sleep disturbance[a]	12 (1%)	14 (2%)	6 (1%)	12 (1%)
Myalgia	1 (<1%)	8 (1%)	1 (<1%)	2 (<1%)
Loss of taste/smell[b]	12 (1%)	10 (1%)	5 (1%)	4 (<1%)
Palpitations[a]	2 (<1%)	11 (1%)	1 (<1%)	7 (1%)
Cough	13 (1%)	12 (1%)	7 (1%)	2 (<1%)
Headache	10 (1%)	18 (2%)	7 (1%)	10 (1%)

Sources: EPIC-HR ADSY dataset, excluding subjects enrolled at Sites 1274 and 1470.
[a.] Due to missing data, for these symptoms at the Week 12 timepoint N=907 and 893 for PAXLOVID and placebo recipients, respectively.
[b.] Due to missing data, N=929 for PAXLOVID at Week 12 for loss of taste/smell.
Abbreviations: COVID, disease caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent-to-treat; N, number of subjects in treatment group

Conclusion

While EPIC-HR did not demonstrate a reduction in symptoms associated with post-COVID conditions at Week 12 and Week 24, these post hoc assessments were not designed to assess for the development of post-COVID conditions and only provide a snapshot of symptoms at two discrete time points. An important limitation of this analysis is that persistence of symptoms for two months or longer is part of the WHO definition for post-COVID conditions, and the existing data did not assess duration of symptoms.

A recent large retrospective cohort study using the U.S. Department of Veterans Affairs healthcare database (N=9217 PAXLOVID recipients versus N=47,123 untreated controls with SARS-CoV-2 infection) suggested that PAXLOVID may reduce the risk of post-COVID conditions; however, this study did not provide sufficient details on the data source, methods, or analytical approach for a thorough review (Xie et al. 2022). Based on the limited information reported in the publication, significant design concerns were identified. The study did not report the validity of their code-based algorithm to capture individual components of "post-COVID conditions." The study also did not capture, nor account for important confounders (e.g., use of certain medications that could influence the risk of the individual clinical condition that consists of "post-COVID conditions") in their analyses.

More data are needed to assess whether PAXLOVID has a role in the prevention of post-COVID conditions.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Nirmatrelvir

Nonclinical safety studies with nirmatrelvir included good laboratory practice (GLP) repeat-dose toxicology studies in rats and dogs; developmental and reproductive toxicology studies in rats and rabbits; and in vitro and in vivo safety pharmacology and genotoxicity studies. Overall, the nonclinical safety assessment for nirmatrelvir is considered acceptable to support approval from a pharmacology/toxicology perspective. Exposure multiples mentioned in the summary text are based on total nirmatrelvir concentration. All pertinent studies and findings are summarized in the following section. Full reviews for all nonclinical safety studies are located in Section 13.

Safety Pharmacology

Safety pharmacology studies with nirmatrelvir were conducted to assess potential pharmacodynamic effects on vital organ systems (central nervous, cardiovascular, and respiratory). Oral administration of up to 1000 mg/kg of nirmatrelvir to male rats produced no effects on functional observatory behavior (FOB) parameters, but nirmatrelvir (at 1000 mg/kg) administration resulted in transient locomotor effects, as evidenced, during a 60-minute observation session composed of twelve 5-minute intervals, by a lower number of mean vertical movement counts during the first 5-minute period and a higher number of mean horizontal and vertical movement counts during the last 30-minute period. Administration of 1000 mg/kg of nirmatrelvir also resulted in transient respiratory effects (higher respiratory rate and minute volume) compared to vehicle control animals. The central nervous system (CNS) and respiratory effects occurred at systemic exposures approximately 12 times higher than clinical exposure at the proposed human dose of nirmatrelvir 300 mg twice daily.

In a cardiovascular safety pharmacology study in cynomolgus monkeys, small transient effects such as increased systolic, diastolic, and mean blood pressure (BP), heart rate (HR) decreases, and associated RR, PR, and QT interval increases were observed following oral administration of 150 (75 BID) mg/kg/day nirmatrelvir. When the QT interval was corrected for HR (QTc), there was a test article-related decrease. No arrhythmias were noted. Nirmatrelvir at 150 (75 BID) mg/kg/day also produced slight decreases in cardiac contractility. All measures returned to vehicle control levels within 24 HPD (hours post first dose). Nirmatrelvir-related cardiovascular findings in monkeys were observed at systemic exposure about 2 times higher than clinical exposure at the proposed human dose of 300 mg twice daily. Several in vitro assays, including a hERG assay, and ex vivo studies in perfused heart and aorta, were conducted to assess for potential effects of nirmatrelvir on cardiovascular function and reported negative findings.

The potential effects on CNS, cardiovascular and respiratory safety pharmacology parameters had no correlating clinical signs or histopathological findings in the 14-day or 15-day repeat-dose toxicity studies in rats or monkeys. ECG data were also collected in the 15-day monkey toxicology study, and there were no test article-related changes in ECG parameters (HR, RR, PR, QRS, QT, QTc intervals) or ECG morphology in that study.

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General Toxicology

Pivotal repeat-dose toxicology studies were conducted in rats (2-week and 1-month durations) up to 1000 mg/kg/day and in monkeys (15-day and 1-month durations) up to 600 mg/kg/day. All the findings discussed below are considered drug-related but non-adverse. The highest doses tested in pivotal toxicity studies were identified as the no observed adverse effect levels (NOAELs).

Reversible hematological effects were noted in rats and monkeys. In the 14-day repeat dose oral study in rats, there were dose-dependent prolongations in prothrombin time (PT) and activated partial thromboplastin time (aPTT). At the high dose, higher platelet counts in both sexes and lower hemoglobin (HGB) in females were observed. Similar reversible coagulation findings (i.e., increase in platelets and prolongation in PT) were found in the 1-month repeat-dose oral rat study. The hematology and coagulation findings had no clinical or microscopic correlates, and all findings were completely recovered at the end of the recovery phase. In monkeys exposed orally to nirmatrelvir for 15-day and 1-month periods, increases in fibrinogen (FIB), compared with baseline (pre-dose) values, were observed in both sexes at the high dose without correlating histopathological findings. FIB was similar to baseline values at the end of the recovery phase.

In the one-month repeat dose study in monkeys, increased ALT and AST were noted in both sexes at the high dose. Neither macroscopic nor microscopic findings were noted in liver. In the recovery animals, no nirmatrelvir-related changes in clinical pathology parameters were observed.

In both the 14-day and 1-month repeat dose oral study in rats, minimal to mild periportal hepatocellular hypertrophy in both sexes with concomitant increased incidence and severity (minimal to mild) of periportal hepatocyte vacuolation in females at the high dose were noted. These microscopic observations were associated with higher mean liver weights and enlarged liver size in males and females at high dose. The hepatocellular hypertrophy was consistent with microsomal enzyme induction. In the thyroid, follicular cell hypertrophy (minimal to mild) was noted in both sexes at high dose in the 14-day study and was noted of all dose groups in the 1-month study. In the 1-month study, but not the 14-day study, minimal to mild cytoplasmic vacuolation in the pituitary gland was noted in the endocrine cells of the pars anterior (males only) at all dose groups. At the end of the recovery phase, in the 14-day study, there were no liver weight differences in either sex. Microscopic changes in the liver and thyroid had completely resolved, indicating full recovery of the dosing phase effects. In the 1-month study, microscopic changes in the liver, thyroid gland, and/or pituitary gland completely recovered at all doses in females and at the low and mid-doses in males, and partially recovered (lower incidence and/or severity) at recovery in males at the high dose of 1000 mg/kg/day. The macroscopic liver findings were completely resolved in both sexes by the end of the 2-week recovery phase. The liver (minimal to mild periportal hepatocyte hypertrophy and vacuolation), thyroid gland (follicular cell hypertrophy) and pituitary gland (vacuolation in the endocrine cells of pars anterior, males only) findings were consistent with secondary adaptive effects related to microsomal enzyme-induced increase in thyroid hormone catabolism, a mechanism that rats are known to be particularly sensitive to relative to humans.

Genotoxicity and Carcinogenicity

Nirmatrelvir was negative for mutagenesis in the in vitro reverse mutation assay, negative for clastogenicity in the in vitro assay using human peripheral lymphocytes, and negative for

genotoxicity in the in vivo micronucleus assay in rats exposed up to 1000 mg/kg/day for 14 days. Additionally, a potential impurity (b) (4) was tested in an Ames test for mutagenesis. Overall, the weight of evidence indicates that nirmatrelvir does not exhibit genotoxic potential.

The carcinogenicity potential of PAXLOVID was not evaluated due to the short treatment duration.

Developmental and Reproductive Toxicology

In a fertility and early embryo developmental (FEED) study in rats, nirmatrelvir was orally administered up to 1000 mg/kg/day, no effects on male systemic toxicity or mortality, clinical observations, or effects on food consumption in females were observed. Although epididymal sperm maturation was not reported, no drug-related abnormalities were observed on male reproductive organs upon macroscopic examination. In females, non-adverse increase in body weights were observed at 1000 mg/kg/day prior to mating. No effects on estrous cyclicity, days to mating, reproductive indices (mating, fecundity, and fertility), or cesarean section observations were observed. The no observed effect level (NOEL) for male and female fertility (and systemic toxicity) was 1000 mg/kg/day.

In an embryo-fetal developmental study in rats, nirmatrelvir administered orally up to 1000 mg/kg/day was not associated with maternal or fetal effects, including fetal body weights and fetal external, visceral, or skeletal morphology. The maternal and developmental NOAEL was the high dose of 1000 mg/kg/day. In an embryo-fetal development study in rabbits, no maternal macroscopic observations, effects on ovarian and uterine parameters, fetal viability, fetal external, visceral, or skeletal morphology were observed. However, lower (9%) fetal body weight was observed at the high dose (1000 mg/kg/day). Based on the lack of nirmatrelvir-related adverse maternal toxicity, the maternal NOAEL was 1000 mg/kg/day. The NOEL for developmental toxicity was 300 mg/kg/day, based on lower fetal body weights at 1000 mg/kg/day.

Rats were administered nirmatrelvir orally at doses of up to 1000 mg/kg/day in a pre- and postnatal developmental (PPND) study. No adverse effects were observed in pregnant rats and offspring at all dose levels. Body weight gain was decreased from PND 10 to 17 in the offspring at the highest dose of 1000 mg/kg/day, resulting in decreased (8% in both males and females compared to controls) body weight at PND 17. No significant difference in body weight was noted at PND 28 (males) or PND 22 (females) to PND 56 (both sexes) and afterwards. The maternal NOAEL was identified at 1000 mg/kg/day. The NOEL for developmental toxicity was 300 mg/kg/day due to an 8% decrease in body weight at PND 17. Drug concentrations in maternal and offspring plasma and breastmilk were not determined.

Additional Toxicology Studies

In an impurity qualification study, nirmatrelvir was administered by oral gavage once daily for 14 days to male and female Wistar Han rats at a dose of 200 mg/kg/day with increased amounts of multiple impurities (b) (4) or (b) (4) or without increased impurities. Non-adverse findings in coagulation, clinical chemistry parameters and liver weight are not different between groups with or without increased impurities. The impurity levels in nirmatrelvir at the NOAEL of 200 mg/kg/day are considered qualified.

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Exposure Multiples

Exposure multiples (Table 34) are based on nirmatrelvir predicted systemic exposure ($AUC_{0\text{-}24h}$) in humans at the recommended dosing regimen.

Table 34. Exposure Margins Based on NOAEL of Nirmatrelvir

Study	NOAEL	Adverse Findings	$AUC_{0\text{-}24hr}$[1] (ng·h/mL)	Exposure Multiple[2]
Repeat-Dose Studies (Oral)				
14-day rat	1000 mg/kg	Rats specific liver-thyroid effects due to thyroid hormone metabolism changes, not human relevant.	292,000	4.8
15-day monkey	600 mg/kg	None	1220,000	20.1
Repeat-Dose Studies (Oral)				
1-month rat	1000 mg/kg	Rats specific liver-thyroid-pituitary effects due to thyroid hormone metabolism changes, not human relevant.	548,000	9.0
1-month monkey	600 mg/kg	None	991,000	16.3
Reproductive Toxicology Studies				
Fertility and Early Embryonic Development				
Rat	1000 mg/kg	None	548,000[3]	9.0
Embryo-Fetal Development				
Rat	1000 mg/kg	None	535,000	8.8
Rabbits	300 mg/kg (NOEL)	None	195,000	3.2
	1000 mg/kg	Lower fetal body weight	689,000	11.3
Pre- and Postnatal Development				
Rat	300 mg/kg (NOEL)	None	346000[4]	5.9
	1000 mg/kg	Decreased body weight at PND 17	535,000[4]	8.8

Source: Reviewer assessment based on Studies 20GR276, 20GR289, 21GR122, 21GR125, 21GR146, 21GR132, 21GR126, and 21GR149.
1. $AUC_{0\text{-}24h}$ values for male and female animals combined unless otherwise stated.
2. Based on AUC_{24hr} 60.8 µg.hr/mL in humans at the proposed dosing regimen.
3. No AUCs in this FEED study were reported. Rats AUC24 were estimated based on the 28-day repeat dose study at 1000 mg/kg/day.
4. No AUCs in this PPND study were reported. Rats AUC24 were estimated based on the EFD rat study 28-day repeat dose study at 300 or 1000 mg/kg/day, respectively.
Abbreviations: AUC, area under the concentration-time curve; $AUC_{0\text{-}24}$, area under the concentration-time curve from 0 to 24 hours; FEED, fertility and early embryonic development; NOAEL, no observed adverse effect level; NOEL, no observed effect level; PPND, pre- and postnatal development

Ritonavir

Based on the review of NDA-22417 (Ritonavir), which was approved in 1996, one-month repeat-dose oral toxicity studies were conducted in rats and dogs. Liver hepatocyte hypertrophy and periportal inflammation, hypertrophy of thyroid follicular epithelium, and retinal hypertrophy were reported in rats, while liver weight increase, thymus weight decrease. and GI tract distress were noted in dogs. Reproductive studies reported no fertility or reproductive effects in rats. An embryo-fetal developmental study in rats reported reduced fetal weight, delayed skeletal ossification, wavy ribs, enlargement of fontanelles, and cryptorchidism

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(See footnote 4 in Table 35) at doses that are maternally toxic. In a fetal and developmental study in rabbits, slight developmental toxicity (reduced fetal size and weight) was noted at dosage that was maternally toxic. No neonatal toxic effects were noted in a pre- and postnatal developmental study in rats.

Exposure Multiples

Exposure multiples (Table 35) are summarized based on the data from the pharmacology review of Ritonavir in 1995.

Table 35. Exposure Margins Based on NOAEL of Ritonavir

Study	NOAEL	Adverse Findings	$AUC_{0\text{-}24hr}$[1] (ng·h/mL)	Exposure Multiple[2]
Repeat-Dose Studies (Oral)				
1-month rat	15 mg/kg	Increase in liver and thyroid weight, periportal inflammation and hepatocyte hypertrophy in liver, thyroid follicular hypertrophy, retinal hypertrophy.	4500	1.3
1-month dog	50 mg/kg	Increase in liver enzymes and weights, decrease in thymus weight, GI distress	17100	5.0
Reproductive Toxicology Studies				
Fertility and Early Embryonic Development				
Rat	75(f)/125(m) mg/kg	No effect on fertility and reproductive performance.	90500 (f)/ 61000 (m)	26.5 (f) / 17.9 (m)
Embryo-Fetal Development				
Rat	15 mg/kg (NOEL)	None	17300	5.1
	35 mg/kg	Reduced fetal weight, delayed skeletal ossification, wavy ribs, enlargement of fontanelles and slight increase in cryptorchidism[4] at maternal toxic doses	34300	10.1
Rabbits	50 mg/kg (NOEL)	None	28550	8.4
	110 mg/kg	Slight reduction in fetal weight and size at maternal toxic dose	Not reported	Not Available
Pre- and Postnatal Development				
Rat	60 mg/kg	None	Not Available[3]	Not Available[3]

Source: Reviewer assessment based on NDA 22417.
[1.] $AUC_{0\text{-}24h}$ values for male and female animals combined unless otherwise stated.
[2.] Based on AUC_{24hr} 3414 ng*hr/mL in humans at the proposed dosing regimen (data from trials under Protocol C4671014).
[3.] No AUCs in this PPND study were reported.
[4.] The interpretation of cryptorchidism in this study is difficult to access because it is not clear how the descent of fetal testes was noted. Typically, the descent of rat testes occurs post-natally (around post-natal day (PND) 15 and completes by PND 40).
Abbreviations: AUC, area under the concentration-time curve; $AUC_{0\text{-}24}$, area under the concentration-time curve from 0 to 24 hours; NOAEL, no observed adverse effect level; NOEL, no observed effect level; PPND, pre- and postnatal development

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Nirmatrelvir is a first-in-class drug, no previously described clinical experience is available to inform any specific safety concern regarding M^{pro} inhibitors.

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Ritonavir was approved in the United States in 1996 and is indicated as chronic use in combination with other antiretroviral agents for the treatment of HIV-1 infection. Ritonavir has potential safety concerns which include risk of serious adverse reaction due to drug interactions, toxicity in preterm neonates, hepatotoxicity, pancreatitis, allergic reactions/hypersensitivity, PR interval prolongation, increased concentrations of total cholesterol and triglycerides, diabetes mellitus/hyperglycemia, immune reconstitution syndrome, redistribution/accumulation of body fat, increased bleeding in patients with hemophilia, and development of resistance by HIV-1 to protease inhibitors. In clinical trials, the most frequently reported adverse drug reactions among patients receiving ritonavir alone or in combination with other antiretroviral drugs were gastrointestinal (including diarrhea, nausea, vomiting, and abdominal pain), neurological disturbances (including paresthesia and oral paresthesia), rash, and fatigue/asthenia (AbbVie 2010).

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

7.3.1. Safety Concerns Identified Through Emergency Use Authorization

The PAXLOVID EUA outlines mandatory reporting of all medication errors and serious adverse events (SAEs) considered to be potentially related to PAXLOVID. Over 11 million patients worldwide have received PAXLOVID for the treatment of COVID-19 since it was first authorized for emergency use in December 2021, including over 8 million patients in the United States. AEs following use of PAXLOVID that were reported to the FDA Adverse Events Reporting System, the FDA American College of Medical Toxicology COVID-19 Toxicology Investigators Consortium Pharmacovigilance Project Subregistry, and the medical literature have been reviewed regularly by the Office of Surveillance and Epidemiology (OSE) to detect new safety signals.

Based on the review of EUA data, anaphylaxis, serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson Syndrome), and other hypersensitivity reactions; headache; hypertension; abdominal pain; nausea and vomiting; and malaise are recommended to be included in (b) (4) the label. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. For further details, please refer to the OSE review by Kate McCartan, Maya Beganovic, Toni Salvatore, Irene Rwakazina, Sonal Goyal, Rachna Kapoor, Sheheryar Muhammad, Neha Gada, Sevan Kolejian, Rajdeep Gill, and Ida-Lina Diak for details (DARRTS ID: 5077785 2022).[3] Routine pharmacovigilance will be in place to detect postmarketing signals.

[3] This document contains proprietary data obtained by FDA under contract and cannot be released to the public. The information contained within is the result of an OSE review as part of PAXLOVID, NDA 217188 and EUA 105. The source can only be accessed by authorized individuals.

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7.3.2. Expectations on Safety in the Postmarket Setting

Safety analyses and conclusions in this review are primarily based upon data from the submitted Phase 2/3 trial populations. The eligibility criteria for EPIC-HR, EPIC-SR, and EPIC-PEP may mitigate potential safety concerns that may be observed with wider usage in the postmarket setting. Emergence of new events can be managed by routine pharmacovigilance activities.

7.4. FDA Approach to the Safety Review

Adequacy of Applicant's Clinical Safety Assessments

The review team identified a major data reliability issue during the NDA review. Briefly, unusual patterns of viral RNA shedding levels, viral sequencing results, and/or daily clinical symptom reporting times from subjects at four selected study sites in EPIC-HR and EPIC-SR were identified. The FDA approach to the safety review excluded those sites. Two clinical trial sites from EPIC-PEP matching the four EPIC-HR and EPIC-SR sites were also excluded. For further details please refer to Section 6.3.1.

No major issues were identified with respect to recording, coding, and categorizing AEs. The Applicant's translations of verbatim terms to Medical Dictionary for Regulatory Activities preferred terms for the events reported in EPIC-HR, EPIC-SR, and EPIC-PEP were coded according to version 24.1 and reviewed and were found to be acceptable. For definitions of AEs, treatment-emergent adverse events (TEAEs), adverse drug reactions, and serious adverse events (SAEs), please see Section 17.1.

Severity grades of AEs were defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (corrected Version 2.1, July 2017) (RSC 2017). Laboratory abnormalities were assessed by threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (August 2022).

EPIC-HR and EPIC-SR included analyses through Day 34 and EPIC-PEP included analyses through Day 38.

Approach to FDA Assessment of Clinical Trial Data

The FDA review approach for assessment of risk consisted of evaluation of the safety data from the Phase 2/3 trials separately (EPIC-HR, EPIC-SR, and EPIC-PEP) as well as the pooled safety data from EPIC-HR and EPIC-SR. Due to differences of treatment duration, EPIC-PEP (where the treatment duration was either 5 or 10 days) was reviewed separately from EPIC-HR and EPIC-SR (where the treatment duration was 5 days). Results of individual trials are highlighted where important differences may have emerged.

Given the data reliability issues as detailed in Section 6.3.1, subjects at sites 1274 and 1470 (including those switched to 1276) in EPIC-HR, at sites 1281 and 1488 (including those switched to 1282) in EPIC-SR, and at sites 1281 and 1483 (including those switched to 1311) in EPIC-PEP were excluded from the safety analysis.

Safety data from EPIC-HR and EPIC-SR were pooled as both trials represent a 5-day treatment regimen in patients with symptomatic COVID-19. These trials were also analyzed independently

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as well given the population differences. EPIC-HR investigated treatment in non-hospitalized symptomatic adult subjects with COVID-19 who were unvaccinated and at increased risk of progressing to severe illness, while EPIC-SR enrolled non-hospitalized symptomatic adults with COVID-19 who were at standard risk of progressing to severe disease (i.e., vaccinated subjects with one or more risk factors for severe COVID-19 and unvaccinated subjects without risk factors for severe COVID-19). Safety data were also analyzed from subjects with at least one risk factor for progression to severe COVID-19 and who were vaccinated in EPIC-SR. Additionally, safety data were analyzed from EPIC-PEP in both 5 and 10-day treatment durations, which investigated a post-exposure prophylaxis regimen in adult household contacts of an individual with symptomatic COVID-19.

Clinical trial data from EPIC-HR, EPIC-SR, and EPIC-PEP were independently analyzed using JMP and JMP Clinical software. Additional analyses were provided by the Clinical Data Scientist support team. All safety assessments and conclusions are those of the clinical review team unless otherwise specified. Prespecified hypothesis testing was not proposed for safety outcomes in EPIC-HR, EPIC-SR, and EPIC-PEP. Comparisons are therefore based on descriptive analyses.

It is recommended that Section 6.1 of the label, 'Adverse Reactions from Clinical Trial Experience', include data from the two PAXLOVID treatment trials, EPIC-HR and EPIC-SR.

7.5. Adequacy of the Clinical Safety Database

Overall, the safety database is adequate to assess the safety of PAXLOVID for the proposed indication, dosage regimen, and patient population. See Table 36 and Table 37. A total of 3608 subjects were exposed to PAXLOVID across 13 clinical trials including four Phase 2/3 trials and nine Phase 1 trials. Across the EPIC-HR, EPIC-SR, and EPIC-PEP trials, 2490 subjects received the proposed PAXLOVID twice daily 5-day regimen. In addition, 911 subjects received PAXLOVID for 10 days in EPIC-PEP. Table 36 and Table 37 summarize the exposure periods for pooled EPIC-HR and EPIC-SR, EPIC-HR, EPIC-SR, and EPIC-PEP. The mean (standard deviation [SD]) duration of the exposure in the pooled EPIC-HR and EPIC-SR trials for the PAXLOVID group was 5 (0.7) days and 5 (0.8) days for the placebo group. In EPIC-PEP, the mean (SD) duration of exposure was 9.9 days (1.3) in the 5-day group[4], 9.8 (1.4) in the 10-day group, and 9.9 (1.2) in the placebo group.

Table 36. Duration of Exposure, Safety Population, EPIC-HR and EPIC-SR[1]

	EPIC-HR		EPIC-SR		Pooled	
Parameter	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)
Duration of treatment, days						
Mean (SD)	5 (0.8)	5 (0.8)	5 (0.7)	5.1 (0.6)	5 (0.7)	5 (0.8)
Median (Q1, Q3)	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)
Min, Max	1, 6	1, 7	1, 6	1, 6	1, 6	1, 7
Total exposure (person years)	14	14	7	7	22	22

[4] Subjects in the 5-day group in EPIC-PEP received five days of PAXLOVID followed by five days of placebo.

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Parameter	EPIC-HR PAXLOVID N=1038 n (%)	EPIC-HR Placebo N=1053 n (%)	EPIC-SR PAXLOVID N=540 n (%)	EPIC-SR Placebo N=528 n (%)	Pooled PAXLOVID N=1578 n (%)	Pooled Placebo N=1581 n (%)
Patients treated, by duration						
≥1 to <3 days	26 (2.5)	40 (3.8)	13 (2.4)	11 (2.1)	39 (2.5)	51 (3.2)
≥3 to <5 days	26 (2.5)	30 (2.8)	5 (0.9)	5 (0.9)	31 (2.0)	35 (2.2)
≥5 to <7 days	986 (95.0)	981 (93.2)	522 (96.7)	512 (97.0)	1508 (95.6)	1493 (94.4)
≥7 days	0	2 (0.2)	0	0	0	2 (0.1)

Source: adex.xpt and adsl.xpt; Software: R
Note: Subjects enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
[1.] Duration of treatment is 5 days.
Abbreviations: N, number of subjects in treatment group; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

Table 37. Duration of Exposure, Safety Population, EPIC-PEP[1]

Parameter	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)
Duration of treatment, days			
Mean (SD)	9.9 (1.3)	9.8 (1.4)	9.9 (1.3)
Median (Q1, Q3)	10 (10, 10)	10 (10, 10)	10 (10, 10)
Min, Max	1, 12	1, 11	1, 11
Total exposure (person years)	25	25	24
Patients treated, by duration			
<3 days	10 (1.1)	9 (1.0)	9 (1.0)
≥3 to <5 days	8 (0.9)	9 (1.0)	6 (0.7)
≥5 to <7 days	15 (1.6)	23 (2.5)	17 (1.9)
≥7 to <10 days	9 (1.0)	11 (1.2)	12 (1.3)
≥10 to <12 days	867 (95.1)	859 (94.3)	854 (95.1)
≥12 days	3 (0.3)	0	0

Source: adex.xpt and adsl.xpt; Software: R.
[1.] Duration of treatment is 5 or 10 days.
Abbreviations: N, number of subjects in treatment group; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

7.6. Safety Results

Safety results in this section are presented by EPIC-HR and EPIC-SR (Section 7.6.1), EPIC-PEP (Section 7.6.2), and submission-specific safety issues (Section 7.6.3). Additional analyses based on prior COVID-19 vaccination and baseline SARS-CoV-2 serostatus had no discernible impact on the safety of PAXLOVID and are not further discussed in this section: please refer to Section 6.3.2 and Section 17.3.

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7.6.1. Safety Results, EPIC HR and EPIC-SR

7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, EPIC-HR and EPIC-SR

PAXLOVID demonstrated an overall favorable safety profile in the EPIC-HR and EPIC-SR clinical trials (Table 38). The incidences of SAEs, AEs leading to permanent discontinuation of study drug, any TEAE, and severe AEs were similar or higher in the placebo group compared to the PAXLOVID group. No deaths occurred in PAXLOVID-treated subjects.

Table 38. Overview of Adverse Events[1], Safety Population, EPIC-HR and EPIC-SR[2]

	EPIC-HR			EPIC-SR			Pooled		
Event Category	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)	Risk Difference (%) (95% CI)[3]
SAE	18 (1.7)	71 (6.7)	-5.0 (-6.7, -3.3)*	8 (1.5)	11 (2.1)	-0.6 (-2.2, 1.0)	26 (1.6)	82 (5.2)	-3.5 (-4.8, -2.3)*
SAEs with fatal outcome	0	13 (1.2)	-1.2 (-1.9, -0.6)*	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	14 (0.9)	-0.9 (-1.3, -0.4)*
Life-threatening SAEs	3 (0.3)	13 (1.2)	-0.9 (-1.7, -0.2)*	1 (0.2)	3 (0.6)	-0.4 (-1.1, 0.4)	4 (0.3)	16 (1.0)	-0.8 (-1.3, -0.2)*
AE leading to permanent discontinuation of study drug	21 (2.0)	45 (4.3)	-2.3 (-3.7, -0.8)*	10 (1.9)	5 (0.9)	0.9 (-0.5, 2.3)	31 (2.0)	50 (3.2)	-1.2 (-2.3, -0.1)*
AE leading to dose modification of study drug	4 (0.4)	4 (0.4)	0.0 (-0.5, 0.5)	1 (0.2)	2 (0.4)	-0.2 (-0.8, 0.4)	5 (0.3)	6 (0.4)	-0.1 (-0.5, 0.3)
AE leading to interruption of study drug	4 (0.4)	4 (0.4)	0.0 (-0.5, 0.5)	1 (0.2)	2 (0.4)	-0.2 (-0.8, 0.4)	5 (0.3)	6 (0.4)	-0.1 (-0.5, 0.3)
AE leading to reduction of study drug	0	0	0 (0, 0)	0	0	0 (0, 0)	0	0	0 (0, 0)
AE leading to dose delay of study drug	0	0	0 (0, 0)	0	0	0 (0, 0)	0	0	0 (0, 0)
Other	0	0	0 (0, 0)	0	0	0 (0, 0)	0	0	0 (0, 0)
Any AE[4]	228 (22.0)	256 (24.3)	-2.3 (-6.0, 1.3)	126 (23.3)	126 (23.9)	-0.5 (-5.6, 4.6)	354 (22.4)	382 (24.2)	-1.7 (-4.7, 1.2)
Severe and worse	42 (4.0)	103 (9.8)	-5.7 (-7.9, -3.6)*	18 (3.3)	22 (4.2)	-0.8 (-3.1, 1.4)	60 (3.8)	125 (7.9)	-4.1 (-5.7, -2.5)*
Moderate	68 (6.6)	71 (6.7)	-0.2 (-2.3, 1.9)	34 (6.3)	35 (6.6)	-0.3 (-3.3, 2.6)	102 (6.5)	106 (6.7)	-0.2 (-2.0, 1.5)
Mild	118 (11.4)	82 (7.8)	3.6 (1.1, 6.1)*	74 (13.7)	69 (13.1)	0.6 (-3.4, 4.7)	192 (12.2)	151 (9.6)	2.6 (0.4, 4.8)*

Source: adae.xpt; Software: R
Note: Subjects enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
[2.] Duration of treatment is 5 days.
[3.] Difference is shown between PAXLOVID and placebo
[4.] Severity as assessed by the investigator.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment group; n, number of subjects with at least one event; SAE, serious adverse event

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7.6.1.2. Deaths, EPIC-HR and EPIC-SR

A total of 14 subjects died in EPIC-HR and EPIC-SR through Day 34, all of whom received placebo. Most deaths were caused by COVID-19 or COVID-19 pneumonia (n=12). Listings of all patient deaths from EPIC-HR and EPIC-SR are summarized in Section 17.2.

7.6.1.3. Serious Treatment-Emergent Adverse Events, EPIC-HR and EPIC-SR

Assessment of SAEs occurring in EPIC-HR and EPIC-SR did not reveal patterns to suggest a serious safety risk attributable to PAXLOVID; the majority of the SAEs were related to the disease under investigation (COVID-19) (Table 39). More SAEs occurred in placebo compared to PAXLOVID in EPIC-HR (1.7% in the PAXLOVID group versus 6.7% in the placebo group), in EPIC-SR (1.5% in the PAXLOVID group versus 2.1% in the placebo group), and in the pooled analysis of EPIC-HR and EPIC-SR (1.6% in the PAXLOVID group versus 5.2% in the placebo group). The most common SAEs (≥2 subjects) in the pooled PAXLOVID group were COVID-19 pneumonia (0.6%), COVID-19 (0.1%), and pneumonia (0.1%). These SAEs occurred at higher frequencies in the placebo group when compared to the PAXLOVID group, overall and by individual trial (with the exception of pneumonia in EPIC-HR which occurred at equal frequencies).

One subject in EPIC-HR (Subject (b) (6)) experienced an SAE considered related to study drug by the investigator. This subject was a 48-year-old female with the risk factor of BMI >25 kg/m^2 in the PAXLOVID group and had treatment-related SAEs of chest discomfort, dyspnea, and palpitations on Day 2. PAXLOVID was permanently discontinued on Day 2 and the SAE resolved on Day 5. There were no other SAEs considered related to study intervention by the investigator in EPIC-HR or EPIC-SR.

SAE assessments were similar using FDA Medical Queries (FMQs). For further details please see Section 17.4.

Table 39. Patients With Serious Adverse Events[1] by System Organ Class and Preferred Term, Safety Population, EPIC-HR and EPIC-SR[2]

	EPIC-HR			EPIC-SR			Pooled		
System Organ Class Preferred Term	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)	Risk Difference (%) (95% CI)[3]
Any SAE	18 (1.7)	71 (6.7)	-5.0 (-6.7, -3.3)*	8 (1.5)	11 (2.1)	-0.6 (-2.2, 1.0)	26 (1.6)	82 (5.2)	-3.5 (-4.8, -2.3)*
Blood and lymphatic system disorders (SOC)	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Anemia	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Cardiac disorders (SOC)	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Palpitations	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Gastrointestinal disorders (SOC)	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Rectal hemorrhage	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
General disorders and administration site conditions (SOC)	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Chest discomfort	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Hepatobiliary disorders (SOC)	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Hepatic mass	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Infections and infestations (SOC)	11 (1.1)	54 (5.1)	-4.1 (-5.5, -2.6)*	5 (0.9)	11 (2.1)	-1.2 (-2.6, 0.3)	16 (1.0)	65 (4.1)	-3.1 (-4.2, -2.0)*
Abscess	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Pneumonia aspiration	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Sepsis	1 (0.1)	0	0.1 (-0.1, 0.3)	0	1 (0.2)	-0.2 (-0.6, 0.2)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Atypical pneumonia	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
COVID-19	2 (0.2)	7 (0.7)	-0.5 (-1.0, 0.1)	0	1 (0.2)	-0.2 (-0.6, 0.2)	2 (0.1)	8 (0.5)	-0.4 (-0.8, 0.0)
Pneumonia	1 (0.1)	11 (1.0)	-0.9 (-1.6, -0.3)*	1 (0.2)	2 (0.4)	-0.2 (-0.8, 0.4)	2 (0.1)	13 (0.8)	-0.7 (-1.2, -0.2)*
COVID-19 pneumonia	7 (0.7)	36 (3.4)	-2.7 (-3.9, -1.5)*	3 (0.6)	8 (1.5)	-1.0 (-2.2, 0.3)	10 (0.6)	44 (2.8)	-2.1 (-3.0, -1.2)*
Injury, poisoning and procedural complications (SOC)	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Craniocerebral injury	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Eye injury	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Hand fracture	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Road traffic accident	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Wrist fracture	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Investigations (SOC)	3 (0.3)	3 (0.3)	0.0 (-0.5, 0.5)	1 (0.2)	0	0.2 (-0.2, 0.5)	4 (0.3)	3 (0.2)	0.1 (-0.3, 0.4)
Hemoglobin decreased	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Hepatic enzyme increased	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Oxygen saturation decreased	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Creatinine renal clearance decreased	1 (0.1)	2 (0.2)	-0.1 (-0.4, 0.2)	0	0	0 (0, 0)	1 (0.06)	2 (0.1)	-0.1 (-0.3, 0.2)
Alanine aminotransferase increased	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Fibrin D dimer increased	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Metabolism and nutrition disorders (SOC)	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Electrolyte imbalance	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)

System Organ Class Preferred Term	EPIC-HR PAXLOVID N=1038 n (%)	EPIC-HR Placebo N=1053 n (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n (%)	EPIC-SR Placebo N=528 n (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n (%)	Pooled Placebo N=1581 n (%)	Pooled Risk Difference (%) (95% CI)[3]
Neoplasms benign, malignant, and unspecified (incl cysts and polyps) (SOC)	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Colon adenoma	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Nervous system disorders (SOC)	2 (0.2)	0	0.2 (-0.1, 0.5)	1 (0.2)	0	0.2 (-0.2, 0.5)	3 (0.2)	0	0.2 (-0.0, 0.4)
Brain stem stroke	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Facial paralysis	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Osmotic demyelination syndrome	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Respiratory, thoracic, and mediastinal disorders (SOC)	1 (0.1)	18 (1.7)	-1.6 (-2.4, -0.8)*	1 (0.2)	0	0.2 (-0.2, 0.5)	2 (0.1)	18 (1.1)	-1.0 (-1.6, -0.5)*
Respiratory distress	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Respiratory failure	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Dyspnea	1 (0.1)	3 (0.3)	-0.2 (-0.6, 0.2)	0	0	0 (0, 0)	1 (0.06)	3 (0.2)	-0.1 (-0.4, 0.1)
Hypoxia	0	2 (0.2)	-0.2 (-0.5, 0.1)	0	0	0 (0, 0)	0	2 (0.1)	-0.1 (-0.3, 0.0)
Interstitial lung disease	0	2 (0.2)	-0.2 (-0.5, 0.1)	0	0	0 (0, 0)	0	2 (0.1)	-0.1 (-0.3, 0.0)
Pulmonary embolism	0	2 (0.2)	-0.2 (-0.5, 0.1)	0	0	0 (0, 0)	0	2 (0.1)	-0.1 (-0.3, 0.0)
Acute respiratory failure	0	5 (0.5)	-0.5 (-0.9, -0.1)*	0	0	0 (0, 0)	0	5 (0.3)	-0.3 (-0.6, -0.0)*
Pneumonitis	0	5 (0.5)	-0.5 (-0.9, -0.1)*	0	0	0 (0, 0)	0	5 (0.3)	-0.3 (-0.6, -0.0)*
Vascular disorders (SOC)	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Hypertensive crisis	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)

Source: adae.xpt; Software: R.
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Note: Subjects enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit. Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
[2.] Duration of treatment is 5 days.
[3.] Difference is shown between PAXLOVID and placebo
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; N, number of subjects in treatment group; n, number of subjects with adverse event; SOC, system organ class

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7.6.1.4. Adverse Events Leading to Treatment Discontinuation, EPIC-HR and EPIC-SR

Rates of discontinuation were generally balanced between PAXLOVID and placebo groups across both trials (Table 40).

Discontinuations due to dysgeusia were higher (≥2 subjects) in the PAXLOVID group in the pooled EPIC-HR and EPIC-SR trials compared to placebo. Assessments of AEs leading to discontinuation were similar using FMQs. For further details please see Section 17.4.

atients With Adverse Events[1] Leading to Treatment Discontinuation by Preferred Term, Safety Population, EPIC-HR and EPIC-SR[2]

	EPIC-HR			EPIC-SR			Pooled		
erm	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)	Risk Difference (%) (95% CI)[3]
ding to discontinuation	21 (2.0)	45 (4.3)	-2.3 (-3.7, -0.8)*	10 (1.9)	5 (0.9)	0.9 (-0.5, 2.3)	31 (2.0)	50 (3.2)	-1.2 (-2.3, -0.1)*
	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	2 (0.4)	0	0.4 (-0.1, 0.9)	3 (0.2)	1 (0.06)	0.1 (-0.1, 0.4)
	5 (0.5)	5 (0.5)	0.0 (-0.6, 0.6)	1 (0.2)	0	0.2 (-0.2, 0.5)	6 (0.4)	5 (0.3)	0.1 (-0.3, 0.5)
	4 (0.4)	2 (0.2)	0.2 (-0.3, 0.7)	1 (0.2)	2 (0.4)	-0.2 (-0.8, 0.4)	5 (0.3)	4 (0.3)	0.1 (-0.3, 0.4)
9	1 (0.1)	3 (0.3)	-0.2 (-0.6, 0.2)	0	0	0 (0, 0)	1 (0.06)	3 (0.2)	-0.1 (-0.4, 0.1)
ıia	0	3 (0.3)	-0.3 (-0.6, 0.0)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	1 (0.06)	4 (0.3)	-0.2 (-0.5, 0.1)
9 pneumonia	1 (0.1)	12 (1.1)	-1.0 (-1.7, -0.4)*	0	2 (0.4)	-0.4 (-0.9, 0.1)	1 (0.06)	14 (0.9)	-0.8 (-1.3, -0.3)*
od cell count d	2 (0.2)	0	0.2 (-0.1, 0.5)	0	0	0 (0, 0)	2 (0.1)	0	0.1 (-0.0, 0.3)
e renal clearance d	2 (0.2)	4 (0.4)	-0.2 (-0.6, 0.3)	2 (0.4)	0	0.4 (-0.1, 0.9)	4 (0.3)	4 (0.3)	0.0 (-0.4, 0.4)
ar filtration rate d	2 (0.2)	2 (0.2)	0.0 (-0.4, 0.4)	0	0	0 (0, 0)	2 (0.1)	2 (0.1)	0.0 (-0.2, 0.2)
aminotransferase d	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	0	0 (0, 0)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
a	2 (0.2)	0	0.2 (-0.1, 0.5)	2 (0.4)	0	0.4 (-0.1, 0.9)	4 (0.3)	0	0.3 (0.0, 0.5)*
	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	1 (0.2)	0	0.2 (-0.2, 0.5)	2 (0.1)	1 (0.06)	0.1 (-0.2, 0.3)
ory distress	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	0	0 (0, 0)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
piratory failure	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
l lung disease	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
ory failure	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
itis	0	3 (0.3)	-0.3 (-0.6, 0.0)	0	0	0 (0, 0)	0	3 (0.2)	-0.2 (-0.4, 0.0)

pt; Software: R.
*) indicates rows where the 95% confidence interval excludes zero.
enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
ergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
eatment is 5 days.
shown between PAXLOVID vs. placebo
CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; N, number of subjects in treatment group; n, number of subjects
vent; SOC, system organ class

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7.6.1.5. Treatment-Emergent Adverse Events, EPIC-HR and EPIC-SR

Table 41 includes TEAEs occurring at 0.5% or higher frequency in EPIC-HR and EPIC-SR. The most common TEAEs (≥2% incidence) in the EPIC-HR PAXLOVID group were dysgeusia and diarrhea, and these occurred at a higher frequency compared to the placebo group (4.6% and 3.0% versus 0.1% and 1.5%, respectively). The most common TEAEs observed in EPIC-SR were consistent with those observed in EPIC-HR.

Assessment of TEAEs was similar using FMQs. For further details, please see Section 17.4.

Of the AEs considered by the investigator to be related to study drug in EPIC-HR and EPIC-SR, dysgeusia (4.4% in the PAXLOVID group versus 0% in the placebo group in EPIC-HR; 4.4% in the PAXLOVID group versus 0.2% in the placebo group in EPIC-SR) was reported at a higher frequency in the PAXLOVID group compared with the placebo group. For further details, please see Section 17.4.

As stated in Section 7.3, anaphylaxis, serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson Syndrome), and other hypersensitivity reactions; headache; hypertension; abdominal pain; nausea and vomiting; and malaise have been identified by OSE or the Applicant during use of PAXLOVID under EUA. Details regarding anaphylaxis, serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson syndrome), and other hypersensitivity reactions; headache; and hypertension are provided in their respective sections in 7.6.3. In EPIC-HR and EPIC-SR, the TEAEs of abdominal pain, nausea, vomiting, and malaise all occurred infrequently and at similar frequencies when comparing the PAXLOVID and placebo groups. For further details refer to Table 41 and Section 17.4.

Table 41. Patients With Common Adverse Events[1] Occurring at ≥0.5% Frequency, Safety Population, EPIC-HR and EPIC-SR[2]

	EPIC-HR			EPIC-SR			Pooled		
Preferred Term[3]	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)	Risk Difference (%) (95% CI)[4]
Any AE	228 (22.0)	256 (24.3)	-2.3 (-6.0, 1.3)	126 (23.3)	126 (23.9)	-0.5 (-5.6, 4.6)	354 (22.4)	382 (24.2)	-1.7 (-4.7, 1.2)
Dysgeusia	48 (4.6)	1 (0.09)	4.5 (3.2, 5.8)*	30 (5.6)	2 (0.4)	5.2 (3.2, 7.2)*	78 (4.9)	3 (0.2)	4.8 (3.7, 5.8)*
Diarrhea	31 (3.0)	16 (1.5)	1.5 (0.2, 2.7)*	22 (4.1)	16 (3.0)	1.0 (-1.2, 3.3)	53 (3.4)	32 (2.0)	1.3 (0.2, 2.5)*
Myalgia	7 (0.7)	1 (0.09)	0.6 (0.0, 1.1)*	0	0	0 (0, 0)	7 (0.4)	1 (0.06)	0.4 (0.0, 0.7)*
Hypertension	6 (0.6)	2 (0.2)	0.4 (-0.1, 0.9)	2 (0.4)	2 (0.4)	-0.0 (-0.7, 0.7)	8 (0.5)	4 (0.3)	0.3 (-0.2, 0.7)
Vomiting	12 (1.2)	9 (0.9)	0.3 (-0.6, 1.2)	10 (1.9)	11 (2.1)	-0.2 (-1.9, 1.4)	22 (1.4)	20 (1.3)	0.1 (-0.7, 0.9)
Dyspepsia	4 (0.4)	4 (0.4)	0.0 (-0.5, 0.5)	4 (0.7)	2 (0.4)	0.4 (-0.5, 1.3)	8 (0.5)	6 (0.4)	0.1 (-0.3, 0.6)
Pyrexia	8 (0.8)	7 (0.7)	0.1 (-0.6, 0.8)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	9 (0.6)	8 (0.5)	0.1 (-0.4, 0.6)
Type 2 diabetes mellitus	1 (0.1)	3 (0.3)	-0.2 (-0.6, 0.2)	3 (0.6)	1 (0.2)	0.4 (-0.4, 1.1)	4 (0.3)	4 (0.3)	0.0 (-0.4, 0.4)
Creatinine renal clearance decreased	14 (1.3)	16 (1.5)	-0.2 (-1.2, 0.8)	5 (0.9)	4 (0.8)	0.2 (-0.9, 1.3)	19 (1.2)	20 (1.3)	-0.1 (-0.8, 0.7)
Headache	12 (1.2)	13 (1.2)	-0.1 (-1.0, 0.9)	6 (1.1)	6 (1.1)	-0.0 (-1.3, 1.2)	18 (1.1)	19 (1.2)	-0.1 (-0.8, 0.7)
Aspartate aminotransferase increased	10 (1.0)	14 (1.3)	-0.4 (-1.3, 0.5)	7 (1.3)	4 (0.8)	0.5 (-0.7, 1.7)	17 (1.1)	18 (1.1)	-0.1 (-0.8, 0.7)
Cough	6 (0.6)	6 (0.6)	0.0 (-0.6, 0.7)	0	1 (0.2)	-0.2 (-0.6, 0.2)	6 (0.4)	7 (0.4)	-0.1 (-0.5, 0.4)
Abdominal pain upper	3 (0.3)	2 (0.2)	0.1 (-0.3, 0.5)	1 (0.2)	3 (0.6)	-0.4 (-1.1, 0.4)	4 (0.3)	5 (0.3)	-0.1 (-0.4, 0.3)
C-reactive protein increased	10 (1.0)	13 (1.2)	-0.3 (-1.2, 0.6)	3 (0.6)	2 (0.4)	0.2 (-0.6, 1.0)	13 (0.8)	15 (0.9)	-0.1 (-0.8, 0.5)
Hyperkalemia	0	1 (0.09)	-0.1 (-0.3, 0.1)	2 (0.4)	3 (0.6)	-0.2 (-1.0, 0.6)	2 (0.1)	4 (0.3)	-0.1 (-0.4, 0.2)
Tachycardia	0	0	0 (0, 0)	1 (0.2)	3 (0.6)	-0.4 (-1.1, 0.4)	1 (0.06)	3 (0.2)	-0.1 (-0.4, 0.1)
Nausea	15 (1.4)	19 (1.8)	-0.4 (-1.4, 0.7)	17 (3.1)	16 (3.0)	0.1 (-2.0, 2.2)	32 (2.0)	35 (2.2)	-0.2 (-1.2, 0.8)
Dyspnea	7 (0.7)	9 (0.9)	-0.2 (-0.9, 0.6)	2 (0.4)	3 (0.6)	-0.2 (-1.0, 0.6)	9 (0.6)	12 (0.8)	-0.2 (-0.8, 0.4)
Dizziness	3 (0.3)	5 (0.5)	-0.2 (-0.7, 0.3)	4 (0.7)	6 (1.1)	-0.4 (-1.6, 0.8)	7 (0.4)	11 (0.7)	-0.3 (-0.8, 0.3)
Blood creatine phosphokinase increased	1 (0.1)	5 (0.5)	-0.4 (-0.8, 0.1)	4 (0.7)	4 (0.8)	-0.0 (-1.1, 1.0)	5 (0.3)	9 (0.6)	-0.3 (-0.7, 0.2)
Blood glucose increased	1 (0.1)	7 (0.7)	-0.6 (-1.1, -0.0)*	2 (0.4)	0	0.4 (-0.1, 0.9)	3 (0.2)	7 (0.4)	-0.3 (-0.6, 0.1)
Serum ferritin increased	2 (0.2)	6 (0.6)	-0.4 (-0.9, 0.1)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	3 (0.2)	7 (0.4)	-0.3 (-0.6, 0.1)
Alanine aminotransferase increased	17 (1.6)	27 (2.6)	-0.9 (-2.2, 0.3)	13 (2.4)	8 (1.5)	0.9 (-0.8, 2.6)	30 (1.9)	35 (2.2)	-0.3 (-1.3, 0.7)
Blood thyroid stimulating hormone increased	5 (0.5)	7 (0.7)	-0.2 (-0.8, 0.5)	2 (0.4)	5 (0.9)	-0.6 (-1.5, 0.4)	7 (0.4)	12 (0.8)	-0.3 (-0.9, 0.2)
Activated partial thromboplastin time prolonged	9 (0.9)	12 (1.1)	-0.3 (-1.1, 0.6)	3 (0.6)	6 (1.1)	-0.6 (-1.7, 0.5)	12 (0.8)	18 (1.1)	-0.4 (-1.1, 0.3)
Fibrin D dimer increased	22 (2.1)	30 (2.8)	-0.7 (-2.1, 0.6)	6 (1.1)	6 (1.1)	-0.0 (-1.3, 1.2)	28 (1.8)	36 (2.3)	-0.5 (-1.5, 0.5)
COVID-19	3 (0.3)	13 (1.2)	-0.9 (-1.7, -0.2)*	0	1 (0.2)	-0.2 (-0.6, 0.2)	3 (0.2)	14 (0.9)	-0.7 (-1.2, -0.2)*
Pneumonia	2 (0.2)	15 (1.4)	-1.2 (-2.0, -0.5)*	2 (0.4)	5 (0.9)	-0.6 (-1.5, 0.4)	4 (0.3)	20 (1.3)	-1.0 (-1.6, -0.4)*
COVID-19 pneumonia	8 (0.8)	40 (3.8)	-3.0 (-4.3, -1.8)*	4 (0.7)	10 (1.9)	-1.2 (-2.5, 0.2)	12 (0.8)	50 (3.2)	-2.4 (-3.4, -1.4)*

Source: adae.xpt; Software: R
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Note: Subjects enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
[2.] Duration of treatment is 5 days.
[3.] Coded as MedDRA preferred terms.
[4.] Difference is shown between PAXLOVID and placebo.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; MedDRA. Medical Dictionary for Regulatory Activities

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7.6.1.6. Laboratory Findings, EPIC-HR and EPIC-SR

Overall, laboratory abnormalities in EPIC-HR and EPIC-SR were similar between the PAXLOVID group and placebo group. For Level 3 laboratory abnormalities as assessed by the Safety Standard & Figures Integrated Guide, PT, high (>1.5x ULN) was the only outlier that occurred more frequently (>1%) in the PAXLOVID group (2.0%) when compared to the placebo group (0.7%). This outlier was noted in EPIC-HR only, overall frequencies of this outlier were similar in EPIC-SR (0.6% in the PAXLOVID group and 0.4% in the placebo group). Given the relatively low frequency of this laboratory finding, specific labeling is not recommended for this PT outlier. For a complete listing of laboratory outliers, please see Section 17.5.

7.6.1.7. Assessment of Drug-Induced Liver Injury, EPIC-HR and EPIC-SR

Figure 17 and Table 42 show screening assessments for potential cases of serious drug-induced liver injury (DILI). There were two cases of potential Hy's Law[5] identified, however, one of these cases did not meet the protocol definition as this subject had baseline hepatic enzyme abnormalities as described below. There were no cases of cholestatic drug-induced liver injury. For further details see Section 17.6.

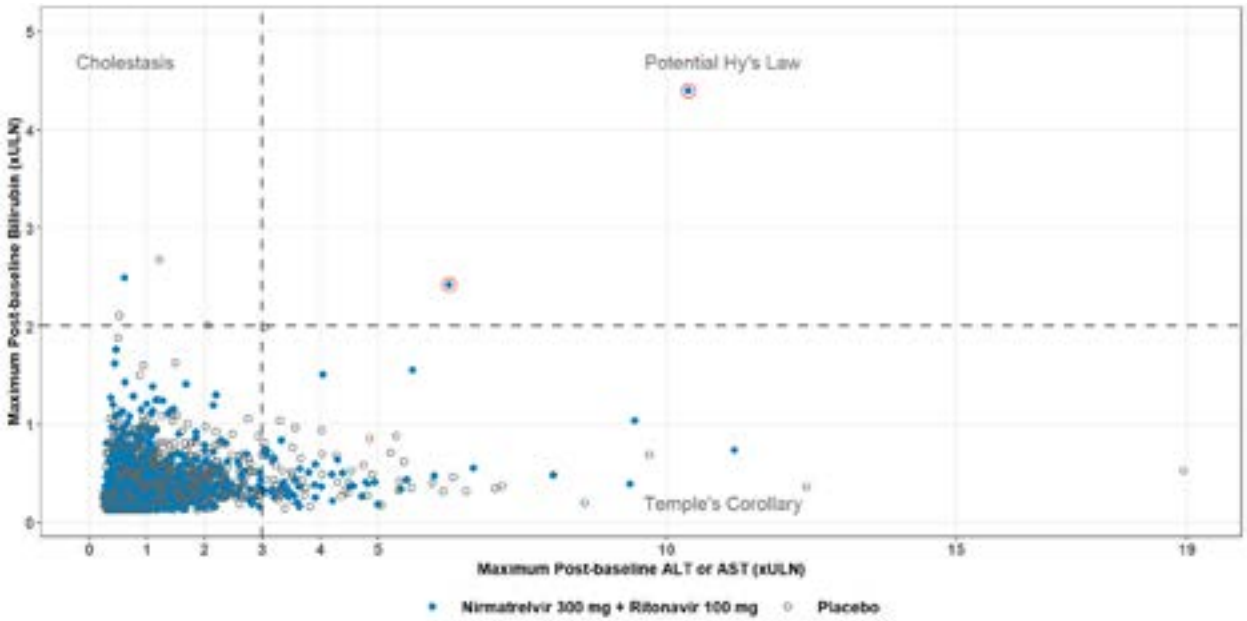
The case of potential Hy's law (EPIC-HR, PAXLOVID group, Subject (b) (6)) occurred during long-term follow-up in a 54-year-old man with hypertension, chronic lung disease, and tobacco use. Liver abnormalities occurred on Day 56 that were in range for potential Hy's Law with both ALT and AST >5x ULN and bilirubin >4x ULN. On the same day it was reported this subject had an AE of moderate (Grade 2) hepatic function abnormality that was not related to study intervention by the investigator and was reported as recovering on Day 168.

Additionally, an event of drug-induced liver injury (EPIC-SR, PAXLOVID group, Subject (b) (6)) occurred in a 31-year-old man who had baseline ALT >13x ULN and bilirubin >3x ULN. These parameters improved on Day 7 and resolved on Day 34. This case did not meet the protocol definition of potential Hy's Law as these abnormalities occurred at baseline. No changes were made to study intervention.

It is unlikely either of these subjects experienced their AEs as a result of study intervention. The laboratory abnormalities noted in Subject (b) (6) were late in follow-up (Day 56), making it unlikely related to study intervention. Subject (b) (6) had the laboratory abnormalities at baseline and improved while on therapy, making it unlikely PAXLOVID contributed to these laboratory abnormalities.

[5] A potential case of Hy's Law was defined as having any postbaseline total bilirubin equal to or exceeding 2x ULN within 30 days after a postbaseline alanine aminotransferase (ALT) or aspartate transaminase (AST) equal to or exceeding 3x ULN and alkaline phosphatase (ALP) <2x ULN.

Figure 17. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, EPIC-HR and EPIC-SR



Source: adlb.xpt; Software: R
Note: Each data point represents a patient plotted by their maximum ALT or AST versus their maximum total bilirubin values in the post-baseline period.
Note: A potential Hy's Law case (red circle) was defined as having any post-baseline total bilirubin equal to or exceeding 2X ULN within 30 days after a post-baseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN (note ALP values are not circled). All subjects with at least one post-baseline ALT or AST and bilirubin are plotted.
Note: Subjects enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; TB, total bilirubin; ULN, upper limit of normal

Table 42. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, EPIC-HR and EPIC-SR

	EPIC-HR		EPIC-SR		Pooled	
Quadrant	PAXLOVID N=1038 n/N_w (%)	Placebo N=1053 n/N_w (%)	PAXLOVID N=540 n/N_w (%)	Placebo N=528 n/N_w (%)	PAXLOVID N=1578 n/N_w (%)	Placebo N=1581 n/N_w (%)
Potential Hy's Law (right upper)	1/984 (0.1)	0/996 (0)	1/515 (0.2)	0/506 (0)	2/1499 (0.1)	0/1502 (0)
Cholestasis (left upper)	1/990 (0.1)	0/997 (0)	0/519 (0)	3/506 (0.6)	1/1509 (0.1)	3/1503 (0.2)
Temple's corollary (right lower)	38/990 (3.8)	48/997 (4.8)	11/519 (2.1)	14/506 (2.8)	49/1509 (3.2)	62/1503 (4.1)
Total	40/990 (4)	48/997 (4.8)	12/519 (2.3)	17/506 (3.4)	52/1509 (3.4)	65/1503 (4.3)

Source: adlb.xpt; Software: R.
Note: Subjects enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
Abbreviations: DILI, drug-induced liver injury; N, number of subjects in treatment group; n, number of subjects meeting criteria; N_w, number of patients with data

7.6.1.8. Vital Signs, EPIC-HR and EPIC-SR

Vital signs were analyzed from EPIC-HR and EPIC-SR. There were no clinically relevant changes from baseline or in median values for pulse, respiration rate, or body temperature. For

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further details, please see Section 17.7. Systolic and diastolic blood pressures are discussed separately in Section 17.14.3.

7.6.1.9. Subgroups, EPIC-HR and EPIC-SR

In regard to the frequency of TEAEs by demographic subgroups in EPIC-HR, frequencies of SAEs were more frequent in subjects ≥65 years of age (3.1%) when compared to those <65 years of age (1.5%) in the PAXLOVID group. For EPIC-SR this was 2.8% in subjects ≥65 years of age and 1.4% in subjects <65 years of age.

Rates of TEAEs were higher in subjects ≥65-years of age (41.9%) compared to those who were <65 years of age (19.1%) in the PAXLOVID group in EPIC-HR. For EPIC-SR this was 44.4% in subjects ≥65 years of age and 27.8% in subjects <65 years of age. These data are consistent with the epidemiology of COVID-19 subjects where elderly patients are at higher risk for severe disease and adverse outcomes (CDC 2023e; CDC 2023d). No overall safety differences were observed between male and female subjects. No clear significant safety differences were apparent based on race, but the lower enrollment percentages of some racial subgroups preclude definitive conclusions. For further details please see Section 17.8.

7.6.2. Safety Results, EPIC-PEP

7.6.2.1. Overview of Treatment-Emergent Adverse Events Summary, EPIC-PEP

PAXLOVID demonstrated an overall favorable safety profile in EPIC-PEP (Table 43). The incidences of SAEs, AEs leading to permanent discontinuation of study drug, any TEAE, and severe AEs were similar or higher in the placebo group compared to the PAXLOVID group. No deaths occurred in EPIC-PEP.

Table 43. Overview of Adverse Events[1], Safety Population, EPIC-PEP[2]

Event Category	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs. Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs. Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs. PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
SAE	3 (0.3)	1 (0.1)	2 (0.2)	0.1 (-0.4, 0.6)	-0.1 (-0.5, 0.3)	0.2 (-0.2, 0.6)
SAEs with fatal outcome	0	0	0	0 (0, 0)	0 (0, 0)	0 (0, 0)
Life-threatening SAEs	0	1 (0.1)	1 (0.1)	-0.1 (-0.3, 0.1)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.1)
AE leading to permanent discontinuation of study drug	10 (1.1)	11 (1.2)	14 (1.6)	-0.5 (-1.5, 0.6)	-0.4 (-1.4, 0.7)	-0.1 (-1.1, 0.9)
AE leading to dose modification of study drug	1 (0.1)	1 (0.1)	0	0.1 (-0.1, 0.3)	0.1 (-0.1, 0.3)	-0.0 (-0.3, 0.3)
AE leading to interruption of study drug	1 (0.1)	1 (0.1)	0	0.1 (-0.1, 0.3)	0.1 (-0.1, 0.3)	-0.0 (-0.3, 0.3)
AE leading to reduction of study drug	0	0	0	0 (0, 0)	0 (0, 0)	0 (0, 0)
AE leading to dose delay of study drug	0	0	0	0 (0, 0)	0 (0, 0)	0 (0, 0)
Other	0	0	0	0 (0, 0)	0 (0, 0)	0 (0, 0)
Any AE	218 (23.9)	212 (23.3)	195 (21.7)	2.2 (-1.7, 6.1)	1.6 (-2.3, 5.4)	0.6 (-3.3, 4.5)
Severe and worse	26 (2.9)	12 (1.3)	16 (1.8)	1.1 (-0.3, 2.5)	-0.5 (-1.6, 0.7)	1.5 (0.2, 2.8)*
Moderate	63 (6.9)	63 (6.9)	60 (6.7)	0.2 (-2.1, 2.5)	0.2 (-2.1, 2.6)	-0.0 (-2.3, 2.3)
Mild	129 (14.1)	137 (15.0)	119 (13.3)	0.9 (-2.3, 4.1)	1.8 (-1.4, 5.0)	-0.9 (-4.1, 2.3)

Source: adae.xpt; Software: R.
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Note: Severity as assessed by the investigator.
Note: Subjects enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 38 visit.
[2.] Duration of treatment is 5 or 10 days.
[3.] Difference is shown between PAXLOVID vs. placebo
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment group; n, number of subjects with at least one event; SAE, serious adverse event

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7.6.2.2. Deaths, EPIC-PEP

There were no deaths reported in EPIC-PEP.

7.6.2.3. Serious Treatment-Emergent Adverse Events, EPIC-PEP

SAEs occurred infrequently in EPIC-PEP across all three groups. The most common SAE was COVID-19 pneumonia (one each in the PAXLOVID 5-day group, PAXLOVID 10-day group, and placebo) which is to be expected as this is the disease under investigation. The remainder of SAEs do not represent concerning safety findings regarding PAXLOVID (see Table 44). SAE assessments were similar using FMQs. For further details please see Section 17.9.

Table 44. Patients With Serious Adverse Events[1] by System Organ Class and Preferred Term, Safety Population, EPIC-PEP[2]

System Organ Class Preferred Term	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs. Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs. Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs. PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Any SAE	3 (0.3)	1 (0.1)	2 (0.2)	0.1 (-0.4, 0.6)	-0.1 (-0.5, 0.3)	0.2 (-0.2, 0.6)
Hepatobiliary disorders (SOC)	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Cholecystitis acute	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Infections and infestations (SOC)	1 (0.1)	1 (0.1)	1 (0.1)	-0.0 (-0.3, 0.3)	-0.0 (-0.3, 0.3)	-0.0 (-0.3, 0.3)
COVID-19 pneumonia	1 (0.1)	1 (0.1)	1 (0.1)	-0.0 (-0.3, 0.3)	-0.0 (-0.3, 0.3)	-0.0 (-0.3, 0.3)
Injury, poisoning and procedural complications (SOC)	1 (0.1)	0	1 (0.1)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.1)	0.1 (-0.1, 0.3)
Road traffic accident	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Tibia fracture	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Overdose	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)

Source: adae.xpt; Software: R.
Note: Subjects enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 38 visit. Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
[2.] Duration of treatment is 5 or 10 days.
[3.] Difference is shown between PAXLOVID vs. placebo.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; N, number of subjects in treatment group; n, number of subjects with adverse event; SAE, serious adverse event; SOC, system organ class

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7.6.2.4. Adverse Events Leading to Treatment Discontinuation, EPIC-PEP

Discontinuation rates were similar and infrequent in all three groups in EPIC-PEP. No patterns of discontinuation from this trial were identified to suggest a serious toxicity concern associated with PAXLOVID (Table 45).

AEs leading to discontinuation assessments were similar using FMQs. For further details please see Section 17.9.

atients With Adverse Events[1] Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population,

an Class Term	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs. Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs. Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs. PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
ng to Discontinuation	10 (1.1)	11 (1.2)	14 (1.6)	-0.5 (-1.5, 0.6)	-0.4 (-1.4, 0.7)	-0.1 (-1.1, 0.9)
s (SOC)	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
nal disorders (SOC)	2 (0.2)	2 (0.2)	0	0.2 (-0.1, 0.5)	0.2 (-0.1, 0.5)	-0.0 (-0.4, 0.4)
	2 (0.2)	1 (0.1)	0	0.2 (-0.1, 0.5)	0.1 (-0.1, 0.3)	0.1 (-0.3, 0.5)
	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
rders and administration site conditions (SOC)	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
d infestations (SOC)	0	1 (0.1)	2 (0.2)	-0.2 (-0.5, 0.1)	-0.1 (-0.5, 0.3)	-0.1 (-0.3, 0.1)
	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
pneumonia	0	1 (0.1)	1 (0.1)	-0.1 (-0.3, 0.1)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.1)
s (SOC)	6 (0.7)	4 (0.4)	10 (1.1)	-0.5 (-1.3, 0.4)	-0.7 (-1.5, 0.1)	0.2 (-0.5, 0.9)
e present	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
partial thromboplastin time prolonged	1 (0.1)	0	1 (0.1)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.1)	0.1 (-0.1, 0.3)
aminotransferase increased	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
nogen decreased	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
r filtration rate decreased	1 (0.1)	2 (0.2)	2 (0.2)	-0.1 (-0.5, 0.3)	-0.0 (-0.4, 0.4)	-0.1 (-0.5, 0.3)
renal clearance decreased	3 (0.3)	1 (0.1)	4 (0.4)	-0.1 (-0.7, 0.5)	-0.3 (-0.8, 0.2)	0.2 (-0.2, 0.6)
ninotransferase increased	0	1 (0.1)	2 (0.2)	-0.2 (-0.5, 0.1)	-0.1 (-0.5, 0.3)	-0.1 (-0.3, 0.1)
em disorders (SOC)	3 (0.3)	2 (0.2)	1 (0.1)	0.2 (-0.2, 0.6)	0.1 (-0.3, 0.5)	0.1 (-0.4, 0.6)
	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
	2 (0.2)	2 (0.2)	1 (0.1)	0.1 (-0.3, 0.5)	0.1 (-0.3, 0.5)	-0.0 (-0.4, 0.4)
inary disorders (SOC)	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
dney disease	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
thoracic, and mediastinal disorders (SOC)	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
cutaneous tissue disorders (SOC)	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)

pt; Software: R.
enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
ergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 38 visit.
eatment is 5 or 10 days.
shown between PAXLOVID vs. placebo.
CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; N, number of subjects in treatment group; n, number of subjects
e event; PT, preferred term; SOC, system organ class

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7.6.2.5. Treatment-Emergent Adverse Events, EPIC-PEP

Table 46 includes TEAEs occurring at 0.5% or higher frequency in any group in EPIC-PEP. The most common TEAEs (≥2% incidence) in the EPIC-PEP PAXLOVID groups were dysgeusia and diarrhea, and these occurred at a higher frequency compared to the placebo group. Similar safety profiles were observed in the PAXLOVID 5-day and 10-day treatment groups. TEAE assessments were similar using FMQs. For further details please see Section 17.9.

Of the AEs considered by the investigator to be related to study drug in EPIC-PEP, dysgeusia (5.9% in the PAXLOVID 10-day group, 6.8% in the PAXLOVID 5-day group versus 0.7% in the placebo group), vomiting (0.7% in the PAXLOVID 5-day group, 0% in the PAXLOVID 10-day group versus 0.1% in the placebo group), and diarrhea (1.2% in the PAXLOVID 5-day group, 1.5% in the PAXLOVID 10-day group versus 0.8% in the placebo group) were reported at a higher frequency in the PAXLOVID group compared with the placebo group. For further details, please see Section 17.9.

As stated in Section 7.3, anaphylaxis, serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson Syndrome), and other hypersensitivity reactions; headache; hypertension; abdominal pain; nausea and vomiting; and malaise have been identified by OSE or the Applicant during use of PAXLOVID under EUA. Details regarding anaphylaxis, serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson syndrome), and other hypersensitivity reactions; headache; and hypertension are provided in their respective sections in Section 7.6.3. In EPIC-PEP, the AEs of abdominal pain, nausea, vomiting, and malaise all occurred infrequently and at similar frequencies when comparing the PAXLOVID and placebo groups. For further details refer to Table 46 and Section 17.9.

Table 46. Patients With Common Adverse Events[1] Occurring at ≥ 0.5% Frequency, Safety Population, EPIC-PEP[2]

Preferred Term[4]	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs. Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs. Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs. PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Any AE	218 (23.9)	212 (23.3)	195 (21.7)	2.2 (-1.7, 6.1)	1.6 (-2.3, 5.4)	0.6 (-3.3, 4.5)
Dysgeusia	54 (5.9)	62 (6.8)	6 (0.7)	5.3 (3.6, 6.9)*	6.1 (4.4, 7.9)*	-0.9 (-3.1, 1.4)
Fibrin D dimer increased	18 (2.0)	13 (1.4)	4 (0.4)	1.5 (0.5, 2.5)*	1.0 (0.1, 1.9)*	0.5 (-0.6, 1.7)
Diarrhea	23 (2.5)	22 (2.4)	15 (1.7)	0.9 (-0.5, 2.2)	0.7 (-0.6, 2.0)	0.1 (-1.3, 1.5)
Nasopharyngitis	13 (1.4)	9 (1.0)	6 (0.7)	0.8 (-0.2, 1.7)	0.3 (-0.5, 1.2)	0.4 (-0.6, 1.4)
Blood fibrinogen decreased	7 (0.8)	5 (0.5)	3 (0.3)	0.4 (-0.2, 1.1)	0.2 (-0.4, 0.8)	0.2 (-0.5, 1.0)
Vomiting	7 (0.8)	3 (0.3)	3 (0.3)	0.4 (-0.2, 1.1)	-0.0 (-0.5, 0.5)	0.4 (-0.2, 1.1)
Creatinine renal clearance decreased	9 (1.0)	5 (0.5)	5 (0.6)	0.4 (-0.4, 1.2)	-0.0 (-0.7, 0.7)	0.4 (-0.4, 1.2)
Nausea	16 (1.8)	12 (1.3)	14 (1.6)	0.2 (-1.0, 1.4)	-0.2 (-1.3, 0.9)	0.4 (-0.7, 1.6)
Upper respiratory tract infection	20 (2.2)	17 (1.9)	18 (2.0)	0.2 (-1.1, 1.5)	-0.1 (-1.4, 1.1)	0.3 (-1.0, 1.6)
Blood thyroid stimulating hormone increased	11 (1.2)	8 (0.9)	10 (1.1)	0.1 (-0.9, 1.1)	-0.2 (-1.2, 0.7)	0.3 (-0.6, 1.3)
Chills	5 (0.5)	0	5 (0.6)	-0.0 (-0.7, 0.7)	-0.6 (-1.0, -0.1)*	0.5 (0.1, 1.0)*
Oropharyngeal pain	7 (0.8)	5 (0.5)	7 (0.8)	-0.0 (-0.8, 0.8)	-0.2 (-1.0, 0.5)	0.2 (-0.5, 1.0)
Blood creatine phosphokinase increased	12 (1.3)	15 (1.6)	13 (1.4)	-0.1 (-1.2, 0.9)	0.2 (-0.9, 1.3)	-0.3 (-1.4, 0.8)
Cough	10 (1.1)	2 (0.2)	12 (1.3)	-0.2 (-1.3, 0.8)	-1.1 (-1.9, -0.3)*	0.9 (0.1, 1.6)*
Rhinorrhea	3 (0.3)	5 (0.5)	6 (0.7)	-0.3 (-1.0, 0.3)	-0.1 (-0.8, 0.6)	-0.2 (-0.8, 0.4)
Pyrexia	1 (0.1)	3 (0.3)	6 (0.7)	-0.6 (-1.1, 0.0)	-0.3 (-1.0, 0.3)	-0.2 (-0.6, 0.2)
Aspartate aminotransferase increased	2 (0.2)	5 (0.5)	7 (0.8)	-0.6 (-1.2, 0.1)	-0.2 (-1.0, 0.5)	-0.3 (-0.9, 0.2)
Myalgia	3 (0.3)	2 (0.2)	9 (1.0)	-0.7 (-1.4, 0.1)	-0.8 (-1.5, -0.1)*	0.1 (-0.4, 0.6)
Nasal congestion	4 (0.4)	3 (0.3)	10 (1.1)	-0.7 (-1.5, 0.1)	-0.8 (-1.6, -0.0)*	0.1 (-0.5, 0.7)
Asthenia	10 (1.1)	7 (0.8)	17 (1.9)	-0.8 (-1.9, 0.3)	-1.1 (-2.2, -0.1)*	0.3 (-0.6, 1.2)
Alanine aminotransferase increased	2 (0.2)	6 (0.7)	11 (1.2)	-1.0 (-1.8, -0.2)*	-0.6 (-1.5, 0.3)	-0.4 (-1.0, 0.2)
COVID-19	27 (3.0)	26 (2.9)	36 (4.0)	-1.0 (-2.7, 0.6)	-1.2 (-2.8, 0.5)	0.1 (-1.4, 1.6)
Activated partial thromboplastin time prolonged	11 (1.2)	14 (1.5)	22 (2.4)	-1.2 (-2.5, -0.0)*	-0.9 (-2.2, 0.4)	-0.3 (-1.4, 0.7)
Headache	15 (1.6)	17 (1.9)	29 (3.2)	-1.6 (-3.0, -0.2)*	-1.4 (-2.8, 0.1)	-0.2 (-1.4, 1.0)

Source: adae.xpt; Software: R.
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Note: Subjects enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 38 visit.
[2.] Duration of treatment is 5 or 10 days.
[3.] Difference is shown between PAXLOVID vs. placebo.
[4.] Coded as MedDRA preferred terms.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment group; n, number of subjects with adverse event

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7.6.2.6. Laboratory Findings, Trial EPIC-PEP

Overall, laboratory abnormalities in EPIC-PEP were similar between the PAXLOVID groups and placebo group. For Level 3 laboratory abnormalities as assessed by the Safety Standard & Figures Integrated Guide, no outliers occurred more frequently (>1%) in the PAXLOVID groups when compared to the placebo group. For a complete listing of laboratory outliers, please see Section 17.10.

7.6.2.7. Assessment of Drug-Induced Liver Injury, EPIC-PEP

In screening analysis for drug-induced liver injury, no subjects met the protocol defined criteria of Hy's Law. For further analyses, please see Section 17.11.

7.6.2.8. Vital Signs' Analyses, EPIC-PEP

Trends in vital signs and body weight in EPIC-PEP were reviewed. There were no clinically relevant changes from baseline or in median values for pulse, respiration rate, or body temperature. For further details please see Section 17.12. Systolic and diastolic blood pressures are discussed separately in Section 7.6.3.4.

7.6.2.9. Subgroups, EPIC-PEP

In regard to the frequency of TEAEs by demographic subgroups in EPIC-PEP, SAEs occurred more frequently in subjects ≥65 years of age when compared to those <65 years of age (for the PAXLOVID 5-day group this was 1.3% in subjects ≥65 years of age versus 0.2% in subjects <65 years of age; for the PAXLOVID 10-day group this was 1.2% subjects ≥65 years of age versus 0% in subjects <65 years of age). This is consistent with the epidemiology of COVID-19 where elderly subjects are at higher risk for severe disease and adverse outcomes (CDC 2023e; CDC 2023d).

Frequencies of TEAEs, however, were similar when comparing subjects ≥65 years of age to those <65 years of age (for the PAXLOVID 5-day group this was 22.8% in subjects ≥65 years of age versus 24.0% in subjects <65 years of age; for the PAXLOVID 10-day group this was 27.7% in subjects ≥65 years of age versus 22.8% in subjects <65 years of age).

No overall safety differences were observed between male and female subjects. No clear significant safety differences were apparent based on race, but the lower enrollment percentages of some racial subgroups preclude definitive conclusions. For further details, please see Section 17.13.

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7.6.3. Analysis of Submission-Specific Safety Issues

This section includes analyses conducted to address submission-specific safety concerns based on nonclinical studies, PAXLOVID clinical experience, and current ritonavir labeling.

7.6.3.1. Thyroid-Related Events

The thyroid was identified as a potential target organ due to microscopic findings in the 14-day GLP rat study with thyroid gland follicular cell hypertrophy. In Trial C4671001, a Phase 1, Randomized, Double-Blind, Sponsor-Open, Placebo Controlled, Single- and Multiple-Dose Escalation Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of PF-07321332 in Healthy Adult Subjects, clinically meaningful changes in thyrotropin were observed. Three subjects exposed to nirmatrelvir in the multiple ascending dose portion of the trial had abnormal (>1.2x ULN) thyrotropin without changes in free T4 or clinical symptoms. Given these findings, thyroid-related events were added to Adverse Events of Special Interest for EPIC-HR, EPIC-SR, and EPIC-PEP.

No compelling acute phase/inflammatory response signal with PAXLOVID use was identified from the clinical trials. Frequencies of thyroid-related AEs[6] and laboratory outliers (thyrotropin, free thyroxine) were generally infrequent and similar in both PAXLOVID and placebo groups across EPIC-HR, EPIC-SR, and EPIC-PEP.

For further details, please see Section 17.14.1.

No specific labelling is recommended for thyroid events. Routine pharmacovigilance will be in place to detect postmarketing signals.

7.6.3.2. Inflammatory Events

In the two pivotal GLP repeat-dose toxicity studies in rats, there was noted to be an increase in white blood cells (due to increases in neutrophils) and decrease in reticulocytes, suggestive of an acute phase/inflammatory response with nirmatrelvir.

No compelling acute phase/inflammatory response signal with PAXLOVID use was identified from the clinical trials. Frequencies of inflammatory-related AEs[7] and laboratory outliers were generally infrequent and similar in both PAXLOVID and placebo groups across EPIC-HR and EPIC-SR. In EPIC-PEP, frequencies of the AE of D-dimer increase were higher in the PAXLOVID groups (2.0% in the 5-day group, 1.4% in the 10-day group) when compared to placebo (0.4%); however, frequencies of the laboratory outlier of D-dimer > 1.5x ULN, however, were similar between the PAXLOVID (8.3% in the 5-day group, 7.0% in the 10-day group) when compared to the placebo group (8.1%). The remainder of inflammatory-related AEs and laboratory outliers were similar between the PAXLOVID and placebo groups in EPIC-PEP. There were no SAEs or deaths in the PAXLOVID-treated groups related to inflammatory events. There was one subject in the PAXLOVID 5-day group in EPIC-PEP who discontinued study

[6] Thyroid-related events defined by Applicant using Preferred Terms – MedDRA v24.1 as detailed in Applicant's Summary of Clinical Safety Appendix 3 (m.2.7.4)

[7] Inflammatory events defined by Applicant using Preferred Terms – MedDRA v24.1 as detailed in Applicant's Summary of Clinical Safety Appendix 3 (m.2.7.4)

drug as a result of an inflammatory event. There was one subject in the PAXLOVID 5-day group in EPIC-PEP who discontinued study drug as a result of an inflammatory event [Grade 3 prolonged activated partial thromboplastin time on Day 8 (Subject (b) (6) in EPIC-PEP)]. There were no discontinuations due to inflammatory events in PAXLOVID-treated subjects in EPIC-HR or EPIC-SR.

No specific labelling is recommended for inflammatory events. Routine pharmacovigilance will be in place to detect postmarketing signals.

For further details, please see Section 17.14.2.

7.6.3.3. Hypersensitivity Events

Hypersensitivity is in the current ritonavir label and is currently in the PAXLOVID EUA Fact Sheet (FS) for Healthcare Providers (HCP) under Section 5, “Warnings and Precautions” and Section 6.2, "Post-Authorization Experience” (Pfizer 2023a).

Hypersensitivity events[8] were infrequent and similar in EPIC-HR and EPIC-SR. In the EPIC-HR frequencies of hypersensitivity events were 0.4% in the PAXLOVID group and 0.5% in the placebo group. For EPIC-SR this was 0.4% in the PAXLOVID group and none in the placebo group. There were no SAEs or deaths related to hypersensitivity events. A single PAXLOVID-treated subject discontinued due to a hypersensitivity event [Grade 3 rash on Day 2 (Subject (b) (6) in EPIC-HR)]. There were no cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, or anaphylaxis reported in either EPIC-HR or EPIC-SR.

In EPIC-PEP, hypersensitivity events were infrequent and similar between the two groups: reported in 0.2% of subjects in the PAXLOVID 5-day group, 0.2% of subjects in the PAXLOVID 10-day group and none in the placebo group. There were no hypersensitivity event SAEs or deaths. A single PAXLOVID-treated subject discontinued due to a hypersensitivity event [Grade 1 rash on Day 4 (Subject (b) (6)]. There were no cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, or anaphylaxis reported in EPIC-PEP.

While hypersensitivity events associated with PAXLOVID use were infrequent in EPIC-HR, EPIC-SR, and EPIC-PEP, inclusion of Hypersensitivity Reactions in Warnings and Precautions is recommended to communicate that anaphylaxis, serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson syndrome) and other hypersensitivity reactions have been reported with PAXLOVID use (in the EUA setting). In addition, inclusion of hypersensitivity events that have been identified under EUA are recommended in Section 6 of labeling. For further information regarding these reports, please refer to the EUA memos dated February 23, 2022, and September 26, 2022 (FDA 2022a; FDA 2022b).

For further details, please refer to Section 17.14.1.

7.6.3.4. Hemodynamic Events

Hypertension is included in Section 6.1, “Adverse Reactions from Clinical Studies”, of the current EUA FS for HCP (Pfizer 2023a); therefore, an assessment of hemodynamic AEs in the

[8] Hypersensitivity events defined by Applicant using Preferred Terms within the Hypersensitivity Standardized MedDRA Query – MedDRA v 24.1 as detailed in Applicant’s Summary of Safety Appendix 3 (m.2.7.4)

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clinical trials was performed. Frequency of hemodynamic AEs[9] were similar between the PAXLOVID groups and the placebo groups in EPIC-HR (0.8% in the PAXLOVID group and 0.8% in the placebo group) and EPIC-SR (1.5% in the PAXLOVID group and 1.5% in the placebo group). There was one SAE and discontinuation related to hemodynamic events in EPIC-HR as detailed below. There were no deaths related to hemodynamic events in EPIC-HR, EPIC-SR, or EPIC-PEP. There were three Grade 3 or higher AEs related to hemodynamic AEs, two in PAXLOVID-treated subjects and one in a placebo-treated subject:

- Subject (b) (6) was a 62-year-old female in the EPIC-HR PAXLOVID group with a history of hypertension and cardiovascular disease. On Day 2, reported SAE of life-threatening (Grade 4) hypertensive crisis. Additionally on Day 2, the subject experienced headache, blurred consciousness, and convulsive seizures. Study intervention was permanently discontinued on Day 2. The event of hypertensive crisis was reported as resolved on Day 14 and the subject was discharged from the hospital on the same day.
- Subject (b) (6) was a 40-year-old male in the EPIC-HR PAXLOVID group who was a current smoker and had a medical history of diabetes mellitus who experienced severe (Grade 3) hypertension on Day 5. Study intervention was permanently withdrawn on Day 3, and on Day 5 the subject was hospitalized with the SAEs of abscess and sepsis. The subject was discharged on Day 9 and the SAEs of abscess and sepsis were resolved on the same day. The event of hypertension was reported as ongoing at time of last available report.
- Subject (b) (6) was a 44-year-old male in the EPIC-HR placebo group who was a current smoker and had a history of hypertension who experienced severe (Grade 3) hypertension on Day 3. The subject was treated with antihypertensives, and no changes were made to study intervention. This AE was reported as resolved on Day 5.

In EPIC-HR and EPIC-SR, the frequencies of systolic blood pressure ≥140 mmHg (19.7% in the PAXLOVID group and 19.1% in the placebo group in EPIC-HR; 18.0% in the PAXLOVID group and 19.2% in the placebo group in EPIC-SR) were similar between the PAXLOVID and placebo groups. Frequencies of diastolic blood pressure ≥90 mmHg (23.4% in the PAXLOVID group and 22.6% in the placebo group in EPIC-HR; 16.9% in the PAXLOVID group and 23.9% in the placebo group in EPIC-SR) were also similar between both groups.

In EPIC-PEP, the AE of hypertension was infrequent and occurred at similar frequencies between the 5-day (0.2%), 10-day (0.2%), and placebo (0.1%) groups. When evaluating vital signs, frequencies of systolic blood pressure >140 mmHg (10.6% in the PAXLOVID 5-day group, 10.5% in the PAXLOVID 10-day group, and 9.9% in the placebo group) and diastolic blood pressure >90 mmHg (11.7% in the PAXLOVID 5-day group, 10.8% in the PAXLOVID 10-day group, and 12.5% in the placebo group) were similar across all groups

For further details, please see Section 17.14.3.

Overall, frequencies of hemodynamic AEs and maximum blood pressures were similar between the PAXLOVID and placebo groups in all three trials with only a single hemodynamic event SAE reported in a PAXLOVID-treated subject. There was no compelling signal detected in the clinical trial data with PAXLOVID use to support labeling for hypertension. Cases of

[9] Hemodynamic events defined by Applicant using Preferred Terms – MedDRA v24.1 as detailed in Applicant's Summary of Clinical Safety Appendix 3 (m.2.7.4)

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hypertension identified under the EUA do support labeling, and therefore labeling is recommended to include hypertension given post-marketing findings under Section 6.1, "Emergency Use Authorization Experience in Subjects with COVID-19." For further details, please refer to the OSE review by Kate McCartan, Maya Beganovic, Toni Salvatore, Irene Rwakazina, Sonal Goyal, Rachna Kapoor, Sheheryar Muhammad, Neha Gada, Sevan Kolejian, Rajdeep Gill, and Ida-Lina Diak for details (DARRTS ID: 5077785 2022).[10]

7.6.3.5. Dysgeusia

Dysgeusia is a known adverse reaction of ritonavir and is currently in the EUA FS for HCP under Section 6.1, "Adverse Reactions from Clinical Studies" (AbbVie 2010; Pfizer 2023a). Dysgeusia was more common in the PAXLOVID group in EPIC-HR (4.6% in the PAXLOVID group versus 0.1% in the placebo group) and in EPIC-SR (5.6% in the PAXLOVID group versus 0.4% in the placebo group). The majority of dysgeusia in these trials was mild (Grade 1) or moderate (Grade 2) in severity. There were no SAEs related to dysgeusia across both trials. Two PAXLOVID-treated subjects experienced severe (Grade 3) dysgeusia across both trials, including one subject who discontinued study treatment on Day 3.

In EPIC-PEP, dysgeusia occurred at a higher frequency in the PAXLOVID 5-day (5.9%) and 10-day (6.8%) groups when compared to the placebo group (0.7%). The majority of dysgeusia in this trial was mild (Grade 1) or moderate (Grade 2) in severity in EPIC-PEP. There were no SAEs associated with dysgeusia. Two subjects experienced severe (Grade 3 dysgeusia), one each in the 5-day and 10-day groups.

Dysgeusia resulted in discontinuation of study drug in two (0.2%) subjects in the 5-day group, two (0.2%) subjects in the 10-day group, and one subject (0.1%) in the placebo group.

Dysgeusia is a known adverse reaction with ritonavir. Although this was a common adverse reaction, most cases were mild or moderate in severity and few resulted in discontinuation of PAXLOVID. Dysgeusia is recommended for inclusion in Section 6 of the label.

7.6.3.6. Diarrhea

Diarrhea is a known adverse reaction of ritonavir and is included in the current EUA FS for HCP under Section 6.1, "Adverse Reactions from Clinical Studies" (AbbVie 2010; Pfizer 2023a). In EPIC-HR diarrhea occurred at higher frequency in the PAXLOVID group (3.0%) when compared to the placebo group (1.6%). In EPIC-SR diarrhea was also more frequent in the PAXLOVID group (4.1%) when compared to the placebo group (3.0%). There were no SAEs, no deaths, or severe (Grade 3) or life-threatening (Grade 4) AEs related to diarrhea in either EPIC-HR or EPIC-SR. Three (0.2%) subjects in the pooled PAXLOVID group discontinued study drug as a result of this AE.

In EPIC-PEP, diarrhea was more frequent in the PAXLOVID 5-day group (2.5%) and 10-day group (2.4%) when compared to the placebo group (1.7%). There were no severe or life-

[10] This document contains proprietary data obtained by FDA under contract and cannot be released to the public. The information contained within is the result of an OSE review as part of PAXLOVID, NDA 217188 and EUA 105. The source can only be accessed by authorized individuals.

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threatening AEs of diarrhea, no cases of diarrhea resulting in discontinuation, no SAEs related to diarrhea, and no deaths associated with diarrhea.

Diarrhea occurred at higher frequencies in the PAXLOVID groups when compared to placebo groups in EPIC-HR, EPIC-SR, and EPIC-PEP. Diarrhea is recommended for inclusion in Section 6 of the label.

7.6.3.7. Headache

Headache is included in the current EUA FS for HCP under Section 6.1, "Adverse Reactions from Clinical Studies" (Pfizer 2023a). In EPIC-HR, headache occurred at similar rates between the PAXLOVID group (1.2%) and placebo group (1.2%). The AE of headache was also similar between the PAXLOVID group (1.1%) and the placebo group (1.1%) in EPIC-SR. All AEs of headache were either mild (Grade 1) or moderate (Grade 2) in severity. There were no SAEs, discontinuations, or deaths associated with the AE of headache in these two trials.

In EPIC-PEP, headache occurred less frequently in the PAXLOVID 5-day group (1.6%) and 10-day group (1.9%) when compared to the placebo group (3.2%). Headache AEs were mild (Grade 1) or moderate (Grade 2) in severity except for one instance of severe (Grade 3) headache in the placebo group. Study drug was withdrawn because of headache in one subject in the PAXLOVID 5-day group and no cases of headache were considered SAEs.

The majority of cases of headache were mild to moderate in severity and few instances led to discontinuation of study drug. In the clinical trials, there was no compelling signal that would support labeling, however, cases identified under the EUA do support labeling. For further details, please refer to the OSE review by Kate McCartan, Maya Beganovic, Toni Salvatore, Irene Rwakazina, Sonal Goyal, Rachna Kapoor, Sheheryar Muhammad, Neha Gada, Sevan Kolejian, Rajdeep Gill, and Ida-Lina Diak for details (DARRTS ID: 5077785 2022).[11] Specific labeling is recommended for inclusion to address headache given postmarketing findings under Section 6.1, "Emergency Use Authorization Experience in Subjects with COVID-19."

7.6.3.8. Myalgia

Myalgia is included in the current EUA FS for HCP under Section 6.1, "Adverse Reactions from Clinical Studies" (Pfizer 2023a). In EPIC-HR, myalgia was infrequent, occurring in 0.7% of subjects in the PAXLOVID group and 0.1% in the placebo group. In EPIC-SR, myalgia occurred in no subjects in either group. There were no myalgia-associated SAEs, discontinuations, or deaths in EPIC-HR and EPIC-SR. There was a single Grade 4 event of blood creatine phosphokinase increased in a PAXLOVID-treated subject (Subject (b) (6), EPIC-SR on Day 1).

In EPIC-PEP, myalgia occurred at similar frequencies in all three groups (0.3% in the PAXLOVID 5-day group, 0.2% in the PAXLOVID 10-day group, and 1.0% in the placebo group). There were no myalgia-associated SAEs, discontinuations, or deaths.

[11] This document contains proprietary data obtained by FDA under contract and cannot be released to the public. The information contained within is the result of an OSE review as part of PAXLOVID, NDA 217188 and EUA 105. The source can only be accessed by authorized individuals.

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Rates of creatine kinase increase was infrequent and similar between PAXLOVID and placebo in EPIC-HR, EPIC-SR, and EPIC-PEP.

While the current EUA FS for HCP includes myalgia, review of EPIC-HR, EPIC-SR, and EPIC-PEP safety data does not identify a compelling signal for myalgia associated with PAXLOVID use. Therefore, myalgia is not recommended for inclusion in product labeling.

7.6.3.9. Hepatoxicity

The liver was considered a potential target organ due to microscopic findings in the 14-day GLP rat study, with findings including minimal to mild periportal hepatocellular hypertrophy and vacuolation in a dose-dependent fashion plus increased liver size and weights. Additionally, hepatotoxicity is currently in the Warnings and Precautions and Adverse Reaction sections of the ritonavir label as well as in the PAXLOVID EUA FS for HCP under "Warnings and Precautions" based on the ritonavir label (AbbVie 2010; Pfizer 2023a).

Comparable frequencies of AEs related to hepatobiliary disorders were reported when comparing the PAXLOVID and placebo groups in EPIC-HR (0.4% in PAXLOVID and 0.2% in placebo) and EPIC-SR (0.2% in PAXLOVID and 0.2% in placebo). No subject with a reported hepatobiliary AE discontinued study drug across all trials. In EPIC-SR, the SAE of hepatic mass was reported in Subject (b) (6) This subject was a 46-year-old female with a risk factor of BMI>25 kg/m^2 but was fully vaccinated. On Day 9 this subject experienced abdominal pain and low-grade fever. On Day 13 this subject was diagnosed with the SAE of moderate (Grade 2) hepatic mass with imaging suggestive of malignancy. On Day 42 this subject underwent colonoscopy and was found to have a sigmoid tumor. This event was not considered related to study intervention by the investigator and did not result in discontinuation of study drug. There were no SAEs related to hepatobiliary disorders in PAXLOVID-treated subjects in EPIC-HR.

In EPIC-HR and EPIC-SR, no cases of Hy's Law were identified in either treatment group through Day 34. There was one case of potential Hy's Law reported in long term follow-up. For further details, please refer to Section 7.6.1.7. In EPIC-PEP, no subjects met the protocol defined criteria of Hy's Law (refer to Section 7.6.2.7).

For further details regarding hepatic laboratory abnormalities, please see Section 7.6.1.6 for EPIC-HR and EPIC-SR and Section 7.6.2.6 for EPIC-PEP.

Overall, hepatobiliary AEs were infrequent in EPIC-HR, EPIC-SR, and EPIC-PEP. Although there was one SAE in the PAXLOVID-treated group in EPIC-PEP, this is unlikely to be related to study drug given the nature of the hepatic mass being related to suspected colon cancer. No specific labeling for these events is recommended; however, hepatotoxicity language in the Warnings and Precautions section, similar to that in the current PAXLOVID EUA FS for HCP, is recommended based on the ritonavir label. Routine pharmacovigilance will be in place to detect postmarketing signals.

7.6.3.10. Ritonavir-Specific Labeling

The following are in Section 5, "Warnings and Precautions", of the current Ritonavir label (AbbVie 2010). Drug-drug interaction, hepatotoxicity, and hypersensitivity are covered in other sections of this review and will not be discussed in this section.

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7.6.3.10.1. Pancreatitis

No cases of pancreatitis were reported across all three trials: no specific labeling is recommended. Routine pharmacovigilance will be in place to detect post-marketing signals.

7.6.3.10.2. PR Interval Prolongation

Ritonavir prolongs the PR interval in some patients and there have been cases of second- or third-degree atrioventricular block. Electrocardiogram data were collected from the sentinel cohorts of EPIC-HR and EPIC-SR. A PR interval >40 msec change occurred in 1/150 (0.1%) in the pooled PAXLOVID group and 3/201 (1.5%) in the pooled placebo group. There was one subject in the PAXLOVID group with a PR interval >40 msec change (Subject (b) (6) in EPIC-HR), however this was isolated and without associated symptoms.

No specific labeling is recommended. Routine pharmacovigilance will be in place to detect postmarketing signals.

7.6.3.10.3. Lipid Disorders and Fat Redistribution

Treatment with ritonavir alone or in combination with saquinavir has resulted in increases in the concentration of total cholesterol and triglycerides. A single PAXLOVID-treated subject (EPIC-PEP, 5-day group) experienced moderate (Grade 2) hyperlipidemia. Laboratory data regarding lipids were not routinely collected in EPIC-HR, EPIC-SR, and EPIC-PEP.

Lipid-related AEs were infrequently reported in all trials. No labeling for lipid disorders or fat redistribution is recommended. Routine pharmacovigilance will be in place to detect post-marketing signals.

7.6.3.10.4. Diabetes Mellitus/Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy.

Review of EPIC-HR, EPIC-SR, and EPIC-PEP safety data does not identify a compelling signal for diabetes mellitus or hyperglycemia associated with PAXLOVID use; therefore, no specific product labeling is recommended. For further details please refer to Sections 7.6.1.5, 7.6.1.6, 7.6.2.5, 7.6.2.6. Routine pharmacovigilance will be in place to detect post-marketing signals.

7.6.3.10.5. Immune Reconstitution Syndrome and Resistance/Cross-Resistance

Subjects living with HIV were permitted to be enrolled in EPIC-HR, EPIC-SR, and EPIC-PEP, however, subjects were required to have an HIV viral load less than 400 copies/mL. There only were two subjects living with HIV who received PAXLOVID across all three trials: no AE of immune reconstitution syndrome was reported.

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A Warning and Precaution regarding the risk of HIV-1 resistance development is recommended for inclusion in the product label, similar to that in the current PAXLOVID EUA FS for HCP, because nirmatrelvir is co-administered with ritonavir; there may be a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection.

7.6.3.10.6. Patients With Hemophilia

There have been reports of increased bleeding in patients with hemophilia type A and B treated with protease inhibitors. No individuals with hemophilia were enrolled in EPIC-HR, EPIC-SR, or EPIC-PEP.

7.7. Key Safety Review Issues

7.7.1. Serious Adverse Reactions Due to Drug-Drug Interactions (DDIs)

Issue

What is the overall risk for serious adverse reactions due to DDIs in the PAXLOVID-eligible population and how can this risk best be mitigated?

Background

PAXLOVID is a co-packaged oral drug product comprising nirmatrelvir, a SARS-CoV-2 M^{pro} inhibitor, and ritonavir, a potent CYP3A inhibitor that is included to increase nirmatrelvir plasma levels. The key safety concern related to PAXLOVID is the risk of serious adverse reactions due to DDIs, mainly related to the ritonavir component (see Section 8.2.2). However, because the Phase 3 clinical trials EPIC-HR, EPIC-SR, and EPIC-PEP excluded subjects with current or expected use of any medications that have DDIs with PAXLOVID that may lead to serious AEs, this risk cannot be evaluated through analysis of these clinical trial data.

Ritonavir exhibits near maximal CYP3A inhibition when administered at a dose of 100 mg and can result in significant elevations of concomitant medications that are metabolized by the CYP3A isoenzyme. In the current PAXLOVID EUA FS for HCP, the table of "Established and Other Potentially Significant Drug Interactions" currently lists 143 drugs that have DDIs with PAXLOVID, as well as a statement that the listed drugs are not considered a comprehensive list. The 143 listed drugs include 37 drugs that are contraindicated with PAXLOVID, 21 drugs for which the recommendation is "avoid concomitant use" or "discontinue use prior to initiation of PAXLOVID", 49 drugs for which a dose adjustment is recommended or suggested, and 6 drugs for which therapeutic drug concentration or pharmacodynamic laboratory marker monitoring is recommended. The contraindications and DDIs included in the PAXLOVID EUA FS for HCP mirror those in the concomitant drug labels and the Norvir and HIV boosted protease inhibitor labels, with several additions based on the National Institutes of Health guidelines for DDIs with PAXLOVID (NIH 2023). Of note, drugs that are not contraindicated or listed as "avoid concomitant use" can still lead to clinically significant DDIs if not appropriately managed, such as renal failure (tacrolimus) or fatal respiratory depression (some narcotic analgesics).

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Multiple risk-mitigation efforts have been employed by FDA to reduce the risk of serious AEs from PAXLOVID DDIs when used under EUA. The current EUA FS for HCP contains a Warning and Precaution about the risk of serious adverse reactions due to DDIs (Pfizer 2023a). Additional measures include 1) posting of a PAXLOVID Patient Eligibility Screening Checklist and Drug Interaction Tool; 2) five separate updates to the FS for HCP to better describe the DDIs; 3) generation of Dear Healthcare Provider letters communicating the risk of DDIs with PAXLOVID; 4) posting information on how to assess for PAXLOVID DDIs in a FAQ document and Center for Drug Evaluation and Research (CDER) conversation; and 5) presentations by PAXLOVID reviewers and OID leadership at multiple outside talks/webinars provided in conjunction with the AMA, CDC, and ASPR.

Assessment

Analysis of Available Data

As noted above, the risk of serious adverse reactions due to DDIs cannot be assessed through the available clinical trial data because the aforementioned clinical trials excluded subjects on medications with clinically significant DDIs. Consequently, the risk of serious adverse reactions due to DDIs was assessed in three analyses conducted by the OSE regarding post-authorization use of PAXLOVID. These analyses describe:

1. The proportion of the PAXLOVID-eligible population who are taking concomitant medications that have DDIs with PAXLOVID
2. The types of healthcare providers who are prescribing PAXLOVID in the United States
3. The AEs reported that are probably or possibly related to PAXLOVID DDIs with concomitant drugs that are labeled to have potential significant DDIs with PAXLOVID

Proportion of the PAXLOVID-Eligible Population Who Are Taking Concomitant Medications That Have DDIs With PAXLOVID

The PAXLOVID-eligible population, i.e., adults who are at high risk for development of severe COVID-19, are likely to be taking concomitant medications that have DDIs with PAXLOVID. Analyses were performed using the Medicare database from December 22, 2021 to September 10, 2022, the Veterans Affairs (VA) database from January 01, 2022 to October 31, 2022, and the Sentinel Rapid COVID data from December 22, 2021 to December 31, 2022, among adults who had COVID-19 and were eligible for PAXLOVID treatment based on being high risk for severe COVID-19 (due to age ≥65 years or high-risk comorbidities[12]) and not having evidence of severe renal or hepatic impairment. Drugs included in the February 1, 2023 update to the PAXLOVID Fact Sheet for Healthcare Providers were used to determine drugs with PAXLOVID DDIs. (see Section 21.1 for details)

In all three databases, 57-66% of PAXLOVID-eligible adults were on a drug that had DDIs with PAXLOVID at the time of COVID-19 diagnosis, including 7-12% on a drug contraindicated with PAXLOVID at the time of COVID-19 diagnosis, 29-40% on a drug for which the

[12] High-risk comorbidities include pregnancy, immunosuppressive disease and immunosuppressive treatment, chronic lung diseases (asthma, reactive airway, other chronic respiratory diseases, and chronic obstructive pulmonary disease), cardiovascular disease, hypertension and congenital heart disease, obesity/overweight, chronic kidney disease, diabetes, and sickle cell disease.

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PAXLOVID fact sheet recommended "avoid concomitant use", and 40-45% on a drug with DDIs with PAXLOVID with other recommended actions (e.g., dose modification, laboratory monitoring, or clinical monitoring) (Table 234). A similar analysis was performed in the VA and Sentinel databases with a broader definition of high risk for severe COVID-19 (age ≥50 years or high-risk comorbidities); in this analysis of the VA and Sentinel databases, respectively, 56% and 53% of eligible adults were on a drug that had DDIs with PAXLOVID at the time of COVID-19 diagnosis, including 8% and 7% on a drug contraindicated with PAXLOVID at the time of COVID-19 diagnosis, 34% and 26% on a drug for which the PAXLOVID fact sheet recommended "avoid concomitant use", and 40% and 39% on a drug with DDIs with PAXLOVID with other recommended actions (Table 235).

In all the analyses, the most common drugs with DDIs being taken by PAXLOVID-eligible adults were atorvastatin and amlodipine, and almost all of the 10 most common DDI drugs from each of the analyses could potentially be managed by holding the drug, adjusting the dose of the drug, or increased monitoring (depending on the clinical situation for each particular patient). (Table 237).

One limitation of these analyses is that populations identified in the study data sources may not fully represent the PAXLOVID-eligible U.S. population. With a few exceptions, adults must be ≥65 years of age to be eligible for Medicare, the VA population is disproportionately male and Sentinel Rapid COVID-19 data included only the population covered by a commercial health plan. However, despite these limitations, these analyses indicate that a sizeable proportion of PAXLOVID-eligible adults are taking medications that have DDIs with PAXLOVID.

Types of Healthcare Providers Who Are Prescribing PAXLOVID in the United States

PAXLOVID is prescribed by a broad range of healthcare providers who may not be familiar with ritonavir DDIs. An OSE analysis was done using the Symphony Health Metys™ drug utilization database which provides dispensed prescription estimates from a sample of U.S. outpatient pharmacies, representing approximately 85% of all retail prescriptions, 73% of all mail-order prescriptions, 75% of all specialty prescriptions, and 50% of all long-term care prescriptions, with prescription estimates projected to the national level. From December 25, 2021 to January 13, 2023, most PAXLOVID prescriptions in the United States were from adult primary care practitioners (74% from family medicine, general medicine, or internal medicine) or emergency room practitioners (7%). In contrast, other ritonavir-containing products that are used to treat HIV are generally prescribed by HIV specialists or providers who focus on HIV treatment who may be more experienced with managing ritonavir DDIs.

Adverse Events Reported That Are Probably or Possibly Related to PAXLOVID DDIs With Concomitant Drugs That Are Labeled to Have Potential Significant DDIs With PAXLOVID

OSE analyzed cases of AEs following use of PAXLOVID for the treatment of COVID-19 under EUA that were reported to the FAERS, which accounted for >99% of reported cases), the FACT (FDA-American College of Medical Toxicology COVID-19 Toxicology Investigators Consortium) Pharmacovigilance Project Subregistry, and the medical literature through January

30, 2023[13]. OSE identified 301 cases of AEs that they assessed as possibly or probably related to DDIs included in the current EUA FS for HCP. A total of 271 of these cases reported at least one serious outcome, including 147 reporting hospitalization. Six cases reported a fatal outcome after a DDI-related AE (four related to concomitant tacrolimus use, one related to concomitant verapamil use, and one related to concomitant use of both nifedipine and atorvastatin). Despite mandatory AE reporting requirements, FDA is aware that not all AEs associated with PAXLOVID were reported; therefore, the incidences of these events cannot be calculated based on these data.

Benefit-Risk Considerations

When considering the benefit versus risk of PAXLOVID in the context of the risk for serious adverse reactions due to DDIs, the benefit-risk assessment at the population level is different than the benefit-risk assessment for an individual patient. This is particularly relevant in the current stage of the pandemic when >90% of U.S. adults have received a COVID-19 vaccine and/or had a prior SARS-CoV-2 infection and when other treatment options are available. While PAXLOVID appears to reduce the risk of hospitalization and death by ~50 to 90% in all high-risk patients (i.e., the RRR), the absolute risk of hospitalization and death without treatment was ~2% in high-risk patients who had previously been vaccinated or had serologic evidence of baseline SARS-CoV-2 immunity in the PAXLOVID clinical trials (see Section 3.1.1.2).

This risk reduction in the COVID-19 vaccinated or SARS-CoV-2 seropositive high-risk population remains a large benefit on a population level. There were approximately 4000 COVID-19 related deaths and 35,000 COVID-19 related hospitalizations each week in the United States in January 2023 (CDC 2023a); consequently, even with a conservative estimate of benefit (25% of PAXLOVID-eligible patients unable to take PAXLOVID due to DDIs and an RRR of 50%), PAXLOVID could still lead to approximately 1500 lives saved and 13,000 hospitalizations averted each week in the United States.

However, on an individual patient level, with an absolute risk reduction with PAXLOVID for the hospitalization/death endpoint of about 1 to 2% for a patient with baseline SARS-CoV-2 immunity, individual patients could have DDIs associated with risks that could outweigh this benefit, particularly if the DDIs are not adequately managed. Whether or not the DDIs can be managed such that PAXLOVID would have a favorable benefit-risk assessment varies both by the specific medication and by the individual patient. Some of the medications that are either contraindicated or have a recommendation of "avoid concomitant use" with PAXLOVID cannot be safely held (either because the DDI risk would not be mitigated by holding the medication because of that medication's PK parameters, such as an extended half-life, or because the medication is needed to manage a serious medical condition), such that PAXLOVID would not be an appropriate choice. For other medications, the DDIs could be managed by temporarily holding the medication (e.g., atorvastatin), adjusting the dose of the concomitant medication, close laboratory monitoring, and/or monitoring for AEs. In addition, prescribers should also consider patient factors, such as a patient's ability to comply with instructions for dose adjustment or monitoring, the patient's estimated risk for development of severe COVID-19, and

[13] Drugs included in the August 25, 2022, update to the PAXLOVID Fact Sheet for Healthcare Providers, plus verapamil (added in the February 1, 2023 update) were used to determine drugs with PAXLOVID DDIs.

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the patient's risk from the particular adverse reaction associated with the DDI, when deciding whether to prescribe PAXLOVID to their individual patient with risk of DDIs.

Risk Mitigation Strategies

Further risk mitigation through addition to PAXLOVID labeling of a boxed warning conveying the risk of serious adverse reactions due to PAXLOVID DDIs was discussed amongst the PAXLOVID review team and at a February 15, 2023, meeting with the FDA Center for Drug Evaluation and Research (CDER) Medical Policy and Program Review Council (MPPRC). A boxed warning could help to highlight the risk of serious adverse reactions due to PAXLOVID DDIs and better ensure that the potential for DDIs is considered by all prescribers, both to determine if actions are needed to manage the DDIs, and also to determine whether PAXLOVID is appropriate for that particular patient.

The following three situations in which Boxed Warnings can be used, per the FDA Guidance for Industry: *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products-Content and Format* , apply to the risk of serious adverse reactions due to PAXLOVID DDIs (October 2011):

1. There is an adverse reaction so serious in proportion to the potential benefit from the drug that it is essential that it be considered in assessing the risks and benefits of using the drug.
   - Some of the PAXLOVID DDIs are potentially life-threatening, and the absolute risk reduction of hospitalization/death with PAXLOVID in the overall high-risk population in 2023, when most adults have some baseline SARS-CoV-2 immunity from vaccination or prior infection, is estimated to be about one to two percent. Consequently, it is essential to consider DDIs when assessing the risks and benefit of using PAXLOVID.
2. There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection and avoiding certain concomitant therapy).
   - Adverse reactions from PAXLOVID DDIs can be prevented or reduced in frequency or severity by adjusting or avoiding certain concomitant medications, by increased monitoring, or by selecting patients who are not taking medications with DDIs that could result in serious adverse reactions.
3. To highlight warning information that is especially important to the prescriber.
   - PAXLOVID is prescribed by a very broad group of healthcare providers, many of whom may not be familiar with ritonavir and its drug interactions. In addition, PAXLOVID is often prescribed in an urgent care setting where prescribers may not be familiar with the patient and their concomitant medications. Consequently, it is especially important that the risk of DDIs be highlighted to prescribers.

The Applicant's main rationale against adding the boxed warning is that a boxed warning may lead to prescriber hesitancy. They state that claims data suggested addition of a boxed warning reduced prescriptions by 12% to 75% for Premarin, Febuxostat, Celebrex, and Chantix. However, the examples provided were for boxed warnings about serious risks that could apply to all patients taking the drug and involved drugs that are indicated for smoking cessation or symptomatic relief of a non-life-threatening condition for which other products are available. The proposed boxed warning for PAXLOVID would only apply to patients taking medications

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with clinically significant DDIs, and PAXLOVID is a product that reduces the risk of COVID-19 related hospitalization and death. Furthermore, a boxed warning would presumably only decrease PAXLOVID prescriptions for patients on medications with DDIs that would make PAXLOVID use inappropriate or for patients being seen by prescribers unwilling or unable to manage DDIs, situations in which the risk would outweigh the benefit for the individual patient.

The following points were discussed at the MPPRC meeting, and the MPPRC unanimously agreed with the review team's proposal to include a boxed warning to communicate the risk of serious adverse reactions due to DDIs in PAXLOVID labeling.

Conclusion

Serious adverse reactions due to DDIs are the key safety concern with PAXLOVID. Safety surveillance data under EUA indicate that many PAXLOVID-eligible patients are on medications with DDIs with PAXLOVID (though the most common medications with DDIs could potentially be managed by holding the drug, adjusting the dose of the drug, or increased monitoring), that the majority of PAXLOVID prescribers are adult primary care practitioners (who may not be experienced in managing ritonavir DDIs), and that serious adverse reactions, including death, have been reported in association with DDIs that are included in the EUA FS for HCP despite previous risk mitigation efforts. For these reasons, and with supportive advice from the CDER MPPRC, the USPI will include a boxed warning to highlight this important safety risk. The specific drugs included in the USPI as having clinically significant drug interactions with PAXLOVID, along with recommended actions, will be carried over from the most recent PAXLOVID EUA FS for HCP with a few updates (see Section 8.2.2).

8. Therapeutic Individualization

8.1. Intrinsic Factors

8.1.1. Age, Weight, Gender, and Race

The population PK model included data from 1237 subjects, including 150 subjects from Phase 1 studies and 1087 subjects from EPIC-HR. Age ranged from 18 to 86 years and baseline BMI ranged from 16.6 to 58.1 kg/m^2. Of the 1237 subjects, 657 (52.6%) were male, 580 (46.4%) were female, 865 (69.2%) were white, 105 (8.40%) were black, 162 (13.0%) were Asian, 95 (7.60%) were American Indian/Alaska Native and 10 (0.8%) were other or unknown. Gender and race were not significant covariates on nirmatrelvir PK. While age was a significant covariate on central volume of distribution, the approximately 25% reduction for subjects aged 80 years or above is not considered to be clinically relevant (See Section 14.5).

Exposure of nirmatrelvir was lower in a subset of four Japanese subjects enrolled in the multiple-dose PK and safety study, Study 1001, (AUC_{tau} and C_{max} approximately 30% and 21% to 26% lower) compared to non-Japanese subjects. These numeric differences in exposures are unlikely to be clinically meaningful. Mean half-life, drug accumulation and urinary recovery of unchanged nirmatrelvir were comparable between the two groups (see Section 14.2).

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8.1.2. Renal Impairment

The primary route of elimination of nirmatrelvir when administered with ritonavir is renal excretion of intact drug. A dedicated renal impairment study (Study 1011) enrolled subjects with mild (eGFR ≥60 to <90 mL/min), moderate (eGFR ≥30 to <60 mL/min) or severe (eGFR <30 mL/min and not requiring dialysis) renal impairment and a control group of subjects with normal (eGFR ≥90 mL/min) renal function. Subjects received 100 mg nirmatrelvir on 0 hours on Day 1 and 100 mg ritonavir on Day 1 and at -12 hours, 0 hours,12 hours, and 24 hours in relation to the Day 1 nirmatrelvir dose. Urinary recovery of unchanged nirmatrelvir was 31%, 43%, 31%, and 18% for the normal, mild impairment, moderate impairment, and severe impairment renal groups, respectively. Mean AUC_{inf} values of nirmatrelvir in subjects with mild (eGFR 60 to <90 mL/min), moderate (eGFR ≥30 to <60 mL/min), and severe renal impairment (eGFR <30 mL/min) were 1.24 (0.99, 1.54), 1.87 (1.49, 2.36) and 3.04 (2.38, 3.90), respectively (see Section 14.2).

No dose adjustment is recommended in patients with mild renal impairment (eGFR 60 to <90 mL/min). In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min) the recommended dose is 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet) twice daily for 5 days.

Study 1011 noted a higher incidence of AEs in patients with severe renal impairment (see Section 14.2). Given the mean 204% increase in AUC_{inf} and anticipated higher exposures at the clinical nirmatrelvir dose of 300 mg twice daily (co-administered with ritonavir 100 mg twice daily), PAXLOVID is not recommended in patients with severe renal impairment until more data are available. A safety and PK study evaluating PAXLOVID as treatment of mild-to-moderate COVID-19 in patients with severe renal impairment (for both patients requiring and not requiring hemodialysis) is ongoing, Study C4671028; NCT05487040, and will provide additional data to inform the appropriate dose for patients with severe renal impairment; therefore, this trial is a recommended postmarketing requirement (PMR) inclusion in the Approval Letter.

8.1.3. Hepatic Impairment

Hepatic elimination is not expected to be a major route of elimination for nirmatrelvir in combination with ritonavir based on Phase 1 data. In Study 1001, the only drug-related entity in plasma was unchanged nirmatrelvir. A dedicated hepatic impairment study (Study 1010) enrolled subjects with moderate (Child-Pugh Class B) hepatic impairment receiving a single dose of nirmatrelvir 100 mg and 4 doses of ritonavir 100 mg at -12 hours, 0 hours, 12 hours, and 24 hours. The exposure of nirmatrelvir in moderate hepatic impairment subjects was comparable to those in subjects with normal hepatic function. Adjusted geometric mean ratio (90% CI) of AUC_{inf} and C_{max} of nirmatrelvir comparing moderate hepatic impairment to normal hepatic function were 0.99 (0.71, 1.38) and 1.02 (0.74, 1.40), respectively (See Section 14).

No dose adjustment is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No PK or safety data are available regarding the use of nirmatrelvir or ritonavir in patients with severe hepatic impairment (Child-Pugh Class C); therefore, PAXLOVID is not recommended for use in patients with severe hepatic impairment.

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8.2. Extrinsic Factors

8.2.1. Food Effect

A dedicated food effect study (Study 1019) evaluated the effect of a high-fat meal (fat is 50% of total caloric content of the meal containing 800 to 1000 calories) on the relative bioavailability of the commercial 150 mg nirmatrelvir tablet boosted with 100 mg ritonavir. When taken orally with a high-fat meal versus fasted, the $AUC_{0-\infty}$ and C_{max} (geometric mean ratio [90% CI] of nirmatrelvir were 1.20 (1.09, 1.32) and 1.61 (1.39, 1.86).

All subjects in EPIC-HR (conducted using the to-be-marketed formulation of nirmatrelvir, co-administered with ritonavir) and the supportive Phase 2/3 trials were dosed without regard to food based on results from the first-in-human Study 1001 which showed co-administration of a high-fat meal with the boosted nirmatrelvir suspension resulted in an increase in AUC and C_{max} of 1.5% and 15%, respectively.

PAXLOVID is recommended to be given without regard to food given the favorable efficacy and tolerable safety profile noted in EPIC-HR when dosed without regard to food.

8.2.2. Drug Interactions

8.2.2.1. Effects of Nirmatrelvir/Ritonavir on Other Drugs

The potential DDI liability of nirmatrelvir as a perpetrator (effect of nirmatrelvir on the PK of other drugs) is based on in vitro studies conducted using nirmatrelvir alone.

The inhibitory potency of nirmatrelvir was determined by measuring the activity of each cytochrome P450 (CYP) enzyme (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5) in pooled human liver microsomes at a concentration range from 0.01 to 300 µM for all CYPs.

Nirmatrelvir reversibly and time-dependently inhibited CYP3A4 and did not reversibly inhibit CYP2D6, CYP2C9, CYP2C19, CYP2C8, CYP2B6 or CYP1A2 in vitro at clinically relevant concentrations (Table 47).

Table 47. Assessment of Risk for CYP Inhibition In Vitro Between Nirmatrelvir and Co-Administered Substrates

Basic (R1) Reversible Model		
CYP	**IC_{50} (µM)**	**R Value**
CYP1A2	>300	<1.02
CYP2B6	>300	<1.02
CYP2C8	>300	<1.02
CYP2C9	>300	<1.02
CYP2C19	>300	<1.02
CYP2D6	>300	<1.02
CYP2A4/5 Midazolam	58.3	1.09
CYP3A4/5 Testosterone	106	1.05
CYP3A4/5 Nifedipine	45.1	1.12

Basic (R1, gut) Reversible Model		
CYP	**IC50 (µM)**	**R Value**
CYP2A4/5 Midazolam	58.3	83.2
CYP3A4/5 Testosterone	106	46.3
CYP3A4/5 Nifedipine	45.1	107
Basic (R2) TDI Model		
CYP	**Ki,u (µM)**	**R Value**
CYP2A4/5 Midazolam	15.5	26.4
CYP3A4/5 Testosterone	13.9	30.8

Source: Study PF-07321332_04Nov20_113907, Study PF-07321332_09Nov20_122202.
Abbreviations: CYP, cytochrome P450; IC_{50}, half-maximal inhibitory concentration; R1, ratio of intrinsic clearance values of a probe substrate in the absence and in the presence of the interacting drug; R2, ratio of intrinsic clearance values of a probe substrate for an enzymatic pathway in the absence and in the presence of the interacting drug for TDI; Ki, u, unbound dissociation constant; TDI, time-dependent inhibition.

The in vitro induction effect of nirmatrelvir on CYP3A4, CYP2B6, CYP1A2, CYP2C9 and CYP2C19 was evaluated in cultured human hepatocytes at nirmatrelvir concentrations of 0.01 to 200 µM. Nirmatrelvir exhibited less than a 2-fold induction of enzyme activity at clinically relevant concentrations in all hepatocytes evaluated.

In a mechanistic model, the predicted net effect of nirmatrelvir on CYP3A was inhibition with no inhibition noted for the other enzymes (Table 48).

Table 48. Mechanistic Model of CYP Mediated DDI Risk Assessment of Nirmatrelvir[a]

	Reversible Inhibition		TDI		Induction						
	Intestinal	Hepatic	Intestinal	Hepatic	Intestinal	Hepatic	AUC_{R1}	AUC_{R2}	AUC_{R3}	$AUC_{R1,2}$	$AUC_{R1,2,3}$
CYP	Ag (≤0.8)	Ah (≤0.8)	Bg (≤0.8)	Bh (≤0.8)	Cg (≥1.25)	Ch (≥1.25)	Rev	Tdi	Ind	Rev,tdi	Rev,tdi,ind
1A2	--	0.99	--	--	--	--	1.01	--	--	--	--
2B6	--	0.99	--	--	--	1.54	1.00	--	0.82	--	--
2C8	--	0.99	--	--	--	1.73	1.00	--	0.75	--	--
2C9	0.94	0.99	--	--	2.05	1.30	1.01	--	0.77	--	--
2C19	0.94	0.99	--	--	1.70	1.28	1.01	--	0.77	--	--
2D6	0.94	0.99	--	--	--	--	1.01	--	--	--	--
3A	0.46	0.82	0.04	0.10	8.76	3.74	1.56	11.87	0.06	13.83	4.36
3Ahepatic	1	0.82	1	0.10	1	3.74	1.20	7.11	0.28	8.14	2.86
3Aintestinal	0.46	1	0.04	1	8.76	1	1.29	1.67	0.23	1.70	1.53

Source: PF-07321332_04Nov20_113907, PF-07321332_09Nov20_122202, PF-07321332_18Oct20_102559.

[a.] The terms listed in the table have the following values:

- Ag = 1 / (1 + [I]g/Ki)
- Ah = 1 / (1 + [I]h/Ki)
- Bg = kdeg,g / (kdeg,g + [I]g•kinact/([I]g + KI))
- Bh = kdeg,h / (kdeg,h + [I]h•kinact/([I]h + KI))
- Cg = 1 + d•E_{max}•[I]g /([I]g + EC50)
- Ch = 1 + d•E_{max}•[I]h / ([I]h + EC50)
- AUCR = 1 / (Ag•Bg•Cg•(1 − fg) + fg) • 1 / (Ah•Bh•Ch•fm + (1 − fm))

Abbreviations: AUC, area under the concentration-time curve; CYP, cytochrome P450; DDI, drug-drug interaction; ind, induction; rev, reversible; TDI, time-dependent inhibition.

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In vitro transporter inhibition studies demonstrated that nirmatrelvir inhibits P-gp ([I]/IC50=34) and OATP1B1 (R1=1.11). In vitro inhibition was not observed for BCRP, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1 or MATE2K transporters.

Ritonavir is a strong CYP3A4 inhibitor that is co-administered with nirmatrelvir to increase plasma nirmatrelvir concentrations. Ritonavir also inhibits P-gp and is a weak inhibitor of CYP2D6. Ritonavir also induces CYP3A (net effect is strong inhibition), CYP1A2, CYP2C9, CYP2C19, and CYP2B6 as well as other enzymes, including glucuronosyl transferase.

Clinical DDI studies were conducted by the applicant to evaluate the effect of nirmatrelvir/ritonavir on the PK of midazolam and dabigatran, a CYP3A substrate and P-gp substrate, respectively. The effects of nirmatrelvir/ritonavir on midazolam and dabigatran AUC and C_{max} are summarized in Table 49. Oral midazolam is contraindicated in the PAXLOVID labeling. Depending on dabigatran indication and patient's renal function, the PAXLOVID label recommends reducing the dose of dabigatran or to avoid concomitant use. There was no additional effect of nirmatrelvir on midazolam PK or dabigatran PK beyond that caused by ritonavir alone in either study (Section 14.2).

Table 49. Effect of Nirmatrelvir/Ritonavir on Pharmacokinetics of Co-Administered Drug

Co-Administered Drug Dose (Schedule)	Nirmatrelvir/Ritonavir Dose (Schedule)	N	Ratio (Test/Reference) of Adjusted Geometric Means (90% CI)	
			C_{max}	AUC[a]
Midazolam[b] 2 mg (1 dose)	300 mg/100 mg BID (9 doses)	10	3.68 (3.19, 4.25)	14.30 (12.04, 17.00)
Dabigatran[b] 75 mg (1 dose)	300 mg/100 mg BID (5 doses)	24	2.33 (1.72, 3.16)	1.94 (1.55, 2.44)

Source: Study 1012, Study 1013.
[a.] AUC = AUC_{inf} for both midazolam and dabigatran.
[b.] For midazolam, Test = nirmatrelvir/ritonavir plus midazolam, Reference= Midazolam. Midazolam is an index substrate for CYP3A4. For dabigatran, Test= nirmatrelvir/ritonavir plus dabigatran, Reference= Dabigatran. Dabigatran is an index substrate for P-gp.
Abbreviations: AUC, area under the plasma concentration-time curve; BID, twice daily; CI, confidence interval; C_{max}, maximum plasma concentration; CYP, cytochrome P450; N, number of subjects in group; P-gp, P-glycoprotein

In the clinical DDI study with midazolam, there was no incremental effect of nirmatrelvir on midazolam PK beyond that caused by ritonavir alone. Further, maximal CYP3A4 inhibition has been noted with ritonavir at doses of 50 mg to 100 mg and is used as a booster with HIV protease inhibitors at a dose of 100 mg once or twice daily (Mathias et al. 2009). Since the DDI potential of PAXLOVID is mainly associated with ritonavir component, with full CYP3A inhibition anticipated at the clinical dose, the list of contraindicated drugs and clinically significant drug interactions generally aligns with the Norvir (ritonavir) and boosted protease inhibitor USPIs. Agents that are extensively metabolized by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in AUC when co-administered with ritonavir. Thus, co-administration of PAXLOVID with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring.

Drugs That Are Contraindicated With PAXLOVID

The review team recommended deletion of (b) (4) from the list of contraindicated drugs in the PAXLOVID label. The inclusion of this drug was originally proposed by the Applicant (b) (4)

(b) (4)

The PAXLOVID label includes a clinical comment in Table 1 recommending careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression when narcotic analgesics are concomitantly administered with PAXLOVID).

Like rifampin, rifapentine is also a strong CYP3A inducer. The review team reclassified rifapentine as a drug that is contraindicated with PAXLOVID based on the risk of significantly reduced nirmatrelvir or ritonavir plasma concentrations that may be associated with the potential for loss of virologic response and possible resistance.

In addition, the following drugs were added to the list of drugs that are contraindicated with PAXLOVID based on their inclusion in the NIH guidelines for DDIs with PAXLOVID, the concomitant drug label, or the Norvir or boosted protease inhibitor labeling: silodisin, eplerenone, ivabradine, voclosporin, lomitapide, eletriptan, ubrogepant, finerenone, naloxegol, flibanserin, tolvaptan, primodine, and lumacaftor/ivacaftor.

Drugs That Should be Avoided With PAXLOVID

Drug interaction recommendations in the PAXLOVID label are generally aligned with recommendations outlined in ritonavir-containing drug labels. In addition, the following drugs are added based on their inclusion in the NIH guidelines for DDIs with PAXLOVID or post-authorization safety reports suggestive of a significant interaction: tamsulosin,aliskiren, ticagrelor, vorapaxar, clopidogrel, ivacaftor, elexacaftor/tezacaftor/ivacaftor, tezacaftor/ivacaftor, everolimus, rimegepant, hydrocodone, oxycodone, suvorexant, tadalafil, avanafil, vardenafil, and sildenafil when used for erectile dysfunction (already included when used for pulmonary arterial hypertension).

Drugs That Require a Dose Adjustment or Additional Monitoring When Co-Administered With PAXLOVID

Similarly, the following drugs are added based on their inclusion in the NIH guidelines for DDIs with PAXLOVID or post-marketing safety reports suggestive of a significant interaction.

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Language added in the PAXLOVID label is consistent with the concomitant drug label and the Norvir or boosted protease inhibitor USPIs: disopyramide, apixaban, clonazepam, cilostazol, saxagliptin, tofacitinib, upadacitinib, darifenacin, brexpiprazole, cariprazine, iloperidone, lumateperone, pimavanserin, buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem, riociguat, tadalafil and verapamil.

While other ritonavir-containing products are generally prescribed by HIV specialists experienced at managing the multiple drug interactions with ritonavir, PAXLOVID is being prescribed by a much broader group of healthcare providers. A boxed warning for DDIs has been added to the PAXLOVID labeling to further highlight this potential serious risk (See 7.7.1).

8.2.2.2. Effect of Other Drugs on Nirmatrelvir/Ritonavir

Clinical DDI studies were conducted with carbamazepine and itraconazole, a CYP3A inducer and CYP3A inhibitor, respectively. The effects of carbamazepine and itraconazole on nirmatrelvir/ritonavir AUC and C_{max} are summarized in Table 50. Co-administration of PAXLOVID with strong CYP3A inducers including carbamazepine is contraindicated due to potential loss of virologic response and possible resistance.

Based on the results of the itraconazole DDI study, no significant increase in nirmatrelvir exposure is expected with concomitant use of additional CYP3A inhibitors, including co-administration with additional boosting agents such as cobicistat or additional doses of ritonavir. The expected increase in nirmatrelvir exposure in this scenario is well below what was noted with the supratherapeutic nirmatrelvir dose (administered with ritonavir) that was well tolerated in Study 1001. Therefore, no dose adjustments are needed when PAXLOVID is given to patients who are also on a ritonavir- or cobicistat-containing regimen.

Table 50. Drug Interactions: Pharmacokinetic Parameters for Nirmatrelvir in the Presence of the Co-Administered Drugs

Co-Administered Drug Dose (Schedule)	Nirmatrelvir/Ritonavir Dose (Schedule)	N	Ratio (Test/Reference) of Adjusted Geometric Means (90% CI)	
			C_{max}	AUC[a]
Carbamazepine[b] 300 mg BID(16 doses)	300 mg/100 mg BID (5 doses)	9	0.57 (0.47, 0.69)	0.45 (0.34, 0.59)
Itraconazole 200 mg QD (8 doses)	300 mg/100 mg BID (5 doses)	11	1.19 (1.13, 1.25)	1.39 (1.29, 1.49)

Source: Study 1014 and Study 1015.
[a.] For carbamazepine, AUC = AUC_{inf}, for itraconazole, AUC = AUC_{tau}.
[b.] Carbamazepine titrated up to 300 mg twice daily on Day 8 through Day 15 (e.g., 100 mg twice daily on Day 1 through Day 3 and 200 mg twice daily on Day 4 through Day 7).
Abbreviations: AUC, area under the plasma concentration-time curve; BID, twice daily; CI, confidence interval; C_{max}, maximum plasma concentration; CYP, cytochrome P450; N, number of subjects in group; P-gp, P-glycoprotein; QD, once per day

The effect of moderate and weak CYP3A inducers on nirmatrelvir/ritonavir PK has not been studied in clinical DDI studies. There are several published clinical DDI reports with other ritonavir combinations (i.e., 100 mg-200 mg total daily dose) and the moderate CYP3A inducer, efavirenz. The effect of efavirenz on ritonavir PK when ritonavir was administered in combination with indinavir, darunavir, or nelfinavir is summarized in Table 51.

Table 51. Effect of Efavirenz (Moderate Inducer of CYP3A4) on PK of Ritonavir in Protease Inhibitor Combinations

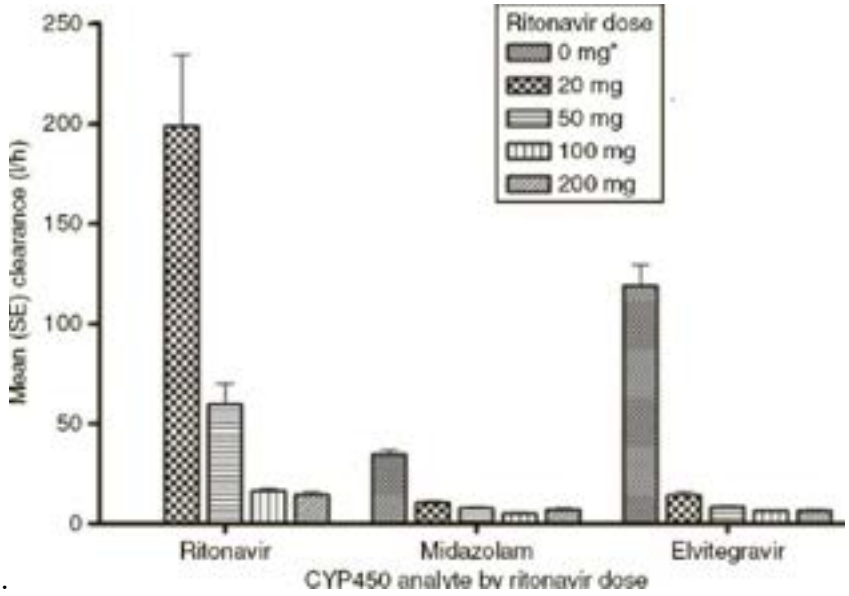
Dose/Regimen of Efavirenz	Dose/Regimen of Ritonavir	AUCR For Ritonavir	AUCR for Protease Inhibitor	Reference
600 mg QD Days 15-29	100 mg BID (in combination with 800 mg BID indinavir) Days 1-29	0.64	0.75	(Aarnoutse et al. 2002)
600 mg QD Days 10-24	100 mg, QD (in combination with 900 mg darunavir QD) Days 1-24	0.74	0.86	(Soon et al. 2010)
600 mg QD Days 11-20	200 mg, QD (in combination with 1875 mg nelfinavir) Days 1-20	0.80	1.30	(la Porte et al. 2004)

Source: Table generated from Reviewer analysis.
[a.] AUCR = AUC ratio = AUC of ritonavir or PI in presence of efavirenz/AUC of ritonavir or PI in absence of efavirenz.
Abbreviations: BID, 2 times per day; PI, protease inhibitor; QD, once per day

The ritonavir dose-response relationship on CYP3A metabolism using the HIV integrase inhibitor elvitegravir and the CYP3A substrate midazolam was evaluated by Mathias et al (Mathias et al. 2009). In this study, the effect of increasing doses of ritonavir on CYP3A activity was assessed by changes in midazolam and elvitegravir clearance (through inclusion of historical CL from an earlier study of elvitegravir administered without ritonavir). The lowest dose of ritonavir tested resulted in substantial reduction (approximately three- and ninefold, respectively) in midazolam clearance and elvitegravir oral clearance. Further increases in the ritonavir dose resulted in more modest additional reductions in midazolam and elvitegravir clearance, indicating that maximum ritonavir-mediated inhibition of CYP3A-mediated metabolism is achieved at ritonavir doses of 50 to 100 mg (Figure 18).

Based on the data provided by Mathias et al, this decrease in ritonavir exposure produced by moderate CYP3A inducer such as efavirenz, and by extension weak CYP3A inducers, is unlikely to affect the ability of ritonavir to inhibit CYP3A (Mathias et al. 2009).

Figure 18. Ritonavir, Midazolam, and Elvitegravir Clearance Values (Mean [SE]) by Ritonavir Dose



Source: (Mathias et al. 2009).
Note: The asterisk represents historical data for elvitegravir.
Abbreviations: CYP, cytochrome P450; SE, standard error

To further investigate the potential effects of moderate CYP3A inducers on ritonavir and ritonavir-boosted drugs, the PBPK reviewer collected and analyzed publicly available data of clinical DDI studies of moderate CYP3A inducers with ritonavir-boosted antiviral products and showed that the maximal reduction in the AUC of ritonavir was 63%. In most cases, lesser reduction was observed in AUCs of the corresponding boosted drugs. The trough concentrations (C_{min}) of the boosted drugs, which are often the more relevant PK parameter to the efficacy of these antivirals, were more vulnerable to the induction than their AUCs. Whether a moderate CYP3A inducer reduces the C_{min} of the boosted drugs may depend on the dose of each co-administered component, the combination of co-administered components, and drug interaction potentials of the boosted drugs. Therefore, it is difficult to estimate the effects of moderate CYP3A inducers on the exposure of ritonavir-boosted nirmatrelvir solely based on these available clinical DDI data. PBPK simulations need to be performed for this purpose. Assuming ritonavir AUC was reduced up to 63% by moderate CYP3A inducers, moderate CYP3A inducers were predicted to have little effects on nirmatrelvir PK by using a ritonavir PBPK model modified by the reviewer and the nirmatrelvir model developed by the Applicant. Based on this result, little changes are expected for weak CYP3A inducers.

Additional Drug Interaction Considerations

Patients on Concomitant Contraindicated HMG-CoA Reductase Inhibitors

Due to the potential for myopathy including rhabdomyolysis, lovastatin and simvastatin are both contraindicated with concomitant use of PAXLOVID. However, forgoing an efficacious outpatient treatment of COVID-19 may have a greater clinical consequence than pausing the concomitant use of simvastatin or lovastatin for a 5-day treatment duration. Given simvastatin and lovastatin are taken in the evening and have a short half-life, a clinical comment was added to labeling to include a timeframe in which patients on simvastatin or lovastatin are eligible for

PAXLOVID therapy. Specifically, patients should discontinue lovastatin and simvastatin at least 12 hours prior to initiation of PAXLOVID.

Instructions were also added to hold these statins during the five days of PAXLOVID treatment and for five days after completing PAXLOVID.

The recommendation to hold the statin for five days after completion of PAXLOVID is based on the estimated time course of CYP3A recovery after removal of enzyme inhibition. In the publication by Stader et al, a modeling approach was used to evaluate the duration of hepatic and intestinal CYP3A inhibition after stopping lopinavir/ritonavir (Stader et al. 2020). lopinavir/ritonavir (400/100mg twice daily) was administered for 7 days in a virtual trial to achieve steady state CYP3A inhibition and the abundance of CYP3A was estimated for 21 consecutive days. The interaction potential after stopping lopinavir/ritonavir was investigated with midazolam (a CYP3A probe substrate) administered orally 5 mg once-daily starting on the seventh day. In all simulations conducted, there was more than 80% disappearance of CYP3A inhibition 5 days after stopping lopinavir/ritonavir. While complete disappearance of CYP3A inhibition took 21 days, the amount of inhibition remaining at five days is not expected to be clinically significant for most drugs.

In another publication by Hong et al, a PBPK simulation-based approach was applied to predict the effect of ritonavir on the PK of elexacaftor-tezacaftor-ivacaftor (ETI) and determine a potential dose alteration of ETI to overcome the CYP3A inhibition mediated by ritonavir (Hong et al. 2022). Steady-state PK of standard dose ETI alone and when co-administered with 100 mg ritonavir twice daily for 5 days were simulated. A dose reduction of ETI during 5 days of ritonavir administration with resumption of full dose of ETI on day 9 (4 days after stopping ritonavir) provided a similar steady-state PK profile of the conventional regimen of ETI alone. Based on the totality of available information, a recommendation to hold lovastatin or simvastatin during the five days of PAXLOVID treatment and for five days after completing PAXLOVID was included in the prescribing information of PAXLOVID.

Patients on Hormonal Contraceptives

Patients on hormonal contraceptives are instructed to consider an additional, non-hormonal method of contraception during the five days of PAXLOVID treatment and until one menstrual cycle after stopping PAXLOVID. This recommendation is based on the theoretical risk of reduced ethinyl estradiol exposure with ritonavir and is supported by data from the darunavir/ritonavir package insert and a study by Kasserra et al, demonstrating a significant decrease ethinyl estradiol exposure when co-administered with darunavir/ritonavir (600 mg/100 mg) for 14 days or 100 mg ritonavir for 10 days, respectively (Janssen Products 2011; Kasserra et al. 2011). While the involvement of CYP enzymes are likely a minor contributor to this interaction, the time course of the additional processes involved in ethinyl estradiol metabolism (including glucuronidation and sulfation) are not well characterized. Generally, contraceptive efficacy is attributed to progestin more than the estrogen component. However, loss of efficacy due to lower ethinyl estradiol exposure cannot be ruled out, since efficacy may be affected by the relative proportions of the estrogen and progestin components and their effects on cervical mucus, ovulation, and endometrial lining changes.

Patients on Immunosuppressant Therapy

Concomitant use of a strong CYP3A inhibitor such as ritonavir can increase the risk of toxicities associated with immunosuppressants that have a narrow therapeutic index (e.g., cyclosporine, tacrolimus and sirolimus). Therapeutic concentration monitoring is recommended for patients on these drugs, although the frequency varies and decreases once the patient is on stable treatment. Therefore, language was added in the PAXLOVID label to avoid concomitant use of PAXLOVID in patients who are unable to undergo close monitoring of cyclosporine or tacrolimus serum concentrations. Concomitant use of sirolimus and a strong CYP3A inhibitor is not recommended even with the option of therapeutic concentration monitoring, consistent with the sirolimus labeling.

8.3. Plans for Pediatric Drug Development

The NDA for PAXLOVID triggers Pediatric Research Equity Act (PREA) as a new active ingredient. In their agreed initial Pediatric Study Plan, (b) (4) Their ongoing trial includes all pediatric patients, including neonates.

EPIC-PEDS is an ongoing open-label, multicenter, single-arm pediatric study to evaluate the safety, pharmacokinetics, and efficacy of PAXLOVID in non-hospitalized, symptomatic pediatric patients who are at risk of progression to severe disease. The following age cohorts will be evaluated:

- Cohort 1: weight ≥40 kgs, 6 to <18 years (b) (4)
- Cohort 2: weight ≥20 to < 40 kg, 6 to <18 years (b) (4)
- Cohort 3: ≥2 to <6 years (b) (4)
- Cohort 4: ≥1 month to <2 years (b) (4)
- Cohort 5: birth to <1 month (b) (4)

PAXLOVID will be supplied as the commercial tablet formulation in Cohort 1 and 2 and as an (b) (4) formulation [supplied as (b) (4))] in Cohorts 3 to 4; and in Cohort 2 for subjects who are unable to be administered tablets.

(b) (4)

Division of Antivirals (DAV) met with Pediatric Review Committee (PeRC) on March 7, 2023. The PeRC agreed with the deferral request in pediatric subjects from birth to less than 18 years of age, including neonates, with mild to moderate COVID-19. To collect safety and PK data in the pediatric population and to help determine the appropriate PAXLOVID dose in specific age

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and weight brackets, the following Pediatric Research Equity Act (PREA) postmarketing requirements (PMRs) are recommended for inclusion in the Approval Letter:

1. Conduct a study to evaluate the safety, tolerability, PK, and treatment response of PAXLOVID in pediatric subjects 6 to less than 18 years of age and weighing 20 kg or higher, with mild-to-moderate COVID-19
2. Conduct a study to evaluate the safety, tolerability, PK, and treatment response of PAXLOVID in pediatric subjects 2 to less than 6 years of age, with mild-to-moderate COVID-19
3. Conduct a study to evaluate the safety, tolerability, PK, and treatment response of PAXLOVID in pediatric subjects from birth to less than 2 years of age with mild-to-moderate COVID-19

(b) (4)

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

Nonclinical Data

The developmental and reproductive toxicology studies with nirmatrelvir and ritonavir are summarized in Section 7.1.

Nirmatrelvir

There were no effects on fertility or reproductive performance in rats exposed to nirmatrelvir at exposures approximately 5 times higher than clinical exposure at the recommended human dose (RHD) of PAXLOVID.

In a rat embryo-fetal developmental study, no biologically significant developmental effects were noted at exposure 10 times higher than clinical exposure at the RHD of PAXLOVID. In the rabbit embryo-fetal developmental study, lower fetal body weights (9% decrease) were observed at approximately 13 times higher than clinical exposure at the RHD of PAXLOVID. No

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developmental effects were observed in rabbits at exposures approximately 4 times higher than clinical exposures at the RHD of PAXLOVID.

In a rat pre- and postnatal developmental (PPND) study, a transient, non-adverse decrease (less than 8%) in the body weight of offspring was observed. Nirmatrelvir exposure was not assessed in the plasma of nursing pups or in the milk of lactating animals. However, it is estimated that no developmental effects occur in pregnant rats at approximately 6 times higher than clinical exposure at the RHD of PAXLOVID.

Ritonavir

No fertility effects were noted in rats administered ritonavir at 18 and 26 times (in males and females, respectively) higher than clinical exposure at the RHD of PAXLOVID.

At a maternally toxic exposure approximately 10 times higher than clinical exposure at the RHD of PAXLOVID, increased incidences of early resorptions, ossification delays, and developmental variations, as well as decreased fetal body weights were observed in rats. In rabbits, resorptions, decreased litter size, and decreased fetal weights were observed at maternally toxic doses approximately 11 times higher than the clinical exposure at the RHD of PAXLOVID. No evidence of teratogenicity was observed in rats and rabbits.

In a rat PPND study, exposure of ritonavir at 3 times higher than clinical exposure, based on a body surface area conversion factor, resulted no developmental effects.

Clinical Data

Across the PAXLOVID clinical trials, there have been seven cases of maternal exposure during pregnancy. In four cases, female subjects received placebo. In the remaining three cases, the pregnancies occurred in female partners of male subjects receiving PAXLOVID and the outcome of the pregnancies in these cases was unknown as of December 31, 2022. In all three cases there were no associated AEs. No female subjects who received PAXLOVID reported a pregnancy.

In a cumulative search of postmarketing AE reports for cases reporting pregnancy or lactation through December 31, 2022, the Applicant identified a total of 101 cases of exposure during pregnancy and 14 cases involving lactation.

Of the 101 cases of exposure during pregnancy, trimester of exposure was unknown in 22 cases. In 13 cases, exposure occurred during the first trimester of pregnancy. In 35 cases, exposure occurred during the second trimester and in 31 cases, exposure occurred in the third trimester of pregnancy. Infant outcome was reported in eight cases: normal in four babies, one baby was born prematurely at 29+1 weeks and was hospitalized in the neonatal ICU due to prematurity of birth (no abnormalities reported). In one case, spontaneous abortion was reported four days after the end of PAXLOVID. One case reported neonatal respiratory failure and congenital abnormalities of brachial cyst and anal fistula in an infant exposed during the seventh month of pregnancy.

A total of 14 cases involved lactation: suppressed lactation in 3 cases, lactation disorder in one case, and exposure via breastmilk in 10 cases.

The OSE also evaluated cases from the FAERS database, Pfizer's Monthly Safety Reports, the ACMT – FDA ACMT COVID-19 Toxicology Investigators Consortium Pharmacovigilance Project Sub-registry, and the published literature for AE and medical errors. Through August 29, 2022, 11 cases of pregnancy were identified. Two cases reported AEs: one case with preterm

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premature rupture of membranes and one case reported spontaneous abortion. There were two cases reporting signs/symptoms consistent with hypersensitivity reaction: one case reported angioedema and skin erythema and one case reported shortness of breath, wheezing, hypoxia, lip and pharyngeal swelling, and pruritus. Four cases reported only COVID-19 rebound with no AEs. The remaining three cases reported AEs similar to those observed in all patients, with the majority being labeled in the PAXLOVID EUA FS for HCP (dysgeusia, diarrhea, nausea).

To collect safety outcome data in pregnant individuals and their infants after PAXLOVID use during pregnancy, to help inform PAXLOVID dosing recommendations during pregnancy, and to inform use of PAXLOVID during lactation, the following PMCs pertaining to ongoing or planned studies are recommended for inclusion in the Approval Letter:

- An observational study to evaluate pregnancy and infant outcomes following exposure to PAXLOVID during pregnancy
- A Phase 1, Open-Label Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Orally Administered PAXLOVID in Pregnant Women With Mild-to- Moderate COVID-19 (Study C4671035; NCT05386472)
- A Phase I, Multiple Dose, Open-Label Pharmacokinetic Study of PAXLOVID in Healthy Lactating Women (Study C4671039; NCT05441215)

9. Product Quality

The Office of Pharmaceutical Quality review team has assessed NDA 217188 with respect to chemistry, manufacturing, and controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such, the Office of Pharmaceutical Quality recommends approval of this NDA from a quality perspective The drug product blisters contain immediate release tablets of nirmatrelvir, 150 mg and ritonavir,100 mg. The marketing of two dosage presentations is proposed - they differ only in having either one or two nirmatrelvir tablets in each dose pack. The blister packs have been updated since the EUA to contain single doses – instead of the daily dose packs in the EUA product. Nirmatrelvir tablets are manufactured by the Applicant whereas the ritonavir tablets are sourced from two previously approved sources - AbbVie (NDA 22417) and Hetero (ANDA 204587). The data provided support the quality and labeling of the proposed product including a (b) (4) retest period for nirmatrelvir and a 24-month expiry period for both nirmatrelvir tablets and ritonavir tablets. The PAXLOVID co-packaged drug product expiry date will reflect the shorter expiry of the two components.

Three Comparability Protocols were found acceptable (b) (4) - all CBE-30 supplements. Pfizer committed to submit CBE-0 supplement with the three-month long-term and accelerated stability data for three nirmatrelvir tablets batches manufactured at (b) (4) site by July 2023. Pfizer also committed to submit additional supporting assay data for the environmental assessment as a CBE-0 submission by December 2023.

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9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

Due to data reliability issues detailed in Section 6.3.1, certain sites in EPIC-HR, EPIC-SR, and EPIC-PEP were excluded from the final analyses. After excluding these sites, the result of the clinical site inspections and Applicant inspection support the conclusion that the clinical trials were conducted adequately, and the data generated support the proposed indication. Review of the financial disclosures did not raise any concerns about the validity or reliability of the data. Please see Section 6.3.1 for a summary of inspection findings and Section 25 for financial disclosures.

11. Advisory Committee Summary

The Antimicrobial Drugs Advisory Committee (AMDAC) met on March 16, 2023 to discuss this NDA. Please refer to the AMDAC meeting web page for full details (FDA 2023). Below are the questions posed to the AMDAC followed by a summary of the discussion.

1. VOTE: Is the overall benefit-risk assessment favorable for PAXLOVID when used for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death?

a. If yes, please provide your rationale.

b. If no, please provide your rationale and list what additional studies/trials are needed

Vote Result: Yes: 16 No: 1 Abstain: 0

Committee Discussion: A majority (94%) of the committee members agreed that the overall benefit-risk assessment is favorable for PAXLOVID when used for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. The committee members acknowledged that it will be important to identify who is still at high risk for progression to severe disease in the current setting when most people have some baseline SARS-CoV-2 immunity to understand who is most likely to benefit from PAXLOVID. Several committee members commented that since the absolute magnitude of benefit from PAXLOVID has decreased since the trials were conducted due to increasing levels of baseline SARS-CoV-2 immunity from vaccination or prior infection, the risks of treatment (mainly the drug-drug interactions) will have greater weight when making a benefit-risk assessment for use of PAXLOVID in an individual patient. There was also discussion about the continued emergence of new SARS-CoV-2 variants, and the committee

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indicated the importance of having an antiviral product like PAXLOVID available, considering that it has retained activity against variants to date and, given the conserved nature of the Mpro drug target, is predicted to retain activity against future variants. Committee members also stated that the absence of other oral, easy-to-administer, effective alternative therapies are also favorable factors when considering the benefit-risk assessment for PAXLOVID. Several committee members commented that it will be important to communicate that PAXLOVID will have the greatest benefit if taken early after symptom onset, specifically within 5 days as was studied in the trials. When it came to safety, drug-drug interactions were an area of significant concern, and many agreed that this is an issue that needs to be addressed further. There was discussion that risk mitigation is needed in terms of better communicating the risk of drug-drug interactions as primary care providers are primarily prescribing PAXLOVID and may not be familiar with ritonavir drug-drug interactions. Completion of studies pertaining to pregnancy, pediatrics, and in the immunocompromised population was emphasized. The committee member who voted "No" was concerned that the community does not understand where PAXLOVID fits in, who will benefit, and therefore who will be able to access and use it in a timely and appropriate way. Please see the transcript for details of the committee discussion.

2. DISCUSSION: Please comment on the strength of evidence for use of PAXLOVID for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death, in the following populations:

a. Individuals who are vaccinated against COVID-19 or had prior SARS-CoV-2 infection

b. Individuals infected with Omicron subvariants

c. Individuals who are immunocompromised

Please comment if additional data are needed in these populations.

Committee Discussion: Committee members agreed that a patient-level benefit-risk assessment, i.e., clinical judgement or personalized medicine, will be needed for the use of PAXLOVID, but more data are needed to guide physicians in understanding who meets the risk criteria and who will benefit in the right population. Members of the committee also stated that having systematic data on which populations are still at high risk for progression to severe disease in the current era of high population immunity will allow physicians to be more informed, as the issue is not whether there is benefit, but rather in which patients the magnitude of benefit of PAXLOVID will outweigh the risks. The committee agreed that ongoing surveillance and research should be conducted to ensure that emerging Omicron subvariants and other future variants continue to be susceptible to PAXLOVID and to detect the possible emergence of resistant variants. The committee recommended that pharmacovigilance plans and nonclinical studies should be implemented to study PAXLOVID activity against new emerging variants. Concerning the immunocompromised population, committee members stated that the clinical development plan for investigating use of PAXLOVID in immunocompromised patients, including the clinical trial EPIC-IC, seems to be comprehensive. However, there was concern that with the wide spectrum of immunocompromising conditions, one study may be insufficient to fully inform decision making with this population. Several committee members commented that collection of samples to look for prolonged viral shedding and emergence of resistant virus would be important in EPIC-IC. Please see the transcript for details of the committee discussion.

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3. DISCUSSION: Please comment on the strength of evidence for an association between use of PAXLOVID in the treatment of mild-to-moderate COVID-19 and 'COVID-19 rebound'. Please comment if additional data are needed.

Committee Discussion: Regarding COVID-19 rebound, many of the committee members highlighted that the clinical trial data clearly show that COVID-19 rebound occurred in both the placebo and PAXLOVID groups and that PAXLOVID use was not the driving factor for COVID-19 rebound. Committee members also commented that they are seeing reassuring data in the published literature, and that as healthcare professionals it is essential to effectively convey the information. Multiple committee members noted that the main issue is that the perception that PAXLOVID causes COVID-19 rebound persists, even among the medical community, although this is not supported by data but rather perpetuated by anecdotal reports and confirmation bias. Members emphasized the importance of communicating information based on the science and data and putting it into context so that those who would benefit from treatment are not turned away due to a concern that is not fully understood. Please see the transcript for details of the committee discussion.

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III. Additional Analyses and Information

12. Summary of Regulatory History

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Federal Food, Drug, and Cosmetic Act (the ACT), the Secretary of the Department of Health and Human Services determined that there is a public health emergency that has a significant potential to affect national security or the health and security of the United States citizens living abroad, and that involves the virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes the coronavirus disease 2019 (COVID-19). On November 25, 2020, Pfizer, Inc. (Pfizer) submitted a pre-investigational new drug (IND) meeting request to obtain Agency feedback on the regulatory and data requirements necessary to rapidly advance development of PF-07321332 as a potential oral treatment of SARS-CoV-2. The Agency provided detailed written feedback on the overall clinical and non-clinical drug development program for initial IND submission on January 13, 2021.

Pfizer submitted IND 153517 for the treatment of COVID-19 on December 22, 2020. Upon review of the IND application, on January 25, 2021, the IND was placed on full clinical hold due to insufficient information to assess risk to human subjects due to the absence of a clinical protocol, insufficient CMC information, lack of investigators' information, and lack of an investigator's brochure. Pfizer submitted a complete response to the clinical hold letter on February 3, 2021, and the Agency removed clinical hold on February 23, 2021.

On May 12, 2021, a meeting request was submitted to obtain Agency's feedback on the type of clinical and nonclinical information that would be needed to support an emergency use authorization (EUA) and full new drug application (NDA) submission for PF-07321332. The Agency's written responses dated May 27, 2021, provided feedback on the Pfizer's plan for the product packaging presentation; proposed nonclinical safety strategy and planned clinical/clinical pharmacology programs to support a future NDA submission; and additional clinical and virology (regarding assessment of antiviral activity of the product). In addition to the planned studies, the Agency recommended conducting drug-drug interaction studies to assess the effect of strong inducers and strong inhibitors of CYP3A4 on the pharmacokinetic (PK) of PF-07321332 and also recommended to initiate the hepatic impairment study. In addition, the Agency provided additional guidance for a future submission of an EUA application for the treatment and pre-exposure of symptomatic COVID-19.

Pfizer submitted the initial Pediatric Study Plan (iPSP) for PF-07321332/ritonavir (b) (4)

[redacted] (b) (4). The final agreed iPSP contains the following:

1. [redacted] (b) (4)
2. Deferral of assessment in the pediatric population from [redacted] (b) (4) to less than 18 years of age with a planned study start of 1Q2022 for adolescents (12 to less than 18 years of age who weigh 40kg or more)

The Agreed Initial Pediatric Study Plan (iPSP) was issued on April 4, 2022.

On August 10 and August 13, 2021, Pfizer requested a waiver from conducting a thorough QT/QTc study and the removal of the requirements for continued electrocardiogram (ECG) monitoring in the phase 2/3 clinical trials (EPIC-SR (C4671002), EPIC-HR (C4671005), and EPIC-PEP (C4671006)) based on preliminary ECG analysis from Part 5 of C4671001, ECG data from the sentinel cohort in trial C4671005 (EPIC-HR) and External Data Monitoring Committee recommendation which found no evidence of a cardiac safety signal. The Agency agreed with the assessment and recommendation to discontinue ECG monitoring in the phase 2/3 trials. In reference to the QT/QTc trial proposal, Pfizer follow up with a subsequent submission dated December 20, 2021 with a proposal to potentially rerun the good laboratory practice (GLP) hERG study in a format that aligns with the ICH S7B guidance currently in development. The Agency notified that the Applicant's strategy to use an integrated clinical (Study #C4671001) and double-negative nonclinical assessment
(hERG study 211129.QHJ and in vivo QT study 20GR275) to support the QT assessment under ICH E14 Q&A 5.1 appeared reasonable.

On November 3, 2021, the proposed proprietary name, PAXLOVID, was found acceptable and the proprietary name was conditionally granted.

Based on the clinical development program conducted under IND 153517 and in pursuant to Section 564 of the Act (21 U.S.C. 360bbb-3), on October 21, 2021, initial Emergency Use Authorization (EUA) request was submitted for treatment of mild-to-moderate COVID-19. Shortly after, Pfizer submitted nonclinical and CMC information to support the EUA application. On December 22, 2021, the Agency issued an EUA for PAXLOVID for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighting at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death based on the totality of scientific evidence available to the Agency, including data from the clinical trial EPIC-HR, a phase 2/3 randomized, double blind, placebo-controlled clinical trial.

On January 28, 2022, Fast Track Designation Request was submitted for treatment of COVID-19 and the request was granted on February 17, 2022, which allowed the following:

1. Interactions with the Agency to discuss the drug's development plan to support a marketing application
2. The eligibility for priority review if supported by clinical data at the time of marketing application submission
3. The ability for the Agency to consider reviewing portions of the marketing application before the complete submission is received by the Agency

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On February 15, 2022, a Type B Meeting Request was submitted to obtain the Agency's advice regarding the submission of a New Drug Application (NDA) for the use of Paxlovid in the treatment of mild-to-moderate COVID-19 in adults (b) (4) who are at high risk for progression to severe COVID 19, including hospitalization or death. The Written Response was issued on April 13, 2022 providing feedback on the structure, format, and data plan for future NDA submission including:

1. Sufficiency of nonclinical toxicology safety studies
2. Nonclinical antiviral resistance assessments
3. Planned integration of safety data (EPIC-HR and EPIC-SR) from PAXLOVID clinical trials and proposed format, standards, and structure of the datasets to be submitted
4. Viral sequencing reports
5. Format and criteria of safety narratives

The Agency recommended to clarify the "Indication/Claims" that will be submitted at the time of original NDA submission and re-iterated that a major amendment to an unapproved NDA may not include data to support an indication or claim that was not included in the original NDA submission, but it may include data to support a minor modification of the indication or claim that was included in the original NDA submission. The Agency agreed with the nonclinical safety studies conducted to support an NDA submission and reminded Pfizer of additional final study report timelines for outstanding animal studies.

The Agency did not fully agree with the proposed nonclinical virology antiviral resistance studies to support the NDA submission and requested the mouse hepatitis virus (MHV) selection study report PF-07321332_12Oct21_035634 be included in the NDA submission as this study could still be supportive for identifying potentially important nirmatrelvir resistance pathways. Based on breakthrough cases observed in EPIC-HR, the Agency recommended Pfizer continue to phenotypically characterize specific amino acids changes potentially associated with reduced nirmatrelvir susceptibility in nonclinical and clinical studies and include a current data with cumulative data from these studies in the NDA submission.

The Agency did not agree with the totality of data proposed to support an NDA submission and recommended to include EPIC-PEP and/or EPIC-SR efficacy data with the original NDA submission.

On May 9, 2022, a Type B, preNDA CMC-only Meeting Request was submitted to obtain the Agency's advice on the Chemistry, Manufacturing, and Controls (CMC) transition strategy for PAXLOVID from EUA 105 to NDA 217188 and to receive feedback on CMC specific questions in preparation for NDA submission. The preliminary comments were sent to the Pfizer on May 20, 2022, and during teleconference held on May 24, 2022, between Pfizer and Office of Pharmaceutical Quality (OPQ), OPQ provided feedback on the CMC information for future NDA submission including:

1. Additional product (DS and DP) manufacturing facilities
2. Plan to align CMC content between NDA and EUA
3. Period of stability data plan
4. Dissolution specification method

The Agency recommended Pfizer to submit all changes that will impact commercial supply to the NDA. The Agency was unable to comment on (b) (4) [redacted]. Generally, the Agency expects that at least 12 months of long-term stability data and 6 months of accelerated stability data for three primary drug product batches be included in the initial NDA submission per the recommendations in ICH Q1A(R2). However, for a product being developed to address an unmet medical need, the Agency agreed to accept less stability data for the primary batches in the initial NDA submission. The Agency agreed with Pfizer's proposal to submit 9-month stability data at the time of NDA submission and 12-month stability data in mid-September. The Office of Pharmaceutical Quality offered regular meetings with the Applicant during NDA review to discuss CMC issues.

On June 29, 2022, Pfizer submitted an original NDA 217188 for PAXLOVID, 300/150mg tablet to support the following indication: "PAXLOVID which includes nirmatrelvir, a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) main protease (M^{pro}: also referred to as $3CL^{pro}$ or nsp5 protease) inhibitor, and ritonavir, an human immunodeficiency virus (HIV-1) protease inhibitor and CYP3A inhibitor, is indicated for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death."

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

Selected nonclinical studies were originally submitted and reviewed under IND 153517 and EUA 105. All nonclinical safety studies conducted in support of PAXLOVID were also submitted to the present NDA 217188 and are reviewed in the following sections. Data supporting ritonavir were reviewed previously under NDA 20659 and are not summarized in this section.

13.2. Individual Reviews of Studies Submitted With the New Drug Application

13.2.1. Pharmacology

13.2.1.1. Secondary Pharmacology

In vitro studies suggest nirmatrelvir has minimal potential for secondary (off-target) pharmacology at clinically relevant concentrations. The in vitro off-target pharmacology of nirmatrelvir was assessed at 100 µM in a broad target profiling panel representing targets with known links to potential safety concerns and includes G-protein coupled receptors, ion channels,

transporters, and enzymes. No activity greater than 50% was observed. The IC_{50} values for nirmatrelvir inhibition of the Nav1.5 (peak) sodium and the Cav1.2 calcium channel currents were both determined to be >300µM, the highest concentration tested. Inhibitory activity of PF-07321332 against 11 phosphodiesterase (PDE) subtypes (1 to 11) and the IC_{50} values were determined to be >200µM (the highest concentration tested) for all tested PDE subtypes.

13.2.1.2. Safety Pharmacology

Table 52. Safety Pharmacology Studies

Study Title/Study No.	Findings
Effects of PF-07321332-00 on Cloned *hERG* Potassium Channels (Study# 22LJ022) • In vitro study, PF-07321332 at 30 and 300 µM was tested	The *hERG* inhibition of PF-07321332 at 300 µM was statistically significant ($p < 0.05$), but the *hERG* inhibition of PF-07321332 at 30 µM was not statistically significant ($p > 0.05$) when compared to vehicle control values. when compared with the vehicle control group. The IC50 for the inhibitory effect of PF-07321332 on *hERG* potassium current was not calculated but was greater than 300 µM.
Effects of PF-07321332 on Cardiac Function and Condition on the Guinea Pig Isolated Langendorff-Perfused Heart Model (Study# 20LJ075) • Ex vivo study	There were no statistically significant ($p<0.05$) effects on cardiac contractility, left ventricular pressure, coronary perfusion pressure, and the PR, QRS or QT intervals at any of the concentrations tested (0.03 µM-100 µM).
Assessment of the Effects of PF-07321332 on the Rat Isolated Aorta Preparation (Study# 20LJ076) • Ex vivo study on aorta cultured in buffer	PF-07321332 (2 pM - 100 µM) did not produce a vasoconstriction response in the rat isolated aorta tissue bath preparation (EC50 value >100 µM).
Safety Pharm-Cardiovascular Assessment of Oral Gavage PF-07321332 in Conscious Telemetry Instrumented Male Cynomolgus MONKEYS (Study# 20GR275) • Male cynomolgus monkeys, 0, 40 (20 BID), and 150 (75 BID) mg/kg • Single dose	PF-07321332 at 40 (20 BID) mg/kg/day produced no test article-related effects. PF-07321332 at 150 (75 BID) mg/kg/day increased systolic, diastolic, and mean blood pressures. Additionally, PF-07321332 decreased heart rate and LV +dP/dt max (an indicator of contractility) as well as increased RR-, PR- and QT-intervals. PF-07321332 at 150 (75 BID) mg/kg/day also produced a decrease in QTc-interval. All measures returned to vehicle control levels within 24 HPD.

Study Title/Study No.	Findings
PF-07321332: Neurofunctional and Pulmonary Assessment in Male Wistar Han Rats Following Oral (Gavage) Administration (Study# 20GR274) • Male rats (6/group) • 0, 60, and 1000 mg/kg, single dose	• In the quantitative locomotor assessment, a single, oral administration of 1000 mg/kg PF-07321332 resulted in test article-related higher number of mean horizontal (+298%) and vertical (+838%) movement counts during the last 30-minute period compared with vehicle control. Administration of 1000 mg/kg PF-07321332 also produced drug-related lower number of mean vertical movement counts (-36%) during the first 5-minute period of the quantitative locomotor assessment compared with vehicle control. There were no test article-related effects on any FOB parameters following oral administration of PF-07321332 up to 1000 mg/kg. • In the pulmonary assessment, administration of 1000 mg/kg PF-07321332 resulted in a test article-related higher respiratory rate (up to +44%) and minute volume (up to +38%) compared with vehicle control from 40 to 160 minutes post dose during a 6-hour continuous monitoring period.

Source: Reviewer assessment.
Abbreviations: BID, twice a day; EC50, half-maximal effective concentration; hERG, human ether-a-go-go-related gene; HPD, hours postdose; IC50, half-maximal inh bitory concentration; PR, period from P wave to the start of the QRS complex; QRS, end of PR interval to the end of S wave; QTc, QT interval corrected for heart rate; RR, cycle length variability and interval between successive Rs; QT, interval from beginning of QRS complex to the end of the T wave

13.2.2. Absorption, Distribution, Metabolism, Excretion/PK

13.2.2.1. Absorption

Single IV or oral dose absorption studies were conducted in Wistar-Han rats (PF-07321332_24Nov20_103131) and Cynomolgus monkeys (PF-07321332_19Nov20_111728). In the rat study, two oral formulations were tested, (b) (4) form of nirmatrelvir (10 or 100 mg/kg) and (b) (4) form (10, 100, 300, 1000 mg/kg). In both species, plasma CL was moderate, with a moderate to low V_{ss}, and $t_{1/2}$ values were 5 hours in rats and <1 hour in monkeys after IV dosing (Table 53). Following oral dosing, the overall bioavailability was moderate to high (29 to >100%) in rats but low (<10%) in monkeys.

Table 53. Pharmacokinetics of Nirmatrelvir in Rats and Monkeys

Dose[a] (mg/kg)	Route	N	CL (mL/min/kg)	V_{ss} (L/kg)	$t_{½}$ (h)	T_{max} (h)	C_{max} (ng/mL)	AUC_{inf} (ng•h/mL)	%F
Rat (PF-07321332_24Nov20_103131)									
1	IV	2	27.2	1.8	5.1	--	--	632	--
10	PO	2	--	--	4.0	1.5	1290	3190	50
10[b]	PO	3	--	--	2.8	0.25	1450	2170	34
100	PO	2	--	--	14[c]	0.75	29100	58600[c]	>100
100[b]	PO	3	--	--	5.7	1.4	5300	18100	29
300	PO	2	--	--	NR[d]	0.38	48900	153000	81
1000	PO	2	--	--	8.7	1.0	88300	750000	>100
Monkey (PF-07321332_19Nov20_111728)									
1	IV	2	17.1	0.33	0.8	--	--	977	--
10	PO	2	--	--	NR[d]	0.25	1450	NR[e]	8.5

Source: Applicant's Pharmacokinetics written summary, Section 2.6.4.3. Table 2.6.4-1.
[a.] All forms of nirmatrelvir were from the (b) (4) lot of material unless noted otherwise.
[b.] The (b) (4) form of nirmatrelvir was dosed.
[c.] N = 1.
[d.] Parameter not reported due to lack of discernible elimination phase.
[e.] Parameter was not reported due to increase in concentration at the last timepoint.
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; CL, apparent clearance; C_{max}, maximum plasma concentration; %F, bioavailability; IV, intravenous; N, number of subjects in analysis; PO, per os (by mouth); $T_{1/2}$, half-life; T_{max} time it takes for the drug to reach maximum concentration; V_{ss}, apparent volume of distribution at steady-state

Toxicokinetic data of nirmatrelvir were evaluated from the GLP repeat dose oral toxicity studies in rats and monkeys. Please see Section 13.2.3.2 for detailed information.

13.2.2.2. Distribution

In Vitro

- Protein binding was evaluated in plasma from rats, human and monkey (07321332_23Nov20_010657). The binding of nirmatrelvir to plasma proteins in rat, monkey, and human was moderate and similar across concentrations and species. Plasma protein binding was also evaluated in rabbits and dogs and concentration-dependent binding was observed (Study PF-07321332_23Nov20_020334; YDP/067/394, Table 54).
- Preliminary data indicates that nirmatrelvir primarily binds to Alpha-1-acid glycoprotein (AAG).
- At a concentration of 1µM, nirmatrelvir preferentially partitioned into plasma relative to red blood cells with Cb/Cp ratios of 0.83 (rat), 0.68 (monkey), and 0.60 (human) (Study PF-07321332_18Nov20_100444).

Table 54. Plasma Protein Binding of Nirmatrelvir

Species (Strain)	0.3 µM[a]	1 µM[a]	Plasma Fu 3 µM[a]	10 µM[a]	Average[b]
Rat (Wistar Han)	0.490	0.474	0.484	0.467	0.479
Monkey (Cynomolgus)	0.386	0.404	0.449	0.499	0.435
Human	0.296	0.300	0.311	0.333	0.310

Species (Strain)	2 µM	10 µM	Plasma Fu[a] 30 µM	50 µM	100 µM	200 µM
Rabbit (New Zealand White)	0.0100	0.449	0.734	0.737	0.817	0.804
Dog (Beagle)	0.0235	0.0977	0.404	0.542	0.640	0.685

Source: Modified based on Applicant's Pharmacokinetics written summary, Section 2.6.4.4. Table 2.6.4-4.
[a.] Geometric mean (n = 12).
[b.] Average value across the 4 concentrations tested.
Abbreviations: Fu, unbound drug

In Vivo

- The tissue distribution of [14C]nirmatrelvir was studied using Quantitative Whole Body Autoradiography (QWBA) in male Long-Evans rats (Study 8476949). Following administration of a single oral dose (1000 mg/kg, 160 µCi/kg) of [14C]nirmatrelvir, the distribution of radioactivity was widespread by 0.5 hours. The majority of tissues (except for liver, intestines, and kidneys) had tissue:plasma AUC_t ratios <1.0. The tissues with the highest C_{max} values (T_{max} = 4 hours for most tissues) excluding the gastrointestinal tract were observed in the liver, kidney, pancreas, and adrenal gland. [14C]nirmatrelvir-derived radioactivity did not cross the blood:brain barrier to a quantifiable extent. These results are consistent with nirmatrelvir being a substrate for P-gp. In most tissues, the elimination of [14C]nirmatrelvir-derived radioactivity was complete by 24 hours. [14C]nirmatrelvir did not associate with melanin-containing tissues.

13.2.2.3. Metabolism

In Vitro

- The metabolic profile of nirmatrelvir was evaluated in vitro in liver microsomes (mouse, rat, hamster, rabbit, monkey, and human), hepatocytes (rat, monkey, and human) (Study PF-07321332_09Nov20_084546).
  - A total of five oxidative metabolites were detected in vitro. The primary metabolite was M4 (PF-07329268), which arose from a mono-hydroxylation at the C-5 position of the pyrrolidinone ring, yielding a pair of interconverting diastereomers. The other sites of oxidation resulted in the formation of minor metabolites.
  - All oxidative metabolites were formed by CYP3A4/5, with other cytochrome P450 (CYP) enzymes contributing very minor amounts.
- The formation of M5 was observed in incubations of nirmatrelvir in human gut microbiota (Study PF-07321332_12Oct21_082057), alongside the destrifluoroacetyl metabolite M8 (PF-07331782). Approximately, 3.1% and 1.4% of nirmatrelvir was converted to M5 and M8 over the course of a 24-hour incubation with gut microbiota.
  - Hydrolysis was not observed in human-derived in vitro systems including human whole blood, intestinal fluid, and S9 fractions from liver, kidney, intestine, and lung.

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- In a reaction phenotyping study using human liver microsomes in the presence of selective CYP inhibitors, CYP3A4 was the major contributor (fm = 0.99) to the oxidative metabolism of nirmatrelvir. No significant CYP3A5 contribution is expected to the metabolism of nirmatrelvir (Study PF07321332_21Nov20_072016).
- Reaction phenotyping studies were conducted in human liver microsomes to identify the UGT enzymes responsible for the in vitro glucuronidation of M5 (PF-07320267). Results indicated UGT2B4 and 2B7 contributed 69.8% and 16.7% of the total metabolism of M5, respectively. The remaining 13.5% of metabolism through the UGT pathway was unassigned (Study PF-07321332_11Aug21_021055).

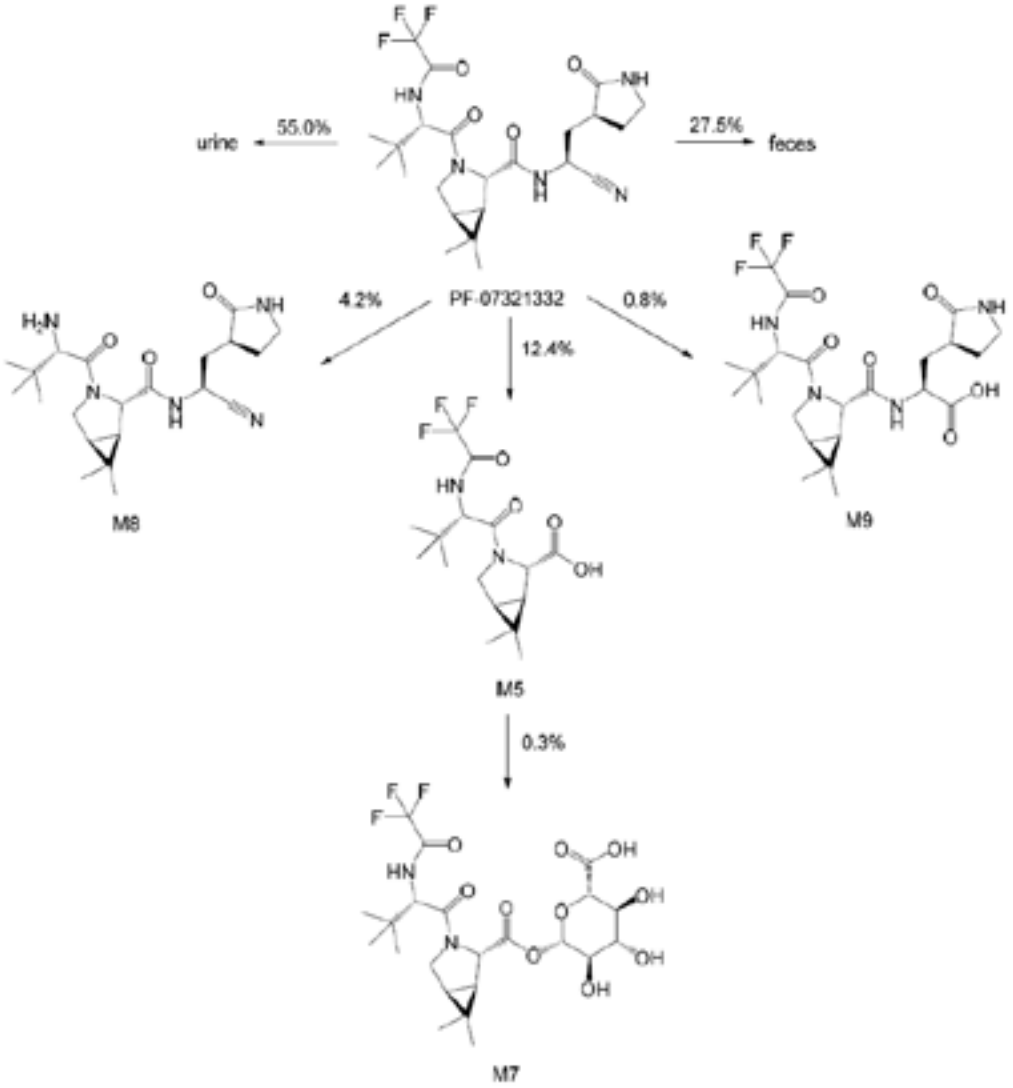
In Vivo

- The metabolism of nirmatrelvir was evaluated in vivo in rat and monkey after repeat oral dosing (Study PF-07321332_09Nov20_084546).
  - Besides oxidative biotransformation pathways, metabolite M5 (PF-07320267) obtained through hydrolytic cleavage across an amide bond in nirmatrelvir, was also detected as a minor metabolite in circulation and excreta from animals.
- M5 was also detected in circulation (trace levels) and excreta in humans when nirmatrelvir was co-administered with ritonavir.
- No unique human circulatory metabolites were detected.

13.2.2.4. Excretion

- Urinary and/or biliary excretion of nirmatrelvir was assessed in single-dose PK studies after IV or oral dosing of nirmatrelvir to rats (Study PF-07321332_24Nov20_103131) and monkeys (Study PF-07321332_19Nov20_111728). The percentage of nirmatrelvir dose excreted unchanged was 17% in the urine, 9% in the bile, and up to 11% in the feces in rats, and 7% in the urine and 4% in the feces in monkeys.
- The mass balance excretory pathways and metabolic profile of unlabeled nirmatrelvir was evaluated in six healthy subjects (C4671001, Cohort 9) following a single dose of 300 mg, co-administered with 100 mg ritonavir (Study PF-07321332_25Aug21_014401, Study PF-07321332_14Sep21_021626).
  - Unchanged nirmatrelvir represented 82.5% of the recovered dose in urine and feces at 55% and 28%, respectively.
  - Metabolite M5 (PF-07320267), arising via hydrolysis, was present at 12.1% of recovered dose almost exclusively in feces.
  - Metabolite M8 (PF-07331782) represented 4.2% of the recovered dose in urine and feces combined,
  - All other fluorine-containing metabolites were relatively minor (<1% of dose).
- The proposed metabolic pathways in humans are presented in Figure 19.

Figure 19. Profile of Nirmatrelvir Metabolism and Disposition in Human Excreta Following Oral Co-Administration of 300 mg Nirmatrelvir With Ritonavir



Source: Applicant's Pharmacokinetic written summary. Section 2.6.4.6. Fig 2.6.4-2.
Abbreviations: M, metabolite

13.2.3. General Toxicology

13.2.3.1. Single-Dose Toxicology/Toxicokinetics

Single IV or oral dose absorption studies were conducted in Wistar-Han rats (PF-07321332_24Nov20_103131) and Cynomolgus monkeys (PF-07321332_19Nov20_111728) for pharmacokinetic parameters. Please see Section 13.2.2.1 for details.

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13.2.3.2. Repeat-Dose Toxicology/Toxicokinetics

13.2.3.2.1. Two-Week Oral Gavage Toxicity and Micronucleus Assessment Study of PF-07321332 in Wistar Han Rats With a Two-Week Recovery (Study# 20GR276)

Key Study Findings

- Hematological, liver, and thyroid effects were observed.
- All of the hematology and coagulation findings (i.e., increase in prothrombin time (PT), APTT, PLT and FIB, decrease in RBC mass) had no clinical or microscopic correlations and all findings were completely resolved at the end of the recovery phase. Mechanisms for the increases in PT and APTT are unclear.
- The liver (i.e., minimal to mild periportal hepatocyte hypertrophy and vacuolation) and thyroid gland (i.e., thyroid follicular cell hypertrophy) findings were consistent with secondary adaptive effects related to microsomal enzyme-induced increase in thyroid hormone clearance in the liver, a mechanism that rats are known to be particularly sensitive to, relative to humans. All of the findings observed in the liver and thyroid were low severity and the absence of associated microscopic evidence of tissue damage or correlating alterations in clinical pathology parameters, and all of these findings fully resolved after the 2-week recovery period.
- The no observed adverse effect level (NOAEL) is the high dose of 1000 mg/kg.
  - Exposure on study Day14 (male and female combined): AUC_{24} was 292,000 ng·h/mL and C_{max} was 51500 ng/mL.
- The exposure margin, based on the lack of adverse effects, was 4.3× based on human exposures

Table 55. Two-Week Oral Toxicity Study Design

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 60, 200, and 1000 mg/kg/day; given once daily for 4 weeks.
Route of administration	Oral gavage
Formulation/vehicle	Suspension / Control 1: (b) (4) Polysorbate 80 in 0.5% (w/v) of methylcellulose A4M in purified water; Control 2 (Vehicle): (b) (4) Polysorbate 80 in 0.5% (w/v) of methylcellulose A4M in purified water
Species/strain	Rat/Wistar Hanover
Number/sex/group	10/sex/group (toxicity main study) 5/sex/group (toxicity recovery study/ 5/sex/control (TK) 5/sex/group (TK)
Age	9 weeks

Study Features and Methods	Details
Conducting laboratory	Pfizer Drug Safety Research & Development Eastern Point Road Groton, CT 06340 USA
Deviation from study protocol affecting interpretation of results	None

Source: Reviewer assessment.
Abbreviations: CT, Connecticut; GLP, good laboratory practices; (b) (4); TK, toxicokinetic

Table 56. Two-Week Rat Oral Toxicity Study Findings

Parameter	Major Findings
Mortality	Animals were examined twice daily for mortality, abnormalities, and signs of pain and distress. No treatment-related deaths.
Clinical signs	Detailed clinical observations were performed once weekly at approximately the same time body weights were performed, and on the days of necropsy. No treatment-related findings.
Body weights	All animals were weighed twice prior to the initiation of dosing on PID Days 1 and 7, predose on Dosing Phase Days 1, 8, 14, and a fasted weight was collected just prior to scheduled necropsy. During the recovery phase, body weights were collected on Recovery Phase Days 1, 8, and 11. There were no effects on body weight parameters in males. There was an increase (1.04x-1.12x mean controls) in body weight in females that was considered non-adverse due to magnitude.
Ophthalmoscopy	Ophthalmic examinations were performed on all animals once prior to the initiation of dosing on PID Days 4/5 (males/females) and on Toxicity animals on Dosing Phase Day 14. No treatment-related findings.
Hematology	Blood samples were collected from animals on the day of necropsy. There were dose-dependent prolongations in PT in males at ≥60 mg/kg/day (16-15%), and at 1000 mg/kg/day in females (40%), prolongations in APTT in males at ≥200 mg/kg/day (9-19%) and at 1000 mg/kg/day in females (11%) with no clinical or microscopic correlates. The mechanism for the increases in PT and APTT is unclear but indicates alterations in the coagulation pathway. Platelets were higher at 1000 mg/kg/day in both sexes (22-25%). In females only, there were lower RBC mass parameters (HGB, HCT, RBC) as indicated by HGB (5%) and higher fibrinogen (10%) at 1000 mg/kg/day. All hematology and coagulation findings recovered at the end of recovery phase.
Clinical chemistry	Drug-related clinical chemistry findings at 1000 mg/kg/day included higher globulin in both sexes (7%), and higher cholesterol (33%), lower ALP (34%) and albumin/globulin ratio (10%) in females. The increases in platelets, fibrinogen, globulin and decrease in AG are suggestive of an underlying inflammatory process but lacked any microscopic correlates. All drug-related clinical chemistry findings recovered at the end of the recovery phase.
Urinalysis	Urine samples were collected from animals on the day of necropsy. Drug-related urinalysis findings at 1000 mg/kg/day included lower pH (10%) in males on Day 15 compared with the control group. All test article-related urinalysis findings recovered at the end of the recovery phase.
Gross pathology	Drug-related macroscopic findings occurred in the liver (abnormal size, enlarged) at 1000 mg/kg/day in males (1/10) and females (1/10). These findings were fully recovered at the end of the recovery phase.

Parameter	Major Findings
Organ weights	Higher mean absolute (Male 36%, female 59%) and relative (Male 35%, Female 54%) liver weights were observed in males and females at 1000 mg/kg/day. A correlating microscopic finding of periportal hepatocyte hypertrophy was observed in males and females at this dose. Lower mean absolute and relative heart weights (15%) were observed only in females at 1000 mg/kg/day. There were no microscopic correlates in the heart. In the recovery phase, there were no drug-related organ weight differences in the liver and heart in males and/or females.
Histopathology Adequate battery: Yes	Liver Minimal to mild periportal hepatocellular hypertrophy was noted in females at ≥200 mg/kg/day and in males at 1000 mg/kg/day. It was characterized by slight enlargement of hepatocytes with abundant homogeneous eosinophilic cytoplasm and sinusoidal compression. Periportal hepatocellular hypertrophy was associated with increased incidence and severity (minimal to mild) of periportal hepatocyte vacuolation in females at 1000 mg/kg/day. Hepatocellular hypertrophy corresponded to higher mean liver weights in males and females and macroscopic liver finding of abnormal size (enlarged) in 1 male and 1 female at 1000 mg/kg/day. At the end of the recovery phase, microscopic changes had completely recovered as there were no drug-related microscopic findings in the liver at ≥200 mg/kg/day. Thyroid Gland Follicular cell hypertrophy was noted in males and females (minimal to mild) at 1000 mg/kg/day and was characterized by increased size and height of follicular cells. At the end of the recovery phase, microscopic changes had completely recovered as there were no drug-related microscopic findings in thyroid gland at 1000 mg/kg/day. Kidney Increased incidence and severity of hyaline droplet in the tubular epithelium was observed in the cortex of males administered vehicle containing (b) (4) or PF-07321332 compared with control males administered vehicle only. The incidence and severity (up to moderate) of this finding was generally comparable between (b) (4) control and 1000 mg/kg/day groups and was less (up to mild) in the 60 and 200 mg/kg/day groups, indicating that this finding was (b) (4) concentration-dependent. At the end of the recovery phase, the hyaline droplets in the kidney were noted in all (b) (4) administered animals but with lower incidence and/or severity and was comparable with vehicle controls indicating complete recovery of this finding.
Special evaluation: Micronucleus assessment	Blood was collected on day 4. Lower mean percent reticulocytes at 1000 mg/kg/day in males was noted, suggesting drug-related effect on erythrocyte production and maturation in males. However, the mean %reticulocyte values fell within the negative historical control range and are considered non-biologically relevant. There was no drug-related higher mean micronucleate reticulocytes in males and females. The oral administration of PF-07321332 did not induce micronuclei in the reticulocytes from peripheral blood of male and female rats.

Parameter	Major Findings
Toxicokinetics Sample collection times: days 1 and 25 at 0.5, 1, 2, 4, and 24 hours postdose.	**Table 57. Toxicokinetic Parameters in Male and Female (Combined) Rats**

Dose (mg/kg)	Day	C_{max} (µg/mL)	AUC_{24} (µg•h/mL)
60	1	12.9	27.3
	14	13.3	17.2
200	1	37.0	291
	14	27.1	80.5
1000	1	62.1	796
	14	51.5	292

Source: Text Table 1 from the toxicology study report.
Abbreviations: AUC_{24}, area under the concentration-time curve to 24 hours; C_{max}, maximum plasma concentration

Source: Reviewer assessment.
Abbreviations: AG, albumin/globulin ratio; ALP, alkaline phosphatase; APTT, activated partial thromboplastin time; HCT, hematocrit; HGB, hemoglobin; (b) (4); PID, prior to initiation of dosing; PT, prothrombin time; RBC, red blood cell

13.2.3.2.2. Fifteen-Day Twice Daily (BID) Oral Gavage Toxicity Study of PF-07321332 in Cynomolgus Monkeys (Study# 20GR289)

Key Study Findings

- Nirmatrelvir-related findings in repeated oral dosing in monkeys for 15 days limited to emesis and increase in fibrinogen (FIB). Increased FIB maybe attributed to an inflammatory state but lacked a microscopic correlate.
- The NOAEL was 600 mg/kg based on the absence of adverse PF-07321332-related findings.

  Exposure on study Day 15 (male and female combined): AUC_{24} was 1220,000 ng·h/mL and C_{max} was 106000 ng/mL.
- The exposure margin, based on the lack of adverse effects, was 17.8x based on human exposures.

Table 58. Fifteen-Day Monkey Oral Toxicity Study Design

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 40 (20 BID), 100 (50 BID), 600 (300 BID) mg/kg/day; once daily for 15 days.
Route of administration	Oral gavage
Formulation/vehicle	Suspension / Control 1: (b) (4) Polysorbate 80 in 0.5% (w/v) of methylcellulose A4M in purified water; Control 2 (Vehicle): (b) (4) Polysorbate 80 in 0.5% (w/v) of methylcellulose A4M in purified water.
Species/strain	Monkey/Cynomolgus
Number/sex/group	3/sex/group
Age	3-5 years old
Conducting laboratory	Pfizer Drug Safety Research & Development Eastern Point Road Groton, CT 06340 USA
Deviation from study protocol affecting interpretation of results	None

Source: Reviewer assessment.
Abbreviations: BID, twice daily; CT, Connecticut; GLP, good laboratory practices; (b) (4); USA, United States of America

Table 59. Fifteen-Day Monkey Oral Toxicity Study Findings

Parameter	Major Findings
Mortality	Animals were examined once daily. No mortality or moribundity.
Clinical signs	Clinical signs were monitored once daily. Drug-related emesis was observed at 600 (300 BID) mg/kg/day in male and ≥100 mg/kg/day in female cynomolgus monkeys. The emesis was generally described as food-like material or clear/foamy liquid and observed approximately 1 hour after the 2nd daily dose or following the overnight period. In both vehicle and (b) (4) control groups, there was single incidence of emesis observed in 1 of 3 males and females each.
Body weights	All animals were weighed twice prior to the initiation of dosing on PID Days 1 and 9, predose on Day 1 and weekly thereafter, and a fasted weight was collected just prior to scheduled necropsy. Drug-related decrease in body weight at 600 (300 BID) mg/kg/day on Day 15 in 1 male Animal (Male 13) (0.91x Day 1).
Ophthalmoscopy	Ophthalmic examinations were performed once prior to the initiation of dosing on PID Days 7/8 (male/female), and on Dosing Phase Day 10. No treatment-related findings.
Hematology	Blood samples were collected from fasted animals on PID Day 5/6 and Day 16. Drug-related increase in fibrinogen (72 -109%), compared with baseline, was observed in 2 males and 1 female administered 600 (300 BID) mg/kg/day.
Clinical chemistry	Blood samples were collected from fasted animals on PID day 5/6 and day 16. Decreases in sodium (4%) and chloride (7%), compared with baseline, were observed in a single animal administered 600 (300 BID) mg/kg/day.
Urinalysis	Urine was collected on day 16. Lower pH (20-27%) in males and females administered 600 (300 BID) mg/kg/day was noted.
Gross pathology	Animals were sacrificed on day 16. No treatment-related findings.
Organ weights	No drug-related organ weight change.
Histopathology Adequate battery: Yes	No drug-related microscopic changes.
Special evaluation: ECG	ECGs were collected once prior to the initiation of dosing (baseline) on PID Days 2/3 (males/females) and predose and approximately 1 hour after the first daily dose on Dosing Phase Day 13 on all animals. No treatment-related changes were noted.

Parameter	Major Findings
Toxicokinetics Sample collection times: days 1 and 15. 0.5, 1, 2, 4, 6 (prior to PM dose), 7, and 24 hours after the AM dose administration	**Table 60. Fifteen-Day Toxicokinetic Parameters in Monkey With Oral Administration** Dose (mg/kg/day)[a, b] | Day | Sex | C_{max} (µg/mL) | AUC_{24} (µg•h/mL) 40 (20 BID) | 1 | Male | 1.72 | 6.14 Female | 1.86 | 14.7 Overall | 1.79 | 10.4 15 | Male | 2.65 | 8.79 Female | 2.18 | 10.4 Overall | 2.42 | 9.61 100 (50 BID) | 1 | Male | 6.80 | 39.7 Female | 15.8 | 129 Overall | 11.3 | 84.2 15 | Male | 7.91 | 33.1 Female | 15.6 | 72.1 Overall | 11.8 | 52.6 600 (300 BID) | 1 | Male | 65.6 | 795 Female | 53.5 | 651 Overall | 59.6 | 723 15 | Male | 121 | 1390 Female | 90.4 | 1060 Overall | 106 | 1220 Source: Table from the Applicant's toxicology report. [a.] Animals were dosed orally twice daily for 15 days. [b.] 3 animals/sex/dose group. Abbreviations: AUC_{24}, area under the concentration-time curve to 24 hours; BID, twice daily; C_{max}, maximum plasma concentration

Source: Reviewer assessment.
Abbreviations: BID, twice daily; ECG, electrocardiogram; (b) (4); PID, prior to initiation of dosing

13.2.3.2.3. One-Month Oral Gavage Toxicity Study of PF-07321332 In Wistar Han Rats with A Two-Week Recovery (Study# 21GR122)

Key Study Findings

- Dose-dependent higher platelets and prolongation in PT were observed at ≥200 mg/kg/day. There were no clinical nor anatomic pathology correlates for these findings.
- In the liver, periportal hepatocellular hypertrophy and vacuolation in males and females at ≥200 mg/kg/day were noted and were associated with higher mean liver weights and macroscopic findings at 1000 mg/kg/day. In the thyroid gland, follicular cell hypertrophy was noted in males and/or females at ≥60 mg/kg/day. In the pituitary gland, cytoplasmic vacuolation was noted in the endocrine cells of the pars anterior (males only) at ≥60 mg/kg/day. At the end of the recovery phase, the changes were completely resolved at all doses in females and at 60 and 200 mg/kg/day in males; partial resolution was observed in recovery males at 1000 mg/kg/day. These findings are likely a rat specific response to hepatic enzyme induction resulting in increased thyroxine catabolism, raised serum thyroid stimulating hormone and thyroid follicular cell hypertrophy and anterior pituitary vacuolation. This mechanism is usually considered to have little to no relevance to humans.
- The NOAEL was 1000 mg/kg/day.
  - Exposure on study Day 25 (male and female combined): AUC_{24} was 548,000 ng·h/mL and C_{max} was 44500 ng/mL.
- The exposure margin, based on the lack of adverse effects, was 7.9x based on human exposures.

Table 61. One-Month Rat Oral Toxicity Study Design

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 60, 200, and 1000 mg/kg/day; one dose each day
Route of administration	Oral gavage
Formulation/vehicle	Suspension / (b) (4) and 0.5% (w/v) methylcellulose A4M in purified water
Species/strain	Rat/Wistar Hanover
Number/sex/group	15/sex/group (toxicity, 10 for main study, 5 for recovery study) 5/sex/group (TK)
Age	8 weeks
Conducting laboratory	Pfizer Drug Safety Research & Development Eastern Point Road Groton, CT 06340 USA
Deviation from study protocol affecting interpretation of results	None

Source: Reviewer assessment.
Abbreviations: CT, Connecticut; GLP, good laboratory practices; TK, toxicokinetic; USA, United States of America

Table 62. One-Month Rat Oral Toxicity Study Findings

Parameter	Major Findings
Mortality	Animals were examined twice daily for mortality, abnormalities, and signs of pain or distress. No drug-related death was noted.
Clinical signs	Detailed clinical observations were performed once weekly at approximately the same time body weights were performed, and on the day(s) of necropsy. Sporadic salivation (all doses) and soft feces (200 and 1000 mg/kg/day) observed during the dosing phase.
Body weights	All animals were weighed twice prior to the initiation of dosing, predose on Dosing Phase Days 1, 8, 15, 22, and 28, and a fasted weight was collected just prior to scheduled necropsy. Body weights were collected on Recovery Phase Days 1, 8, 13 (females) and 14 (males). No drug-related wight difference was noted.
Feed consumption	Food intake was measured weekly. No treatment-related findings.
Ophthalmoscopy	Ophthalmic examinations were performed on all animals once prior to the initiation of dosing (PID Day 6) and on Dosing Phase Day 23. No treatment-related findings.
Hematology	Blood samples were collected from fasted animals at terminal sacrifice Day 29 or Day 43/44. Dose-dependent higher platelets (1.12x-1.28x) were observed in males and females administered ≥200 mg/kg/day; in males administered ≥200 mg/kg/day and females administered 1000 mg/kg/day, this was accompanied by dose-dependent prolongations in PT (1.06x-1.15x). These findings lacked clinical and microscopic correlates.
Clinical chemistry	Blood samples were collected from fasted animals at terminal sacrifice Day 29 or Day 43/44. No treatment-related findings.
Urinalysis	Urine was collected prior to terminal sacrifice Day 29 or Day 43/44. No treatment-related findings.
Gross pathology	Enlargement and/or abnormal color (mottled) in females and 1 male at 1000 mg/kg/day. These were completely recovered at the end of the 2-week recovery phase.
Organ weights	Higher mean liver weights (1.07x-1.83x control) in males and females at ≥60 mg/kg/day were noted. Increase of liver weight was completely recovered at all doses in females and at 60 and 200 mg/kg/day in males. Higher liver weights (1.11x- 1.20x) was observed in recovery males at 1000 mg/kg/day.

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<table>
<tr><th>Parameter</th><th>Major Findings</th></tr>
<tr><td>Histopathology
Adequate battery: Yes</td><td>• In the liver, minimal to mild periportal hepatocellular hypertrophy in males and females at ≥200 mg/kg/day with concomitant increased severity (mild) of periportal hepatocyte cytoplasmic vacuolation (females only) at 1000 mg/kg/day were noted.
• In the thyroid gland, minimal to mild follicular cell hypertrophy was noted in males and/or females at ≥60 mg/kg/day.
• In the pituitary gland, minimal to mild cytoplasmic vacuolation was noted in the endocrine cells of the pars anterior (males only) at ≥60 mg/kg/day.
• At the end of the recovery phase, the microscopic changes in the liver, thyroid gland, and/or pituitary gland (males only) were completely recovered at all doses in females and at 60 and 200 mg/kg/day in males; partial recovery (lower incidence and/or severity) of the microscopic findings in the liver, thyroid gland, and pituitary gland was observed in recovery males at 1000 mg/kg/day.
• The pattern of linked findings in the liver, thyroid and pituitary glands are consistent with a rat specific response to hepatic enzyme induction resulting in increased thyroxine catabolism, raised serum thyroid stimulating hormone and thyroid follicular cell hypertrophy and anterior pituitary vacuolation. This mechanism is usually considered to have little to no relevance to humans mostly because of the marked differences in plasma half-life of thyroid hormones and in binding to transport proteins between rodents and humans.</td></tr>
<tr><td>Special evaluation:
NA</td><td></td></tr>
<tr><td>Toxicokinetics
Sample collection times: days 1 and 25, and 0.5, 1, 2, 4, 24 hours postdose.</td><td>Table 63. Mean Overall (Male + Female) Toxicokinetic Parameters of PF-07321332 in Wistar Han Rat Plasma
<table>
<tr><th>Dose (mg/kg)</th><th>Day</th><th>C_{max} (ng/mL)</th><th>T_{max} (hours)</th><th>AUC_{24} (ng•h/mL)</th></tr>
<tr><td>60</td><td>1</td><td>16200</td><td>0.50</td><td>34800</td></tr>
<tr><td></td><td>25</td><td>12800</td><td>0.50</td><td>19200</td></tr>
<tr><td>200</td><td>1</td><td>35000</td><td>1.0</td><td>252000</td></tr>
<tr><td></td><td>25</td><td>26000</td><td>1.0</td><td>94900</td></tr>
<tr><td>1000</td><td>1</td><td>87300</td><td>2.0</td><td>982000</td></tr>
<tr><td></td><td>25</td><td>44500</td><td>1.0</td><td>548000</td></tr>
</table>
Source: Text Table 1 from the Applicant's toxicology study report.
Abbreviations: AUC_{24}, area under the concentration-time curve to 24 hours; C_{max}, maximum plasma concentration; T_{max}, time for drug to reach maximum concentration</td></tr>
</table>

Source: Reviewer assessment.
Abbreviations: PID, prior to initiation of dosing

13.2.3.2.4. One-Month BID Oral Gavage Toxicity Study of PF-07321332 in Cynomolgus Monkeys with a Two-Week Recovery (Study# 21GR125)

Key Study Findings

- Sporadic occurrences of emesis at 600 (300 BID) mg/kg/day were the only clinical observation.
- Increases in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) in males and a female at 600 (300 BID) mg/kg/day and increases in fibrinogen in males and

females at 600 (300 BID) mg/kg/day. Fibrinogen increases from baseline were also noted in controls, but the magnitude was slightly greater in nirmatrelvir treated animals. No nirmatrelvir-related changes in clinical pathology parameters were observed at the end of the recovery phase, although recovery couldn't be evaluated in males that had increased AST and ALT, as those animals were euthanized at the end of the dosing phase.

- The NOAEL was 600 mg/kg/day.
  - Exposure on study Day 28 (male and female combined): AUC_{24} was 991,000 ng·h/mL and C_{max} was 87500 ng/mL.
- The exposure margin, based on the lack of adverse effects, was 14x based on human exposures.

Table 64. Twenty-Eight-Day Monkey Oral Gavage Toxicity Study Design

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 40 (20 BID), 100 (50 BID), or 600 (300 BID) mg/kg/day, daily dosing
Route of administration	Oral gavage
Formulation/vehicle	Suspension / (b) (4) and 0.5% (w/v) methylcellulose A4M in purified water
Species/strain	Rat/Wistar Hanover
Number/sex/group	Control and high dose: 5/sex/group (first three for main study, remaining two for recovery study) Low and mid doses: 3/sex/group
Age	3-3.5 years
Conducting laboratory	Pfizer Drug Safety Research & Development Eastern Point Road Groton, CT 06340 USA
Deviation from study protocol affecting interpretation of results	None.

Source: Reviewer assessment.
Abbreviations: BID, twice daily; CT, Connecticut; GLP, good laboratory practices; USA, United States of America

Table 65. Twenty-Eight-Day Monkey Oral Gavage Toxicity Study Findings

Parameter	Major Findings
Mortality	On dosing days, 1 hour after the last animal dosed in the AM, before the 2nd daily dose, and 1 hour after the last animal dosed in the PM. Twice daily on recovery days. No mortality or moribundity in this study.
Clinical signs	Detailed clinical observations were performed once weekly at approximately the same time body weights were performed, and on the day(s) of necropsy. Sporadic occurrences of emesis (1-4 bouts) were observed in 9 of 10 monkeys at 600 (300 BID) mg/kg/day for at least 1-5 days during the dosing phase, beginning Day 1 through 23. In the vehicle control, 40 (20 BID), and 100 (50 BID) mg/kg/day group, there were isolated incidences of emesis (single bouts) observed in 2 of 5 males, 1 of 3 females, and 1 of 3 males, respectively. No other drug-related clinical signs are noted.
Body weights	Body weights were recorded weekly. A fasted weight was collected just prior to scheduled necropsy. No treatment related effects.
Feed consumption	Food intake was measured daily in the AM. No treatment related effects.
Ophthalmoscopy	Ophthalmic examination was performed once prior to the initiation of dosing on PID Days 10/11 (M/F), and on Dosing Phase Day 22. No treatment-related findings.

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<table>
<tr><th>Parameter</th><th>Major Findings</th></tr>
<tr><td>Hematology</td><td>Blood samples were collected from fasted animals on PID day 2/3 (M/F), dosing phase day 29, recovery phase day 15/14 (M/F). Increases in fibrinogen (1.20x - 1.91x) in males and females at 600 (300 BID) mg/kg/day was noted. Fibrinogen increases from baseline were also noted in controls, but the magnitude was slightly greater in nirmatrelvir treated animals. No fibrinogen changes were noted at the recovery animals.</td></tr>
<tr><td>Clinical chemistry</td><td>Blood samples were collected from fasted animals on PID day 2/3 (M/F), dosing phase day 29, recovery phase day 15/14 (M/F). Increases in ALT (1.63x - 3.53x) and/or AST (2.68x - 7.41x) in males and a female at 600 (300 BID) mg/kg/day was noted. The recovery of ALT and AST was not determined.</td></tr>
<tr><td>Urinalysis</td><td>Urine was collected on day 29 and recovery phase day 15/14 (M/F). No treatment-related findings.</td></tr>
<tr><td>Gross pathology</td><td>Animals were sacrificed on days 29 and 45/44 (M/F). No treatment related findings.</td></tr>
<tr><td>Organ weights</td><td>No treatment-related effects.</td></tr>
<tr><td>Histopathology
Adequate battery: Yes</td><td>No treatment related findings.</td></tr>
<tr><td>Special evaluation:
ECG</td><td>ECG collection was performed prior to the initiation of dosing (baseline) on PID Days 4 (M) and 5 (F) and predose and 2 HPD (+/- 15 minutes) on Dosing Phase Days 24 (M) and 27 (F) on all animals. No drug-related changes in HR, RR-, PR-, QRS-, QT- or QTc-intervals for any of the comparisons described. There were no drug-related changes in ECG morphology.</td></tr>
<tr><td>Toxicokinetics
Sample collection times: On Day 1 and Day 28, 0.5, 1, 2, 4, 6 (prior to second daily dose), 7, and 24 hours after the first daily dose</td><td>Table 66. Mean Overall (M+F) Toxicokinetic Parameters ± Standard Deviation for PF-07321332 in Cynomolgus Monkey Plasma
<table>
<tr><th>Dose (mg/kg/day)</th><th>Day</th><th>Mean C_{max} (ng/mL)</th><th>Mean AUC_{24} (ng•h/mL)</th></tr>
<tr><td>40[a]</td><td>1</td><td>1250±584</td><td>4110±1340</td></tr>
<tr><td></td><td>28</td><td>1380±700</td><td>5620±1420</td></tr>
<tr><td>100[a]</td><td>1</td><td>5320±3060</td><td>29600±12100</td></tr>
<tr><td></td><td>28</td><td>7800±3440</td><td>45900±16800</td></tr>
<tr><td>600[b]</td><td>1</td><td>76600±21300</td><td>885000±239000</td></tr>
<tr><td></td><td>28</td><td>87500±21000</td><td>991000±227000</td></tr>
</table>
Source: Text Table 1 from the Applicant's toxicology study report.
[a.] 3 animals/sex/group with serial sampling.
[b.] 5 animals/sex/group with serial sampling.
Abbreviations: AUC_{24}, area under the concentration-time curve to 24 hours; C_{max}, maximum plasma concentration; F, female; M, male</td></tr>
</table>

Source: Reviewer assessment.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; F, female; HPD, hours postdose; HR, heart rate; M, male; PID, prior to initiation of dosing; PR, pulse rate; QRS, end of PR interval to the end of S wave; QT, interval from beginning of QRS complex to the end of the T wave; QTc, QT interval corrected for heart rate; RR, respiratory rate

13.2.3.3. General Toxicology, Additional Studies (Nonpivotal)

13.2.3.3.1. Four-Day Oral Gavage Exploratory Toxicity Study of Nirmatrelvir in Wistar Han Rats (Study# 20GR250)

Administration of nirmatrelvir (PF-07321332) to Wistar Han rats once daily by oral gavage at doses of 30, 100, or 1000 mg/kg/day for 4 days resulted in no test article-related clinical observations, effects on body weight, hematology and clinical chemistry parameters, no macroscopic findings, and no microscopic test article-related findings in the bone marrow of the

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sternum. Mean systemic exposure increased with increasing dose. Mean AUC_{24} values increased in a greater than dose-proportional manner suggestive of saturation of clearance mechanisms. There was no evidence for accumulation between Days 1 and 4.

13.2.3.3.2. Four-Day Oral Gavage Exploratory Toxicity Study of Nirmatrelvir in Cynomolgus Monkeys (Study# 20GR271)

Nirmatrelvir (PF-07321332) administered to male and female cynomolgus monkeys by oral gavage twice daily (BID) at doses of 30 (15 BID), 300 (150 BID), or 1000 (500 BID) mg/kg/day for 4 days was tolerated at all doses. Test-article-related emesis was observed at ≥300 mg/kg/day that was generally dose dependent and improved with repeat dosing. There were test article-related increases in fibrinogen (76 to 110%) and monocytes (102 to 145%) at ≥300 mg/kg/day on Day 5. At 1000 mg/kg/day on Day 5 there were also increases in white blood cells (103 to 112%) due to neutrophils (245 to 315%) and decreases in reticulocytes (63-79%). These changes at ≥300 mg/kg/day were indicative of an acute phase/inflammatory response with the decreased reticulocytes likely due to decreased production. Evidence of hemoconcentration or dehydration due to vomiting induced fluid loss were reported including increased red blood cells (6%), hemoglobin (4%), total protein (11%), due to increases in both albumin (10%) and globulin (11%), blood urea nitrogen (200%), and creatinine (57%) in high dose female group. Decreases in sodium (7%), potassium (20%), and chloride (23%), alongside increases in bilirubin (200%), triglycerides (167%), and glucose (60%) were also present. Mean systemic exposure increased with increasing dose. Based on mean AUC_{24} values, there was no evidence for accumulation between Days 1 and 4. There were no sex-related differences in systemic exposure (as assessed by C_{max} and AUC_{24}) across dose groups.

13.2.4. Genetic Toxicology

Table 67. Genetic Toxicology

Study Title/Study No.	Key Study Findings
PF-07321332: Bacterial Reverse Mutation Assay (20GR288) GLP compliance: Yes Study is valid: Yes	• TA98, TA100, TA1535, TA1537 and WP2uvrA strains were incubated with up to 5000 µg/plate with and without S9 metabolic activation. • No dose-related, two-fold increase in the number of revertant colonies was observed for the five tester strains. • PF-07321332 was not mutagenic under the experimental conditions.
PF-07321332: *In Vitro* Mammalian Cell Micronucleus Assay in TK6 Cells (20GR286) GLP compliance: Yes Study is valid: Yes	• Cultured human peripheral lymphocytes were exposed with up to 500 µg/mL for 4 or 27 hours without S9 metabolic activation and for 4 hours with up to 500 µg/mL with S9 metabolic activation. • PF-07321332 was considered negative for inducing chromosomal aberrations in in vitro human peripheral blood lymphocytes and was negative for clastogenicity under the experimental conditions.
Assay for Micronucleus Induction in Rat Bone Marrow	• Please see Section 13.2.3.2.1.

Study Title/Study No.	Key Study Findings
Other genetic toxicology studies	Evaluation of the Mutagenic Activity of (b) (4) in the *Salmonella typhimurium* Reverse Mutation Assay and the *Escherichia coli* Reverse Mutation Assay (Plate Incorporation and Pre-Incubation Methods) • (b) (4) was a step 1 product. • Direct plate assay – Dose-range from 52, 164, 512, 1600 to 5000 µg/plate was selected for the mutation assay with the tester strains, TA1535, TA1537 and TA98 in the absence and presence of S9-mix. – No increase in the number of revertants was observed upon treatment with the test item under all conditions tested. • Pre-incubation assay. – Test item was tested up to the dose level of 5000 µg/plate in the tester strains TA1535, TA1537, TA98, TA100 and WP2*uvrA* in the absence and presence of S9-mix. – No increase in the number of revertants was observed upon treatment with the test item under all conditions tested.

Source: Reviewer assessment.
Abbreviation: GLP, good laboratory practices; S9 fraction, contains metabolizing enzymes from the cytosol and microsomes

13.2.5. Carcinogenicity

Carcinogenicity studies were not conducted due to the short duration of nirmatrelvir treatment.

13.2.6. Reproductive and Developmental Toxicology

13.2.6.1. Fertility and Early Embryonic Development

13.2.6.1.1. Oral Gavage Male and Female Fertility Study of PF-07321332 in Wistar Han Rats (Study# 21GR146)

Key Study Findings

- No nirmatrelvir (PF-07321332)-related effects on male systemic toxicity or mortality, clinical observations, or effects on food consumption in females were observed. Although epididymal sperm maturation was not reported, no drug-related abnormalities were observed on male reproductive organs upon macroscopic examination. In females, non-adverse increase in body weights (compared to control animals) were observed at 1000 mg/kg/day prior to mating. No effects on estrous cyclicity, days to mating, reproductive indices (mating, fecundity, and fertility), or cesarean section observations were observed. The NOAEL for male and female fertility (and systemic toxicity) was 1000 mg/kg/day.

Table 68. Methods of Fertility and Early Embryo Development Study in Female and Male Rats

Parameter	Method Details
GLP compliance	Yes
Dose and frequency of dosing:	0 (vehicle), 60, 200 or 1000 mg/kg/day Daily dosing

Parameter	Method Details
Route of administration:	Oral gavage
Formulation/vehicle:	Suspension / vehicle consisting of (b) (4) and 0.5% (w/v) methylcellulose A4M in purified water
Species/strain:	Rat / Wistar Han
Number/sex/group:	20/sex/group (blood samples were collected 0.5 hours post dose from 5 females and 5 males per group on Dosing Phase Day 10 to determine plasma drug concentration.)
Satellite groups:	None.
Study design:	Dosing begins at 14 days prior to the mating phase, throughout the mating phase, and continued through GD 6 for females and for a total of 32 doses for males. Cesarean sections were performed on females on GD 14.
Conducting laboratory and location	Pfizer Drug Safety Research & Development Eastern Point Road Groton, CT 06340 USA
Deviation from study protocol affecting interpretation of results:	No

Source: Reviewer assessment.
Abbreviations: CT, Connecticut; GD, gestation day; GLP, good laboratory practices; USA, United States of America

Table 69. Observations and Results, Study 21GR146

Parameter	Major Findings
Mortality	No treatment-related findings.
Clinical signs	No treatment-related findings.
Food consumption	No treatment-related findings.
Body weights	PF-07321332-related, statistically higher body weight change was observed throughout the Premating Phase at 1000 mg/kg/day, resulting in nonsignificant slightly higher PF-07321332-related body weights on Premating Phase Day 14 (1.04x controls). No other treatment-related findings.
Sperm count	Not determined.
Sperm velocity	Not determined.
Necropsy findings [Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.]	No treatment-related findings.
Toxicokinetics Blood samples were collected 0.5 hours postdose on dosing Day 10.	**Table 70. Mean Concentration Data (ng/mL) on Dosing Phase Day 10 at 0.5 Hours Postdose for PF-07321332 in Wistar Han Rat Plasma**

Dose (mg/kg/day)	Sex	Mean	SD	n
60	Male	10400	3170	5
	Female	15800	4330	5
	Combined	13100	4580	10
200	Male	21000	5740	5
	Female	33000	11800	5
	Combined	27000	10800	10
1000	Male	19100	9050	5
	Female	46700	10500	5
	Combined	32900	17300	10

Source: Text Table 1 of the Toxicology Report from the sponsor.
Abbreviations: n, number of subjects in sample; SD, standard deviation

Source: Reviewer assessment.

13.2.6.2. Embryo-Fetal Development

13.2.6.2.1. Oral Gavage Embryo-Fetal Developmental Study of PF-07321332 in Pregnant Wistar Han Rats (Study# 21GR132)

Key Study Findings

- There were no nirmatrelvir-related maternal effects observed. In addition, no effects on fetal body weights or fetal external, visceral, or skeletal morphology were observed.

  The NOAEL for maternal and embryo-fetal development was 1000 mg/kg which corresponded to an $AUC_{0\text{-}24h}$ of 535,000 ng·h/mL for gestation day (GD) 17.

- The exposure margin was 7.8x based on the proposed human dose.

Table 71. Methods of Oral Embryo-Fetal Developmental Study in Rats

Parameter	Method Details
GLP compliance	Yes
Dose and frequency of dosing:	0, 100, 300, or 1000 mg/kg/day Once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	Suspension / (b) (4) and 0.5% (w/v) methylcellulose A4M in purified water
Species/strain:	Rats, Wistar Han
Number/sex/group:	20 females/group
Satellite groups:	None
Study design:	Dosing GD 6 to GD 17
Conducting laboratory and location	Pfizer Drug Safety Research & Development Eastern Point Road Groton, CT 06340 USA
Deviation from study protocol affecting interpretation of results:	No

Source: Reviewer assessment.
Abbreviations: CT, Connecticut; GD, gestation day; GLP, good laboratory practices; USA, United States of America

Table 72. Observations and Results, Study 21gr132

Parameter	Major Findings
Mortality	No drug-related fatality.
Clinical signs	No treatment-related findings.
Body weights	No treatment-related findings.
Necropsy findings Cesarean section data	There were no PF-07321332-related effects on cesarean section observations.
Necropsy findings Offspring	There were no PF-07321332-related external, visceral, or skeletal malformations or variations.

Parameter	Major Findings
Toxicokinetics Blood samples were collected on GD 17 at 0 (predose), 0.5, 1, 2, 4 hours postdose from 1-4 animals of each group.	**Table 73. TK Parameters for PF-07321332 in Rat EFD Study, GD 6 and 17**

Dose	C_{max} (ng/mL)			T_{max} (hours)			AUC_{24} (ng•h/mL)		
(mg/kg/day)	Mean	SD	n	Mean	SD	n	Mean	SD	n
100*	29000	11000	4	0.60	0.25	4	75500	12400	4
300	43200	14400	5	1.0	0.00	5	346000	92000	5
1000	65400	18700	5	1.1	0.55	5	535000	330000	5

Source: Table from Section10.3 of the Toxicology Report.
*Animal 009 had no viable fetuses and was excluded from mean calculations.
Abbreviations: AUC_{24}, area under the concentration-time curve to 24 hours; C_{max}, maximum plasma concentration; EFD, embryo-fetal development; GD, gestational day; n, number of subjects in sample; SD, standard deviation; TK, toxicokinetic; T_{max}, time for drug to reach maximum concentration

Source: Reviewer assessment.
Note: (Kuwagata et al. 2019).
Abbreviations: GD, gestation day

13.2.6.2.2. Oral Gavage Embryo-Fetal Developmental Study of PF-07321332 in Pregnant New Zealand White Rabbits (Study# 21GR126)

Key Study Findings

- Lower (9%) fetal body weight was observed at the high dose of nirmatrelvir. No maternal macroscopic observations, effects on ovarian and uterine parameters, fetal viability, fetal external, visceral, or skeletal morphology were observed. Based on the lack of nirmatrelvir (PF-07321332)-related adverse maternal toxicity, the maternal NOAEL was 1000 mg/kg/day.
- There were also no nirmatrelvir (PF-07321332)-related effects on fetal viability or morphological development in the study. However, the no observed effect level (NOEL) for developmental toxicity was 300 mg/kg/day based on lower fetal body weights at 1000 mg/kg/day.
  - At the NOEL for embryo-fetal development of 300 mg/kg, with $AUC_{0\text{-}96.5h}$ of 195,000 ng·h/mL for GD 19, the exposure margin was 2.8x based on human exposures.

Table 74. Methods of Oral Embryo-Fetal Developmental Study in Rabbit

Parameter	Method Details
GLP compliance	Yes
Dose and frequency of dosing:	0, 100, 300, or 1000 mg/kg/day; once daily
Route of administration:	Oral gavage
Formulation/vehicle:	Suspension / (b) (4) and 0.5% (w/v) methylcellulose A4M in purified water
Species/strain:	Rabbits / New Zealand White
Number/sex/group:	20 females/group
Satellite groups:	None
Study design:	Dosing GD 7 to GD 19. The post-treatment period was from GD 20 to 29 and animals were euthanized on GD 29.
Conducting laboratory and location	Pfizer Drug Safety Research & Development Eastern Point Road Groton, CT 06340 USA

Parameter	Method Details
Deviation from study protocol affecting interpretation of results:	No

Source: Reviewer assessment.
Abbreviations: CT, Connecticut; GD, gestation day; GLP, good laboratory practices; USA, United States America

Table 75. Observations and Results

Parameter	Major Findings
Mortality	No treatment-related mortality.
Clinical signs	No treatment-related clinical signs.
Body weights	• At 1000 mg/kg/day, PF-07321332-related lower mean body weight change (0.58x control) was noted for the GD 7-20 interval in the absence of effects on body weight. • There were no other PF-07321332-related effects on maternal body weights, body weight change, corrected body weight, or corrected body weight change.
Necropsy findings Cesarean section data	There were no PF-07321332-related effects on cesarean section observations, including fetal viability.
Necropsy findings Offspring	• Treatment-related lower mean fetal body weight (0.91x control) was noted at 1000 mg/kg/day (statistically significant). • There were no PF-07321332-related fetal external, visceral, and skeletal observations.
Toxicokinetics Blood samples were collected on GD 19 at 0 (predose), 0.5, 1, 2, 4 hours post dose.	**Table 76. Toxicokinetic Parameters for PF-07321332 in Rabbit EFD Study**

Dose	C_{max} (ng/mL)			T_{max} (hours)			AUC_{24} (ng•h/mL)		
(mg/kg/day)	Mean	SD	n	Mean	SD	n	Mean	SD	n
100	17000	6100	5	0.60	0.22	5	98700	27400	5
300	42900	11100	5	0.90	0.65	5	195000	56800	5
1000	99600	46500	5	1.1	0.55	5	689000	206000	5

Source: Table in Section 10.3 of the Toxicology Study Report.
Abbreviations: AUC_{24}, area under the concentration-time curve to 24 hours; C_{max}, maximum plasma concentration; EFD, embryo-fetal development; GD, gestational day; n, number of subjects in sample; SD, standard deviation; T_{max}, time for drug to reach maximum concentration

Source: Reviewer assessment.
Abbreviations: EFD, embryo-fetal development; GD, gestation day

13.2.6.3. Pre- and Postnatal Development

13.2.6.3.1. An Oral (Gavage) Study of the Effects of PF-07321332 on Pre- and Postnatal Development, Including Maternal Function in Rats (Study# 21GR149)

Key Study Findings

- No adverse nirmatrelvir-related effects were observed in pregnant rats and F1 offspring at all dose levels. Body weight gain was decreased from PND 10 to 17 in the offspring at the highest dose of 1000 mg/kg/day, resulting in a decrease (8% in both males and females

compared to controls) of body weight at PND 17. No significant difference in body weight was noted at PND 28 (males) or PND 22 (females) to PND 56 (both sexes) and afterwards.

- NOAEL was identified at 1000 mg/kg/day for maternal toxicity.
- NOEL for developmental toxicity was 300 mg/kg/day due to an 8% decrease in body weight at PND 17. Drug concentrations in maternal and offspring plasma and breastmilk were not reported.

Table 77. Methods of Oral Gavage Pre- and Postnatal Developmental Toxicity Study in Rats

Parameter	Method Details
GLP compliance	Yes
Dose and frequency of dosing:	0, 100, 300, 1000 mg/kg Daily
Route of administration:	Oral gavage
Formulation/vehicle:	suspension / vehicle control: (b) (4) in 0.5% (w/v) methylcellulose A4M in Deionized Water; vehicle: (b) (4) and 0.5% (w/v) methylcellulose A4M in Deionized water
Species/strain:	Rat/ Wistar Han
Number/sex/group:	22 females per group
Satellite groups:	None
Study design:	PF-07321332 was administered once daily by oral gavage to time-mated female rats from Gestation Day (GD) 6 through Lactation Day (LD) 20. The growth, viability, and development of the F1 offspring, and reproductive performance of the F1 generation were assessed.
Conducting laboratory and location	(b) (4)
Deviation from study protocol affecting interpretation of results:	No

Source: Reviewer assessment.
Abbreviations: GLP, good laboratory practices; (b) (4); SC, subcutaneous

Table 78. Observations and Results

Generation	Major Findings
F0 dams	The only PF-07321332-related effects on the F0 generation was a lower mean body weight gain following the initiation of dosing at 1000 mg/kg/day and higher mean body weight gain during GD 19–20 and when the entire gestation dosing period (GD 6–20) was evaluated, which were not considered adverse due to the lack of impact on F0 body weights.
F1 generation	PF-07321332-related lower male and female pup body weight gains were observed at 1000 mg/kg/day during PND 10–17. As a result, mean F1 male and female pup body weights in this group were 0.92x the control group on PND 17. Mean male and female pup body weight gains at 1000 mg/kg/day were similar to the control group during PND 17–21 but mean absolute body weights remained slightly lower (0.93x and 0.94x the control group, respectively) on PND 21. The effects on F1 pups body weight parameters during PND 10–17 were considered PF-7321332-related but not adverse because the effect was transient, the pups had normal birth weights and growth was comparable to the control group prior to PND 10, and the body weight deficit began to resolve prior to weaning and did not persist to the postweaning period.

Generation	Major Findings
F2 generation	No assessment conducted
Toxicokinetics	Not determined.

Source: Reviewer assessment.
Abbreviations: GD, gestation day; PND, postnatal development

13.2.7. Other Toxicology Studies

13.2.7.1. Impurity Studies

13.2.7.1.1. A Two-Week Oral Gavage Impurity Qualification Toxicity Study of PF-07321332 in Wistar Han Rats (Study# 21GR206)

Nirmatrelvir (PF-07321332) was administered by oral gavage once daily for 14 days to male and female Wistar Han rats at a dose of 200 mg/kg/day with increased amounts of multiple impurities (b) (4) or without increased impurities.

Test article-related clinical observations were limited to salivation noted prior to dose administration on Day 14 in all groups administered nirmatrelvir with or without additional impurities.

When compared with controls, non-adverse findings in coagulation and clinical chemistry parameters were observed in male rats administered nirmatrelvir with and without additional impurities including prolongations in mean PT (1.05x to 1.07x) and APTT (1.10x-1.18x). In addition, compared with controls, male rats administered nirmatrelvir without additional impurities (Group 2) and male rats administered nirmatrelvir with the additional impurities (b) (4) (Group 3) had higher mean had higher mean globulin (1.04x to 1.07x) leading to higher total protein (1.04x), also resulting in a lower mean AG ratio in male rats administered PF-07321332 with additional impurities (Group 3; (b) (4)). This series of findings were not adverse due to the small magnitude of difference and lack of microscopic or clinical correlates.

Non-adverse test article-related higher liver weights (1.11x to 1.18x) were noted in females administered nirmatrelvir without additional impurities (Group 2) and with additional impurities (b) (4) (Group 4), compared with controls. These weight differences were not adverse due to the small magnitude of difference and lack of macroscopic and/or microscopic correlates.

There were no consistent sex-related differences in systemic exposure for nirmatrelvir observed at 0.5 hours post-dose, and exposures were similar across groups administered nirmatrelvir with or without additional impurities.

Based on the data, impurities are qualified at the levels in Table 79.

Table 79. PAXLOVID Drug Substance Organic Impurity Specifications

(b) (4)

14. Clinical Pharmacology

14.1. In Vitro Studies

Protein Binding

Protein binding of nirmatrelvir at a concentration of 0.3, 1, 3, and 10µM in human plasma was evaluated using equilibrium dialysis (Study PF 07321332_23Nov20_010657). The binding of nirmatrelvir to human plasma proteins was not concentration dependent. The mean fraction unbound of nirmatrelvir in human plasma proteins at concentration of 0.3, 1, 3, and 10µM was 0.296, 0.300, 0.311, and 0.333, respectively.

Blood to Plasma Partitioning

Human whole blood samples were used to measure red blood cell partitioning of nirmatrelvir (Study PF-07321332_18Nov20_100444). Nirmatrelvir mean (standard deviation) blood to plasma ratio was estimated to be 0.60 (0.024).

Metabolism

The metabolism of nirmatrelvir was evaluated in human liver microsomes and human hepatocytes (Study PF-07321332_09Nov20_084546). The primary metabolite was M4, which results from a mono-hydroxylation at the C-5 position of the pyrrolidinone ring. The other sites of oxidation resulted in the formation of minor metabolites. Across a panel of human recombinant CYPP450 enzymes, all oxidative metabolites were formed by CYP3A4/5, with other CYP enzymes contributing very minor amounts.

Metabolite M5 was detected as a minor metabolite at trace levels in human circulation and excreta when nirmatrelvir was co-administered with ritonavir. M5 is formed through hydrolytic cleavage across an amide bond in nirmatrelvir. Metabolite M7, the acyl-glucuronide conjugate of M5, was also identified in human urine in trace amounts (Study PF07321332_14Sep21_021626).

In a reaction phenotyping study using human liver microsomes in the presence of selective CYP inhibitors, CYP3A4 was the major contributor (fm = 0.99) to the oxidative metabolism of nirmatrelvir. (Study PF07321332_21Nov20_072016).

When co-administered with ritonavir, oxidative metabolism was a minor component of overall nirmatrelvir clearance. Unchanged nirmatrelvir was the predominant drug-related entity in circulation in plasma from healthy adults administered with a single oral dose of 300 mg nirmatrelvir in the presence of ritonavir (Study C4671001, Cohort 9). Only trace amounts of M4, M5, and M8 were detected in circulation when nirmatrelvir was co-administered with ritonavir (Study PF-07321332_08Sep21_090141).

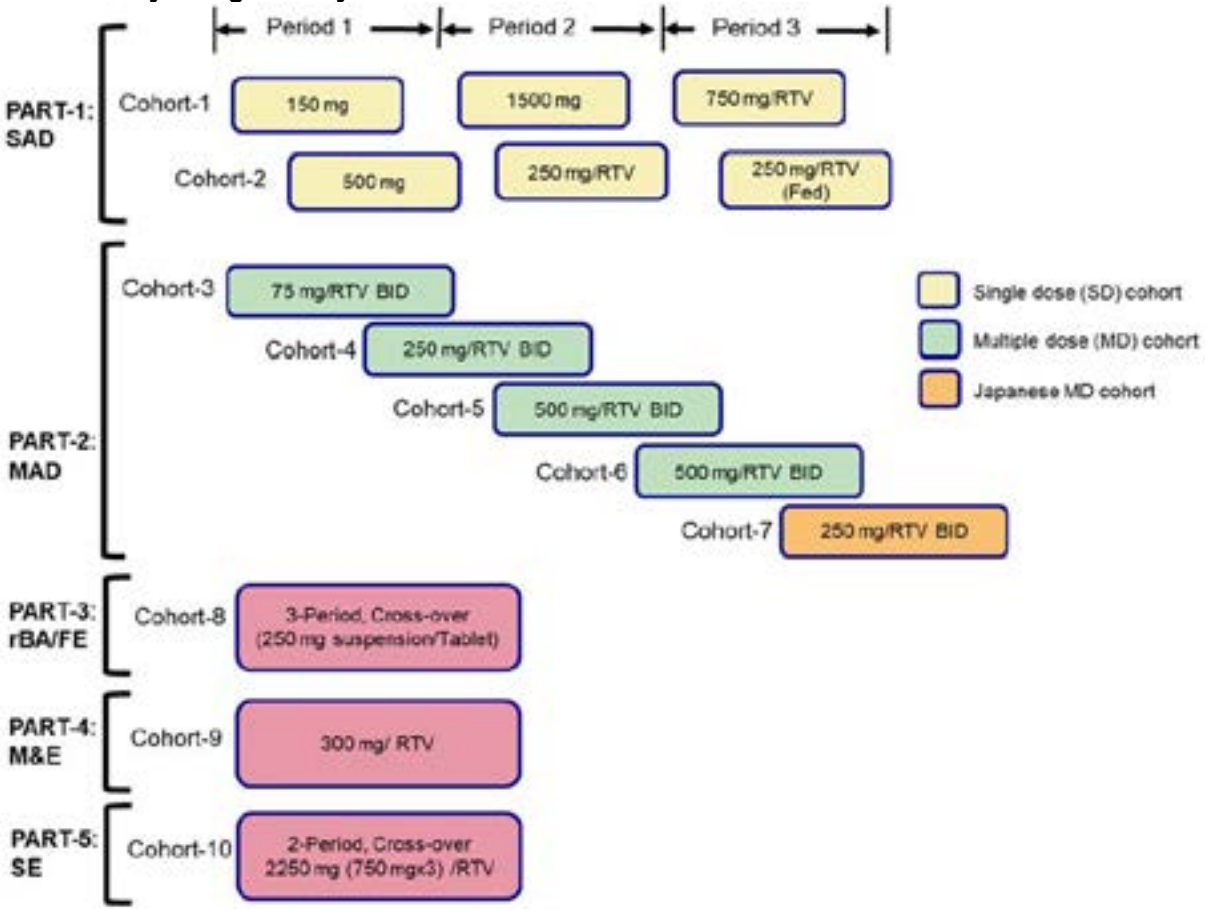
Nirmatrelvir as a Substrate, Inhibitor, and Inducer of Drug-Metabolizing Enzymes and Transporters

See Table 47 and Table 48 in Section 8.2.2.1.

14.2. In Vivo Studies

Study 1001 was the first-in-human study with nirmatrelvir alone and nirmatrelvir co-administered with ritonavir. This was a 5-part study consisting of part 1: single ascending dose, part 2: multiple ascending dose, part 3: relative bioavailability/food effect, part 4: metabolism and excretion, and part 5: supratherapeutic exposure (Figure 20).

Figure 20. Study Design: Study 1001



Source: Study 1001.
Abbreviations: BID, twice daily; MAD, multiple ascending dose; MD, multiple dose; M&E, metabolism and excretion; rBA/FE, relative bioavailability/food effect; RTV, ritonavir; SAD, single ascending dose; SE, supratherapeutic exposure

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Part 1: Single Ascending Dose

Part 1 evaluated a single dose of 150 mg, 500 mg, and 1500 mg nirmatrelvir alone and at 250 mg and 750 mg nirmatrelvir dose with ritonavir 100 mg (dosed at -12hours, 0hours, and 12hours). The effect of food was also evaluated in a cohort of subjects receiving nirmatrelvir 250 mg + ritonavir 100mg at -12, 0 and 12 hours with a high-fat meal. A total of 12 subjects were included in 2 cohorts, each consisting of 4 active and 2 placebo subjects with three periods in each cohort (Table 80). A washout interval of at least 5 days was given between dosing to each subject. Nirmatrelvir and placebo were administered as an extemporaneously prepared oral suspension, and ritonavir was administered as the 100 mg commercial tablet.

Table 80. Study 1001, Part 1: SAD Dosing Scheme

Cohort	N	Period 1	Period 2	Period 3
1	2	150 mg	1500 mg	Placebo/ritonavir
	2	150 mg	Placebo	750 mg/ritonavir
	2	Placebo	1500 mg	750 mg/ritonavir
2	2	500 mg	250 mg/ritonavir	250 mg/ritonavir (fed)
	2	500 mg	Placebo/ritonavir	Placebo/ritonavir (fed)
	2	Placebo	250 mg/ritonavir	250 mg/ritonavir (fed)

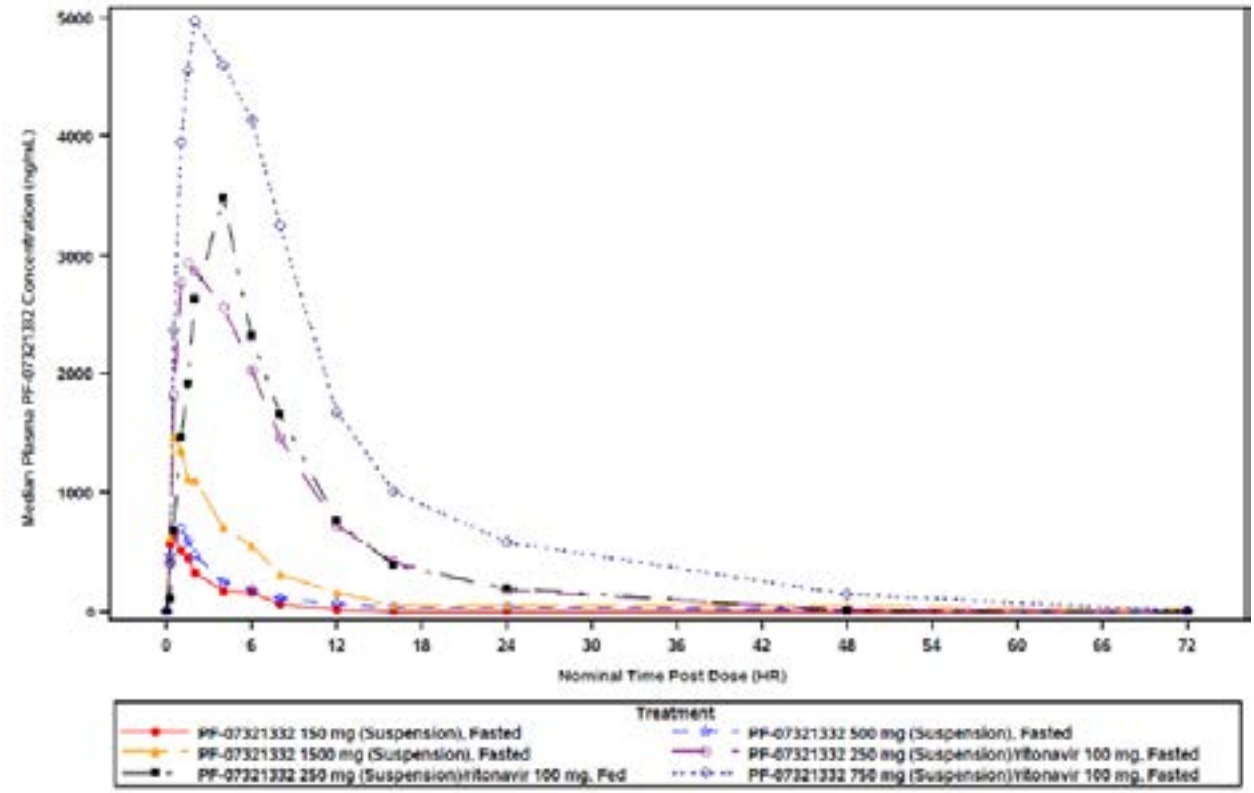
Source: Study 1001.
Abbreviations: N, total number of subjects; SAD, single ascending dose

Blood samples were collected pre-dose and up to 96 hours post dose for measurement of nirmatrelvir plasma concentrations. At the nirmatrelvir dose of 1500 mg (Cohort-1, Period 2), urine and feces samples were collected up to 120 hours post-dose for fluorine-19 nuclear magnetic resonance (^{19}F-NMR) spectroscopy and metabolite profiling.

Nirmatrelvir exposures increased in a less-than dose-proportional manner following administration of nirmatrelvir as an oral suspension at doses of 150 mg, 500 mg, and 1500 mg without ritonavir and 250mg and 750 mg nirmatrelvir co-administered with 100 mg ritonavir. Mean nirmatrelvir plasma concentration-time profiles and PK parameters by treatment are summarized in Figure 21 and Table 81, respectively. Ritonavir administered with nirmatrelvir as a CYP3A inhibitor resulted in higher systemic concentrations of nirmatrelvir (Table 82).

Following administration of a 250 mg oral suspension of nirmatrelvir co-administered with ritonavir 100 mg under fed and fasted conditions, the test/reference ratios of the adjusted geometric means (90% CI) for nirmatrelvir AUC_{last} and C_{max} were 101.53% (90.18%, 114.31%) and 115.30% (99.36%, 133.79%) respectively, for nirmatrelvir/ritonavir fed treatment (Test) compared to nirmatrelvir/ritonavir fasted treatment (Table 81).

Figure 21. Median Plasma Nirmatrelvir Concentration-Time Profiles Following Single Oral Doses of Nirmatrelvir Alone or Enhanced With Ritonavir in Part 1, Study 1001



Source: Study 1001.

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Table 81. Descriptive Summary of Plasma Nirmatrelvir PK Parameters, Part 1: SAD, Study 1001

Parameter [a,b]	NIR 150 mg (N=4)	NIR 500 mg (N=4)	NIR 1500 mg (N=4)	NIR 250 mg/ritonavir 100 mg (N=4)	NIR 250 mg/ritonavir 100 mg (Fed; N=4)	NIR 750 mg/ritonavir 100 mg (N=4)
N1, N2[c, d]	4, 3	4, 2	4, 0	4, 4	4, 4	4, 4
AUC_{inf} (ng.hr/mL)	2247 (42)	5480, 5450	NR	28220 (14)	28640 (17)	66760 (45)
AUC_{last} (ng.hr/mL)	2125 (34)	3753 (29)	10870 (47)	27600 (13)	28020 (16)	64230 (39)
CL/F (L/hr)	66.83 (43)	91.2, 91.8	NR	8.865 (14)	8.735 (17)	11.22 (45)
C_{max} (ng/mL/mg)	667.7 (28)	674.4 (38)	1538 (32)	2882 (25)	3323 (13)	5086 (25)
$t_{1/2}$ (hr)	2.023 ± 0.54556	18.5, 25.6	NR	6.935 ± 1.0794	6.005 ± 1.6502	12.86 ± 8.4196
T_{max} (hr)	0.634 (0.550 - 1.50)	1.00 (0.517 - 1.00)	1.00 (0.533 - 2.00)	2.75 (1.50 - 4.00)	4.00 (4.00 - 4.00)	2.00 (1.50 - 4.00)
Vz/F (L)	190.6 (36)	2440, 3390	NR	87.98 (28)	73.48 (47)	181.9 (35)

Source: Study 1001.
Note: Summary statistics were not presented if fewer than 3 participants had reportable parameter values.
[a.] Geometric Mean (Geometric %CV) for all except: Median (Range) for T_{max} and arithmetic mean ± SD for t1/2
[b.] Individual values were listed when there were less than 3 evaluable measurements
[c.] N1 = Number of participants contributing to the summary statistics.
[d.] N2 = Number of participants where t1/2, AUC_{inf}, $AUC_{inf(dn)}$, CL/F and Vz/F were determined
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing to the last measurable concentration; CL/F, apparent clearance; C_{max}, maximum plasma concentration; N, total number of subjects in the treatment group; NIR, nirmatrelvir; NR, not reported; PK, pharmacokinetic; SAD, single ascending dose; $T_{1/2}$, half-life; T_{max}, time for drug to reach maximum concentration; Vz/F, apparent volume of distribution

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Table 82. Single Dose Pharmacokinetics of Nirmatrelvir Alone vs. Nirmatrelvir With Ritonavir in Healthy Subjects,Study 1001 (Oral Suspension Formulation)

	Geometric Mean (%CV)	
Treatment	**AUC_{last} (ug.hr/mL)**	**C_{max} (ug/mL)**
Nirmatrelvir alone[a]	3.32	0.88
Nirmatrelvir+Ritonavir[b]	27.6	2.88

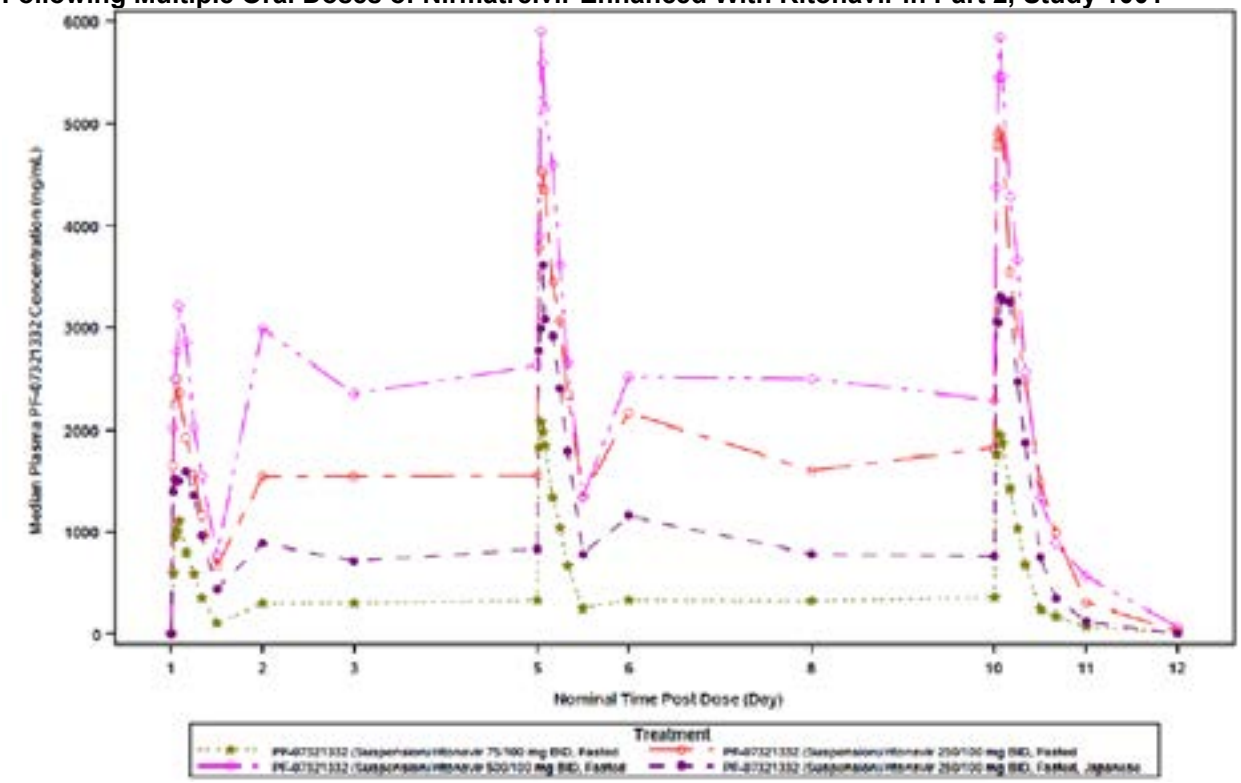
Source: Study 1001.
[a.] 250 mg (oral suspension formulation)
[b.] 250 mg (oral suspension formulation with 100 mg ritonavir (tablet formulation) administered together
Abbreviations: AUC_{last}, area under the concentration-time curve from the time of dosing to the last measurable concentration; C_{max}, maximum plasma concentration; CV, coefficient of variation

Part 2: Multiple Ascending Dose

In Part 2, the multiple dose pharmacokinetics of nirmatrelvir were evaluated in healthy subjects. Nirmatrelvir was administered twice daily for 10 days at doses of 75mg, 250 mg, and 500 mg or placebo. All subjects received ritonavir 100 mg at -12hours, 0hours and 12hours with respect to nirmatrelvir dosing. The dosing regimen of 250mg/100mg twice daily for 10 days was also evaluated in a cohort of Japanese subjects (n=6) to compare the PK with non-Japanese subjects. Six subjects were enrolled per cohort, (4 subjects randomized to nirmatrelvir plus 2 subjects to placebo) and all subjects received the study drug under fasted conditions. A total of 29 subjects were enrolled, 6 were white (21%), 16 were black (55%) and 7 (24%) identified as Asian. Blood samples were collected up to 12 days post dose for measurement of nirmatrelvir plasma concentrations**.**

Following multiple oral doses of nirmatrelvir enhanced with ritonavir, nirmatrelvir exposure on Days 1, 5, and 10 increased in a less than dose proportional manner with an increase in dose. Steady state was achieved around Day 2 for all treatments. Nirmatrelvir accumulation was approximately 2-fold following multiple dosing and values were similar on Day 5 and Day 10. Geometric mean accumulation ratios ranged from 1.8 to 2.1 for AUC_{tau} (R_{ac}) and C_{max} (R_{ac},C_{max}) on Day 10, across all treatments. Urinary recovery of unchanged nirmatrelvir was 64%, 52% and 23% for the 75 mg, 250 mg, and 500 mg nirmatrelvir enhanced with 100 mg ritonavir. Plasma nirmatrelvir concentration-time profiles across all dosing groups and PK parameters by treatment and day are summarized in Figure 22 and Table 83, respectively.

Figure 22. Median Plasma Nirmatrelvir Concentration-Time Profiles Across All Dosing Days Following Multiple Oral Doses of Nirmatrelvir Enhanced With Ritonavir in Part 2, Study 1001



Source: Study 1001.
Abbreviations: BID, twice daily

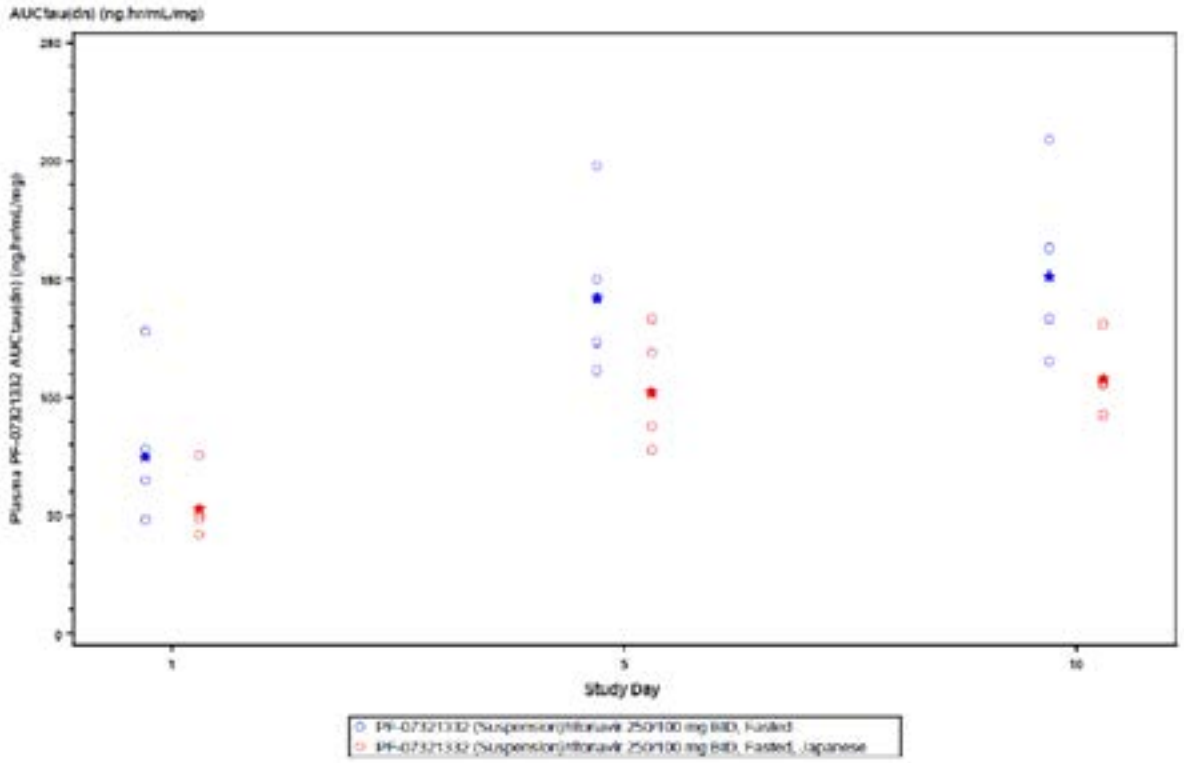
Table 83. Descriptive Summary of Plasma and Urine Nirmatrelvir PK Parameters, Part-2: MAD, Study 1001

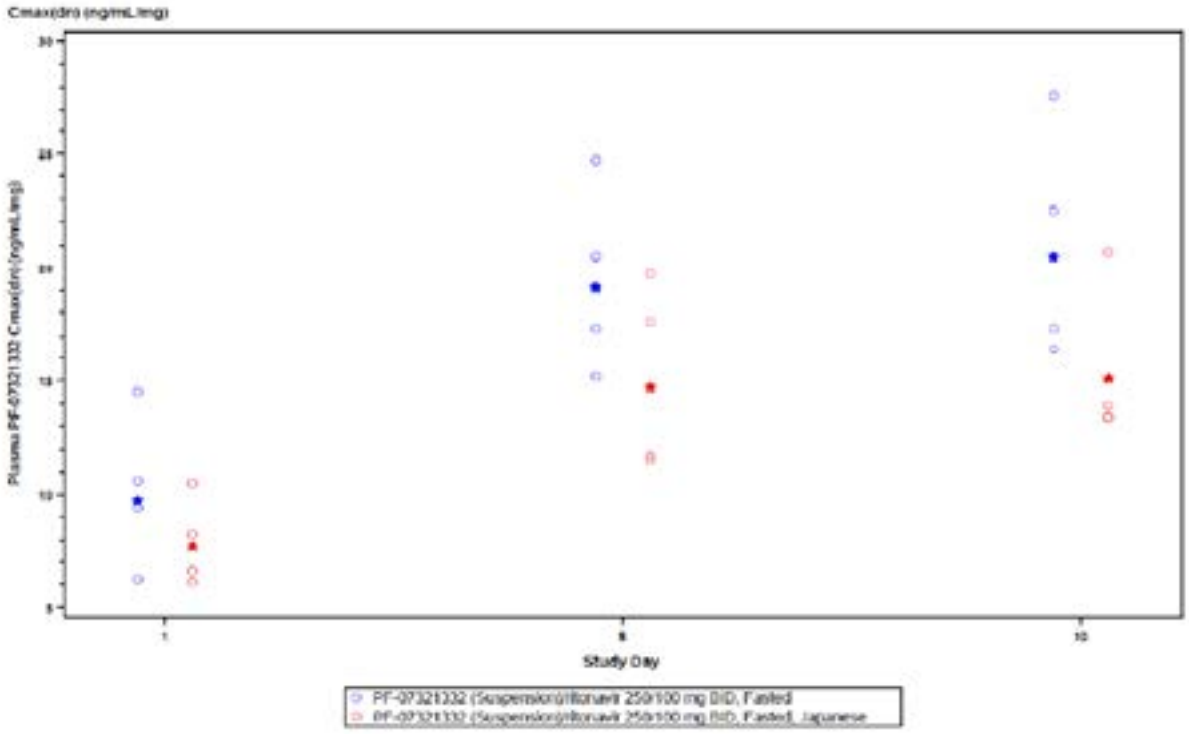
Parameter (unit)	Nirmatrelvir/ Ritonavir 75/100 mg BID (N=4)	Nirmatrelvir/ Ritonavir 250/100 mg BID (N=4)	Nirmatrelvir/ Ritonavir 500/100 mg BID (N=7)	Nirmatrelvir/ Ritonavir 250/100 mg BID Japanese (N=4)
Day 1				
AUC_{tau} (ng.hr/mL)	6017 (33)	18700 (43)	22610 (37)	13130 (26)
C_{max} (ng/mL)	1042 (28)	2435 (36)	3051 (32)	1925 (25)
T_{max} (hr)	1.75 (1.00 - 2.00)	1.50 (1.00 - 4.00)	2.00 (1.50 - 2.17)	2.75 (1.00 - 4.02)
Day 5				
AUC_{tau} (ng.hr/mL)	12570 (17)	35560 (26)	38150 (23)	25480 (26)
C_{max} (ng/mL)	2224 (27)	4774 (21)	5296 (21)	3674 (28)
T_{max} (hr)	1.00 (1.00 - 1.50)	0.750 (0.500 - 1.50)	1.50 (1.00 - 2.02)	1.26 (1.00 - 2.02)
Day 10				
AUC_{tau} (ng.hr/mL)	12650 (16)	37780 (27)	39780 (20)	26930 (15)
C_{max} (ng/mL)	2055 (14)	5123 (24)	5607 (17)	3772 (21)
T_{max} (hr)	1.00 (1.00 - 2.00)	1.00 (1.00 - 2.00)	1.50 (1.00 - 2.00)	1.50 (0.500 - 2.02)

Source: Study 1001.
Abbreviations: AUC_{tau}, area under the concentration-time curve over the dosing interval; BID, twice daily; C_{max}, maximum plasma concentration; MAD, multiple ascending dose; N, total number of subjects in treatment group; T_{max}, time for drug to reach maximum concentration

The geometric mean dose-normalized AUC_{tau} and C_{max} of nirmatrelvir was approximately 30% and 21% to 26% lower in Japanese subjects compared to that observed for non-Japanese subjects across all days (Table 83 and Figure 23). This exposure difference is not expected to be clinically significant. Drug accumulation on Day 10 based on AUC_{tau} (R_{ac}) and C_{max} ($R_{ac,}C_{max}$) ratios was similar between the Japanese and non-Japanese participants. Urinary recovery of unchanged nirmatrelvir was similar between Japanese and non-Japanese participants.

Figure 23. Individual and Geometric Mean Plasma Nirmatrelvir Dose Normalized AUC_{tau} (Upper Panel) and C_{max} (Lower Panel) Values Following Multiple Oral Doses of Nirmatrelvir Enhanced With Ritonavir in Part 2: MAD, Japanese Cohort Comparison, Study 1001





Source: Study 1001.
Abbreviations: AUC_{tau}, area under concentration-time curve over the dosing interval; BID, twice daily; C_{max}, maximum plasma concentration; MAD, multiple ascending dose

Part 3: Relative Bioavailability and Food Effect

Part 3 was a randomized open-label study to evaluate relative bioavailability and food effect of an early 250 mg oral tablet formulation relative to the 250 mg oral suspension used in part 1 and part 2. Subjects (n = 12 per group) received a 250 mg nirmatrelvir tablet as a single dose in either the fasted or fed state, or a single 250 mg dose of the nirmatrelvir suspension (without ritonavir). The 250 mg tablet strength when dosed with ritonavir was expected to be in the efficacious dose range and was chosen based on the PK, safety and tolerability data from single ascending dose (SAD) and multiple ascending dose (MAD) cohorts, and the available tablet strength.

Under fasting conditions, nirmatrelvir plasma exposure for the tablet was lower compared to the suspension following a single 250 mg oral dose of nirmatrelvir, with approximately 19% and 44% lower geometric mean AUC_{last} and C_{max} values, respectively (Table 84).

Nirmatrelvir plasma exposure was higher for the fed treatment following administration of a 250 mg high-fat, high-calorie meal, with approximately 1.5 and 2.4-fold higher geometric mean AUC_{last} and C_{max} values for fed treatment compared to the fasted treatment, respectively (Table 85).

Table 84. Statistical Summary of Plasma Nirmatrelvir PK Parameters – Relative Bioavailability, Part 3, Study 1001

	Adjusted Geometric Mean			
Parameter	Nirmatrelvir 250 mg Tablet (Fasted)	Nirmatrelvir 250 mg Suspension (Fasted)	Ratio (Test/Reference) of Adjusted Geometric Means	90% CI for Ratio
AUC_{inf} (ng.hr/mL)	2955	3884	0.76	(0.60, 0.96)
AUC_{last} (ng.hr/mL)	2695	3318	0.81	(0.69, 0.95)
C_{max} (ng/mL)	497.8	883.1	0.56	(0.43, 0.73)

Source:Study 1001.
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; AUC_{last}, area under the concentration-time curve tfrom the time of dosing to the last measurable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; PK, pharmacokinetic

Table 85. Statistical Summary of Plasma Nirmatrelvir PK Parameters – Food Effect, Part 3, Study 1001

	Adjusted Geometric Means			
Parameter	Nirmatrelvir 250 mg Tablet (Fed)	Nirmatrelvir 250 mg Tablet (Fasted)	Ratio (Test/Reference) of Adjusted Geometric Means	90% CI for Ratio
AUC_{inf} (ng.hr/mL)	4337	2955	1.47	(1.18, 1.81)
AUC_{last} (ng.hr/mL)	4012	2695	1.49	(1.27, 1.75)
C_{max} (ng/mL)	1219	497.8	2.45	(1.89, 3.18)

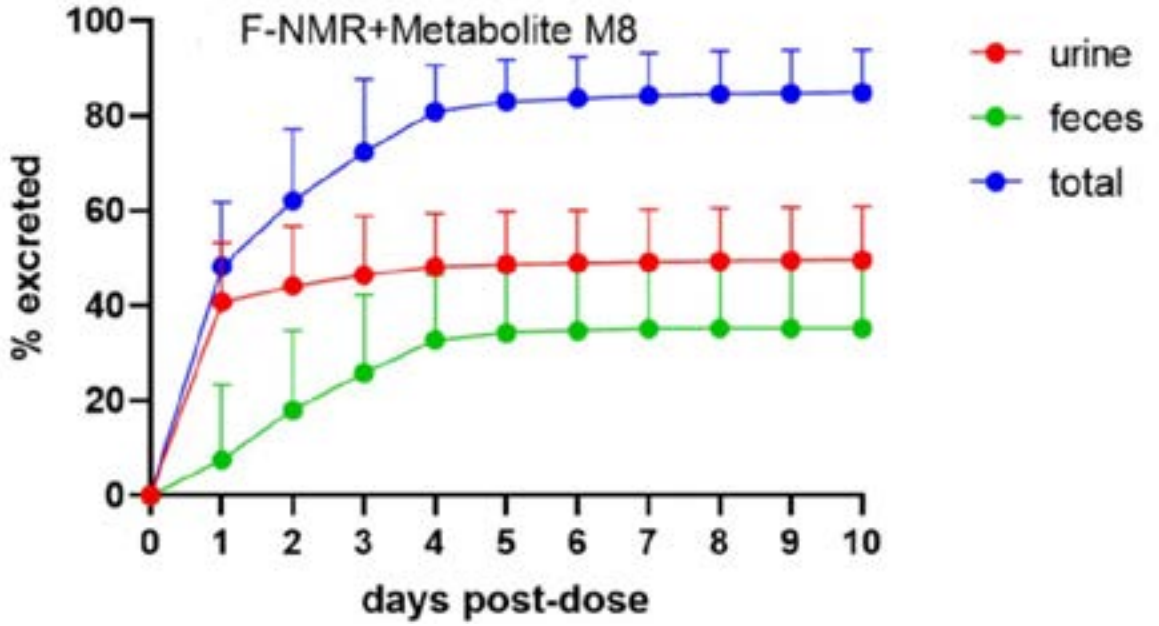
Source:Study 1001.
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; AUC_{last}, area under the concentration-time curve tfrom the time of dosing to the last measurable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; PK, pharmacokinetic

Part 4: Metabolism and Excretion

Part 4 was conducted to determine the excretion of drug-related material in urine and feces after a single oral administration of nirmatrelvir with ritonavir. A single oral dose of 300 mg nirmatrelvir oral suspension co-administered with ritonavir (4 doses of 100 mg at -12, 0, 12, and 24 hours relative to nirmatrelvir), was administered to a total of 6 healthy subjects. Excretion of nirmatrelvir-related material in urine and feces was quantified using ^{19}F-NMR and high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) methods.

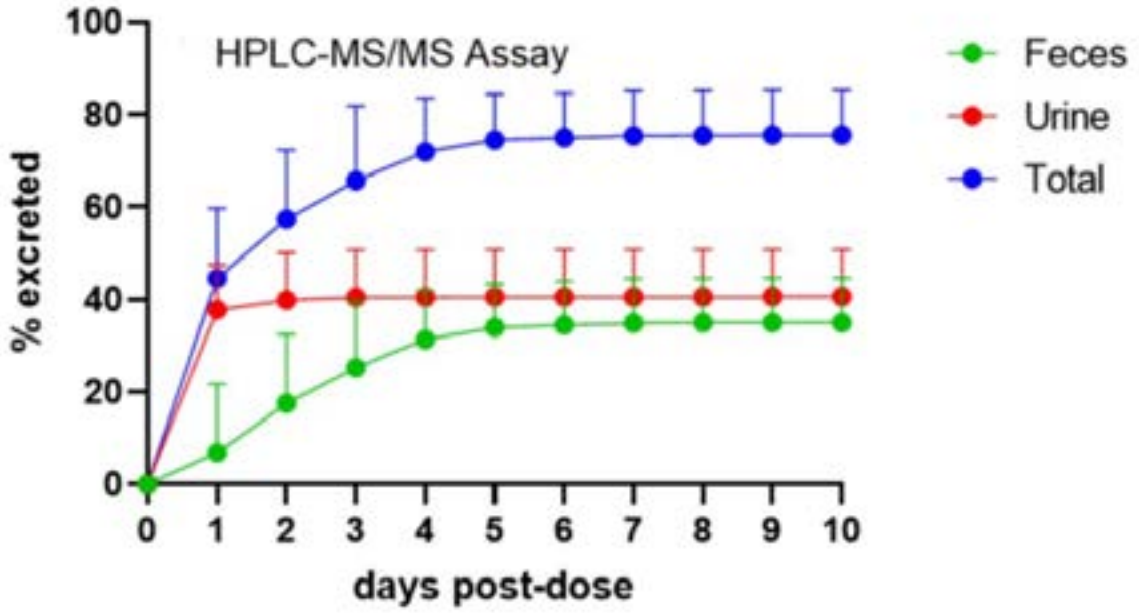
Overall mean ± SD (range) mass recovery of nirmatrelvir-related material in excreta (urine and feces) was 84.9% ± 8.9% (70.7%, 95.5%), which included 80.7% ± 8.0% nirmatrelvir by quantitative ^{19}F-NMR and 4.2% ± 1.3% excreted as metabolite M8 (^{19}F-NMR silent due to loss of trifluoroacetyl group) quantified by UHPLC-HRMS (ultra-high-performance liquid chromatography-high resolution mass spectrometry). The excretion into urine and feces was 49.6% and 35.3% of the dose, respectively (Figure 24). Quantifying nirmatrelvir and M5 (most prevalent metabolite in preliminary metabolite profiling) by HPLC-MS/MS showed overall mean ± SD mass recovery of 75.6 ± 9.7% with 40.6% and 35.0% excretion into urine and feces, respectively (Figure 25).

Figure 24. Cumulative Mean (+ SD) Excretion Nirmatrelvir-Related Material in Urine and Feces of Healthy Participants Following Oral Administration of Nirmatrelvir Suspension Enhanced With Ritonavir Measured by ^{19}F-NMR Spectroscopy



Source:Study 1001.
Abbreviations: M8, metabolite 8; NMR, nuclear magnetic resonance; SD, standard deviation

Figure 25. Cumulative Mean (+ SD) Excretion of Nirmatrelvir and M5 in Urine and Feces of Healthy Participants Following Oral Administration of Nirmatrelvir Suspension Enhanced With Ritonavir Using HPLC-MS/MS



Source: Study 1001.
Abbreviations: HPLC, high-performance liquid chromatography; M5, metabolite 5; MS/MS, tandem mass spectrometry; SD, standard deviation

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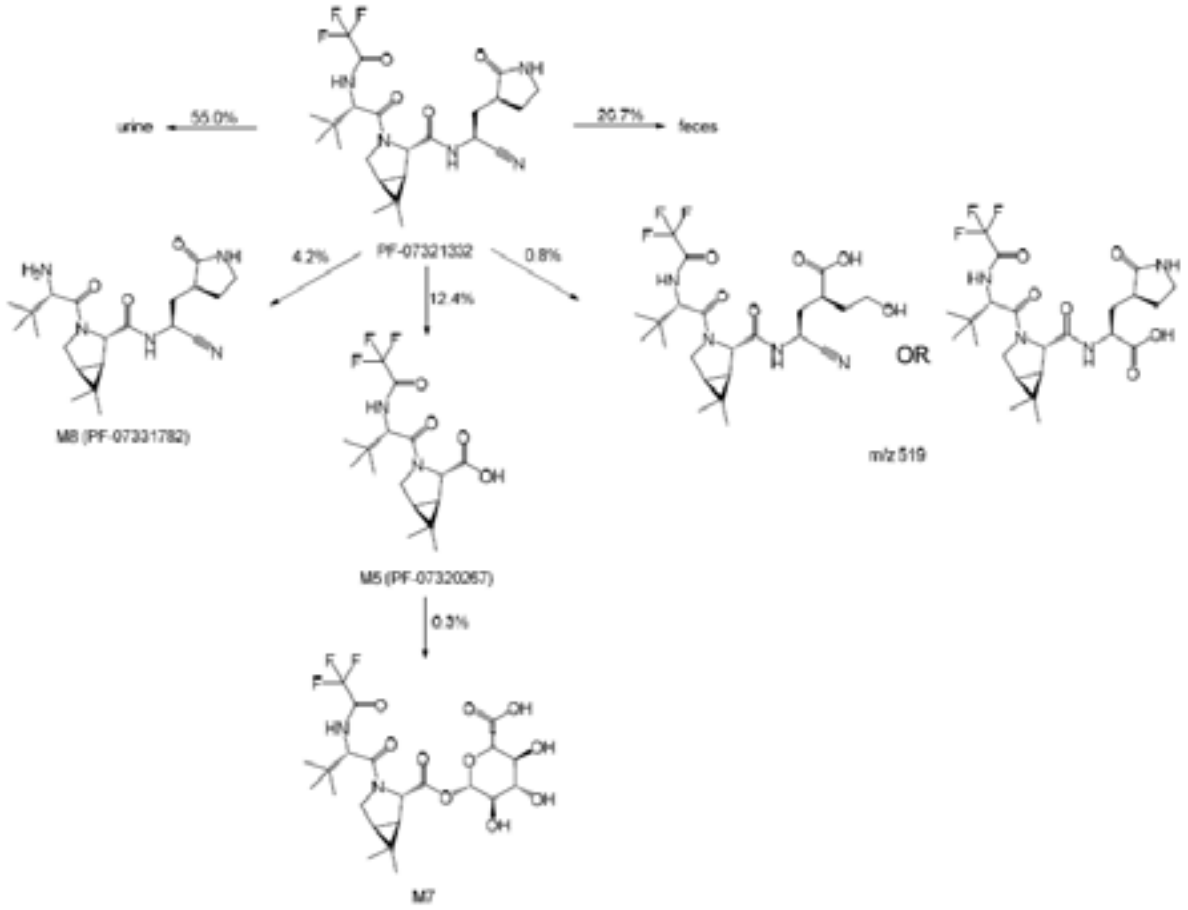
In plasma, the only drug-related entity quantifiable by ^{19}F-NMR was unchanged nirmatrelvir. In excreta, nirmatrelvir was the predominant drug-related entity. Unchanged nirmatrelvir represented the majority of the drug-related material, with 55.0% in urine and 27.5% in feces. These values were calculated based on dose normalization to 95.8% mass balance (i.e., 100% minus the 4.2% of dose comprised by non-fluorine containing metabolite M8). Metabolite M5, arising via hydrolysis, was present at 12.1% of dose with almost all in the feces. All other fluorine-containing metabolites were minor (<1% of dose), and M8 was 4.2% of dose (Table 86). A metabolic scheme for nirmatrelvir is shown in Figure 26.

Table 86. Summary of Metabolites of Nirmatrelvir in Urine and Feces of Healthy Participants Following Oral Administration of Nirmatrelvir Suspension Enhanced With Ritonavir

	% of Normalized Dose		
Metabolite	**Urine**	**Feces**	**Total**
Nirmatrelvir	55	27.5	82.5
M5	0.4	11.7	12.1
M8	0.3	ND	0.3
m/z 519	ND	0.8	0.8
M8	2.6	1.6	4.2
Total	58.4	41.6	100

Source: Study 1001.
Abbreviations: M, metabolite; m/z, mass-to-charge ratio; ND, not detected

Figure 26. Summary of Profile of Nirmatrelvir Metabolism and Disposition in Healthy Participants

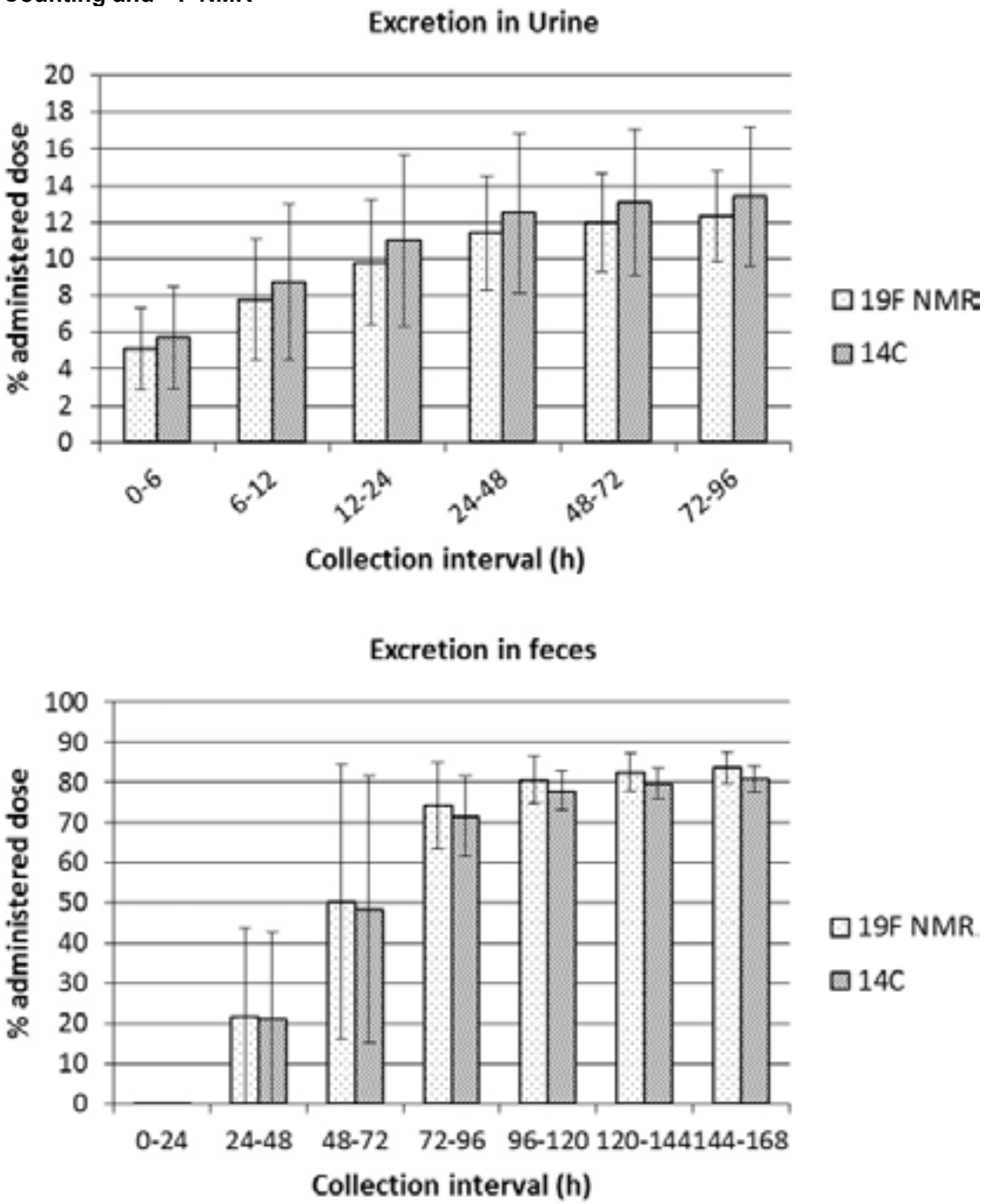


Source: Study 1001.
Abbreviations: M, metabolite; m/z, mass-to-charge ratio

The review team found the use of ^{19}F-NMR and UHPLC-HRMS to be an acceptable alternative to a radiolabeled mass balance study given 1) a published clinical study cross validating ^{14}C data with that obtained by ^{19}F-NMR and 2) additional nonclinical and clinical data provided by the Applicant to quantify the absorption, distribution, metabolism, and excretion (ADME) properties of nirmatrelvir.

The capability of ^{19}F-NMR to characterize the ADME properties of a drug was demonstrated in a clinical study by James et al (James et al. 2017). In this study, remaining samples from a ^{14}C human mass balance study conducted on Alpelisib, a compound for the treatment of solid tumors, were used to cross-validate the data obtained by ^{19}F-NMR. Mean cumulative excretion of the dose in urine and feces was comparable between the ^{14}C radiolabeled and ^{19}F-NMR samples (Figure 27). Comparable data was also obtained for total drug related material in plasma and metabolite profiling and identification in plasma and excreta.

Figure 27. Mean Cumulative Excretion of Dose in Urine and Feces After a Single Oral Dose of 400 mg [^{14}C]BYL719 (Alpelisib) to Four Healthy Volunteers, Determined by Liquid Scintillation Counting and ^{19}F NMR



Source: (James et al. 2017).
Abbreviations: NMR, nuclear magnetic resonance

Additional nonclinical and clinical data provided by the Applicant included 1) characterization of the metabolic profile in animals and 2) Phase 1 urine and plasma data. Animal data showed rats and monkeys to have a similar metabolic profile, with no notable human specific metabolites or metabolite specific toxicities reported (see Section 13). Phase 1 plasma and urine data showed similar urinary recovery, with 52% in the MAD arm of Study 1001 (250 mg nirmatrelvir/ 100

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mg ritonavir dose) and 31% in subjects with normal renal function in Study 1011 (100mg nirmatrelvir/ 100 mg ritonavir dose), excreted as unchanged nirmatrelvir, respectively.

Part 5: Supratherapeutic Exposure

Part 5 was a double-blind (participant and investigator blinded and sponsor unblinded), randomized, 2-sequence, cross-over design to explore safety, tolerability, and PK at supratherapeutic exposure of nirmatrelvir. For each period, subjects received 2250 mg of nirmatrelvir as 3 split doses of 750 mg at 0 hours, 2 hours, and 4 hours, pharmacokinetically enhanced with ritonavir (3 doses of 100 mg at -12, 0 and 12 hours relative to nirmatrelvir) or placebo in the fasted state on Day 1 (n = 10 per group). Doses were split in this part of the study to achieve supratherapeutic exposures of nirmatrelvir that were not achieved in the SAD and MAD cohorts due to the less than dose proportional increase in exposure. Plasma samples for measurement of nirmatrelvir PK were obtained pre-dose and up to 96 hours post dose or at early termination if applicable.

Nirmatrelvir pharmacokinetic parameters following a supratherapeutic dose of 2250 mg administered with ritonavir are presented in Table 87. The safety data, including adverse events (AEs), laboratory abnormalities, vital signs, and ECGs indicate that nirmatrelvir has an acceptable safety and tolerability profile in healthy adult subjects at supratherapeutic exposures.

Table 87. Descriptive Summary of Plasma Nirmatrelvir PK Parameters Following Administration of Nirmatrelvir (Suspension)/Ritonavir 100 mg in Part 5, Study 1001

Parameter	Measurement
N	10
AUC_{inf} (µg.hr/mL)	188.82 (35)
CL/F (L/hr)	3.970 (35)
C_{max} (µg/mL)	15.94 (27)
$T_{1/2}$ (hr)	7.45 ± 2.94
T_{max} (hr)	5.0 (3.02 – 6.03)

Source: Study 1001.
Note: Geometric Mean (Geometric %CV) for all except: Median (Range) for T_{max} and arithmetic mean ± SD for t1/2
Note: Nirmatrelvir 2250 mg Was Divided Into Three Doses of 750 mg Administrated at 0h, 2h and 4h; Ritonavir Dosed at -12h, 0h and 12h post-dose
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; CL/F, apparent clearance; C_{max}, maximum plasma concentration; N, total number of subjects in the treatment group; PK, pharmacokinetic; $T_{1/2}$, half-life; T_{max}, time for drug to reach maximum concentration

Renal Impairment

In Study 1011, the PK of nirmatrelvir was evaluated in the fasted state after a single 100 mg dose of nirmatrelvir co-administered with 100mg ritonavir -12, 0 and 12 hours relative to nirmatrelvir in the following groups:

- Mild renal impairment: eGFR 60 to <90 mL/min
- Moderate renal impairment: eGFR >30 to <60 mL/min
- Severe renal impairment: eGFR <30 and not requiring dialysis
- Normal renal function: eGFR >90 mL/min

The 100 mg nirmatrelvir dose (one third the total daily dose) was chosen due to the less-than dose-proportional increase in exposures within the 250 mg to 750 mg dose range evaluated, and

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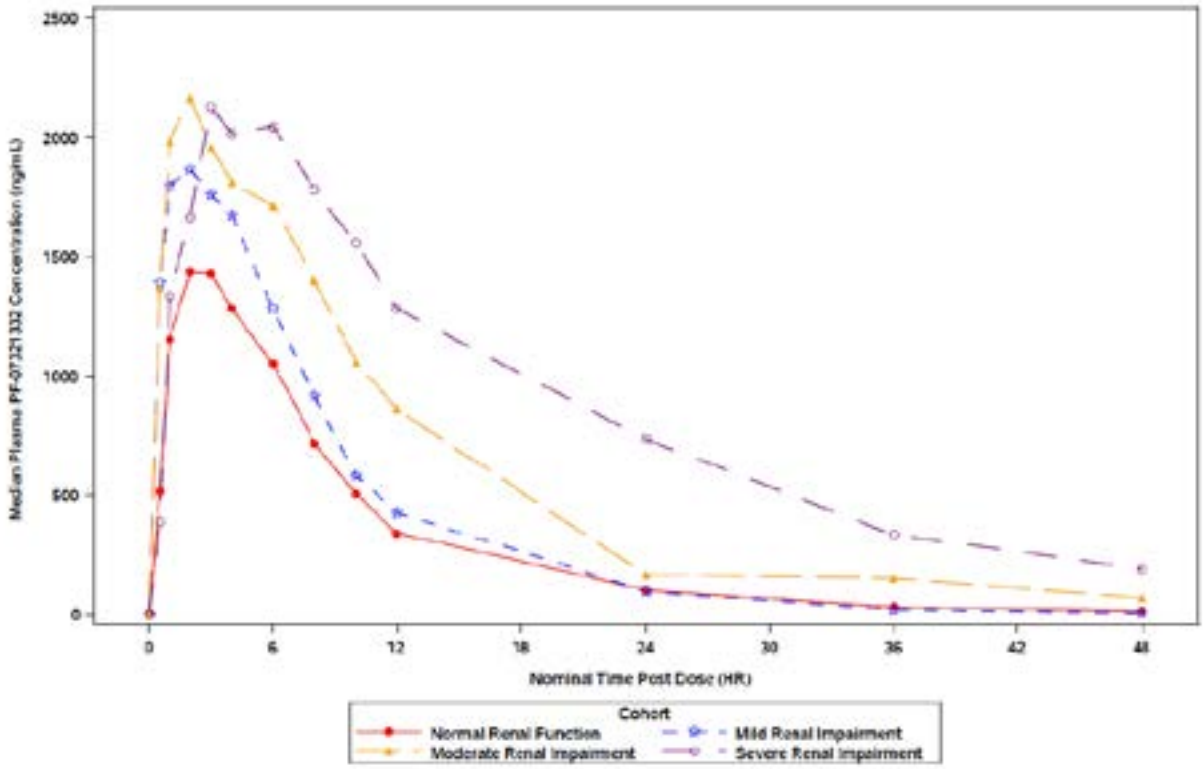
the anticipated higher exposures in renal impairment. As ritonavir is not eliminated renally and is not expected to be significantly altered by renal impairment, no dose reduction of ritonavir was considered necessary for subjects with renal impairment.

Blood and urine samples were collected through 48 hours for measurement of nirmatrelvir in plasma. Given that nirmatrelvir has a low extent of plasma protein binding (approximately 69%), a description and analysis of nirmatrelvir PK in terms of total concentrations is sufficient since changes in PK resulting from alterations in protein binding due to impaired renal function are generally expected to be small relative to those in patients with normal renal function.

Nirmatrelvir systemic exposure increased with increasing severity of renal impairment, with mean AUC_{inf} values of approximately 24%, 87%, and 204% higher for the mild, moderate, and severe renal impairment groups, respectively, compared to the normal renal functional group. Geometric mean C_{max} values also increased approximately 30%, 38%, and 48% for the mild, moderate, and severe renal impairment groups, respectively, compared to the normal renal functional group. See Figure 28, Table 88 and Table 89.

Urinary recovery of unchanged nirmatrelvir was 31.2%, 42.7%, 30.8%, and 18.5% for the normal functional group, mild, moderate, and severe renal impairment groups, respectively.

Figure 28. Median Plasma Nirmatrelvir Concentration-Time Plot, Following a Single Oral Dose of Nirmatrelvir/Ritonavir, Linear Scale



Source: Study 1011.

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Table 88. Descriptive Summary of Plasma and Urine Nirmatrelvir PK Parameters -Study 1011

Parameter	Normal Renal Function (N=10)	Mild Renal Impairment (N=8)	Moderate Renal Impairment (N=8)	Severe Renal Impairment (N=8)
N1, n[a,b]	10, 10	8, 8	8, 6	8, 7
AUC_{inf} (ng.hr/mL)	14460 (20)	17910 (30)	27110 (27)	44040 (33)
AUC_{last} (ng.hr/mL)	14270 (20)	17770 (30)	26660 (21)	39420 (28)
C12 (ng/mL)	341.9 (35)	438.0 (30)	785.6 (33)	1213 (33)
C24 (ng/mL)	99.10 (35)	112.8 (55)	179.1 (108)	694.2 (42)
CL/F (L/hr)	6.913 (20)	5.581 (30)	3.689 (27)	2.270 (33)
C_{max} (ng/mL)	1600 (31)	2077 (29)	2210 (17)	2369 (38)
$t_{1/2}$ (hr)	7.725 ± 1.8234	6.606 ± 1.5344	9.948 ± 3.4171	13.37 ± 3.3225
T_{max} (hr)	2.000 (1.00 - 4.00)	2.000 (1.00 - 3.00)	2.500 (1.00 - 6.00)	3.000 (1.00 - 6.05)
VZ/F (L)	74.95 (35)	51.95 (32)	50.34 (27)	42.73 (26)
Ae (mg)	31.20 (45)	42.65 (23)	30.83 (56)	18.46 (50)
CLr (L/hr)	2.180 (50)	2.395 (33)	1.154 (71)	0.4398 (73)

Source: Study 1011.
Note: Geometric mean (Geometric %CV) for all: except Median (Range) for T_{max} and arithmetic mean ± SD for t1/2.
[a.] N1 = Number of participants contributing to the summary statistics.
[b.] n = Number of participants contr buting to the summary statistics for t1/2, AUC_{inf}, CL/F and VZ/F.
Abbreviations: Ae, amount of unchanged drug excreted in urine; AUC_{inf}, area under the concentration-time curve to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing to the last measurable concentration; C12, 12-hour postdose plasma concentration; C24, 24-hour postdose plasma concentration; CL/F, apparent clearance; CLr, renal clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; N, total number of participants in the cohort in the indicated population; PK, pharmacokinetic; SD, standard deviation; $t_{1/2}$, half-life; T_{max}, time for drug to reach maximum concentration; VZ/F, apparent volume of distribution

Table 89. Statistical Summary of Plasma Nirmatrelvir PK Parameters, Study 1011

Parameter	Renal Impairment (n=8/group)	Test	Reference	Ratio	90% CI
C_{max} (ng/mL)	Mild	2077	1600	1.29	(1.02,1.65)
	Moderate	2210	1600	1.38	(1.13, 1.69)
	Severe	2369	1600	1.48	(1.11, 1.97)
AUC_{inf} (ng.hr/mL)	Mild	17910	14460	1.24	(0.99, 1.54)
	Moderate	27110	14460	1.87	(1.49, 2.36)
	Severe	44040	14460	3.04	(2.38, 3.90)

Source: Study 1011.
Note: Values in table are the adjusted geometric means.
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; n, number of subjects in sample; PK, pharmacokinetic

There was an imbalance in safety findings between subjects with severe renal impairment and subjects with normal to moderate renal impairment, with one of the eight subjects with severe renal impairment developing a serious adverse event of moderate acute kidney injury the day after receiving nirmatrelvir (see Section 8.1.2). While it is unclear if these safety findings were related to nirmatrelvir receipt or to the increased comorbidities generally associated with severe renal impairment, this finding raises safety concerns about nirmatrelvir/ritonavir dosing in patients with severe renal impairment (as the therapeutic dose would be higher than 100 mg nirmatrelvir administered with ritonavir).

Study 1028 is an ongoing safety and pharmacokinetic study evaluating PAXLOVID as treatment of mild-to-moderate COVID-19 in patients with severe renal impairment (for both patients requiring and not requiring hemodialysis). This study is evaluating a PAXLOVID dose of 300 mg nirmatrelvir/100mg ritonavir on Day 1 followed by 150 mg nirmatrelvir/100 mg ritonavir daily on Days 2 to 5 of treatment in subjects with severe renal impairment, which was determined based on population PK modeling and the relative change in CL resulting from renal

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impairment from study 1011. Data from this study will inform the appropriate dosing regimen in patients with severe renal impairment.

Hepatic Impairment

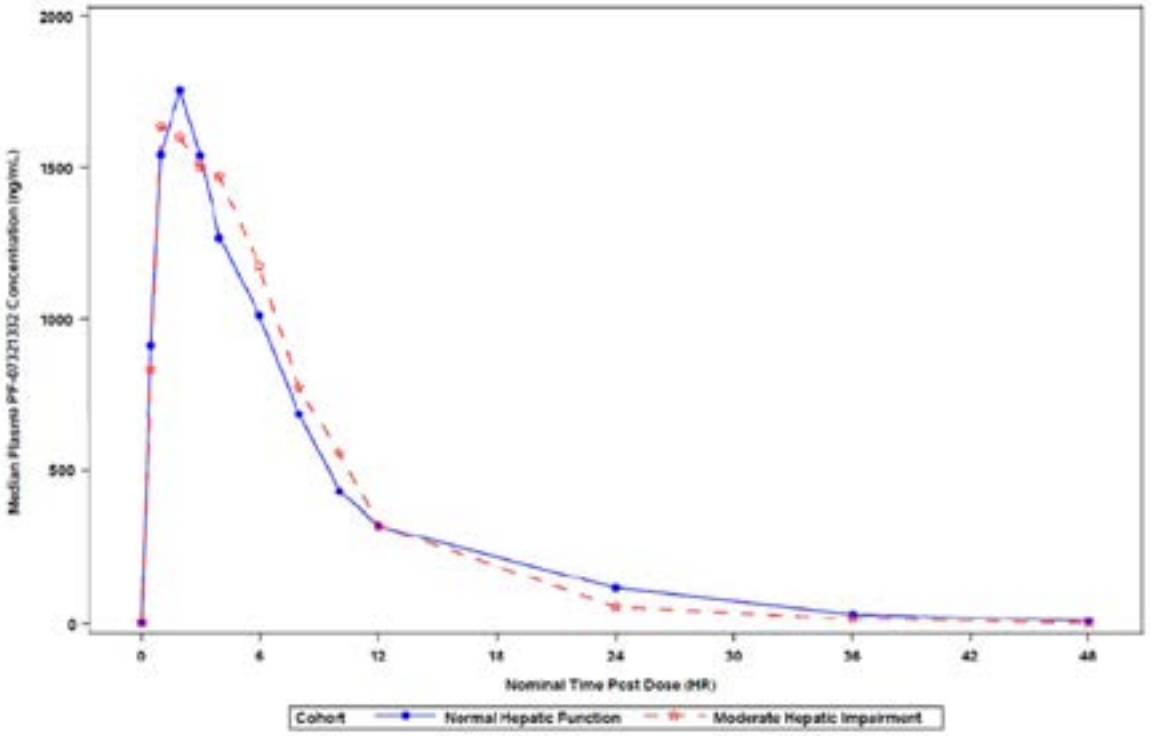
In study 1010, the PK of nirmatrelvir and ritonavir was evaluated in the fasted state in 8 subjects with moderate hepatic impairment (Child-Pugh Class B [score of 7 to 9)] and 8 matched controls with normal hepatic function. All subjects received a single 100 mg dose of nirmatrelvir (as an early 100 mg tablet formulation) administered orally in combination with ritonavir administered as a 100 mg dose at -12, 0, 12, and 24 hours relative to nirmatrelvir dosing.

Blood samples were collected for plasma PK assessment of nirmatrelvir and ritonavir pre-dose through 12 hours on Day 1, at 24 and 36 hours on Day 2, 48 hours on Day 3 and at early termination (if before 48 hours post-dose for nirmatrelvir), if needed. Urine samples were collected at intervals of 0-24 hours after nirmatrelvir dosing on Day 1.

Only total drug concentrations were reported for nirmatrelvir and ritonavir. A description and analysis of nirmatrelvir PK in terms of total concentrations was sufficient for nirmatrelvir since it is not extensively bound to plasma proteins. Despite the increase in ritonavir exposures (as described in next paragraph), nirmatrelvir systemic exposure was nearly identical between the normal hepatic function group and the moderate hepatic impairment group (See Figure 29, Table 90 and Table 91).

Ritonavir systemic exposure following the second dose was higher in subjects with moderate hepatic impairment compared to those with normal hepatic function. Geometric mean ritonavir AUC_{12} and C_{max} in subjects with moderate hepatic impairment was approximately 1.68- and 1.84-fold higher compared to those with normal hepatic function, respectively (See Figure 30 and Table 92). These results are consistent with those of previous studies which showed an AUC_{12} increase of approximately 50 to 60% in moderate hepatic impairment (matched healthy control subjects and cirrhotic patients (matched to a control group of HIV-infected patients with normal liver function test results and without history of HCV or HBV co-infection) receiving the 100mg booster dose in combination with a protease inhibitor, respectively (Seminari et al. 2007; Sekar et al. 2010). It should be noted that these results are based on total concentrations and ritonavir is highly bound to plasma proteins (98-99%). No significant laboratory trends or clinically relevant changes in vital signs were observed in study 1010 after single dose of nirmatrelvir pharmacokinetically enhanced by 100 mg ritonavir. Similarly, the current ritonavir and boosted protease inhibitor labels do not recommend a dose adjustment for mild or moderate hepatic impairment and contribute additional safety data for the use of ritonavir in COVID-19 patients with mild or moderate hepatic impairment. PAXLOVID is not recommended in patients with severe hepatic impairment (Child-Pugh Class C) as no PK or safety data regarding the use of nirmatrelvir or ritonavir are available in this population.

Figure 29. Median Plasma Nirmatrelvir Concentration-Time Profiles Following a Single 100 mg Oral Dose of Nirmatrelvir Co-Administered With Ritonavir



Source: Study 1010.

Table 90. Descriptive Summary of Plasma and Urine Nirmatrelvir PK Parameters, Study 1010

Parameter (Unit)	Normal Hepatic Function (N=8)	Moderate Hepatic Impairment (N=8)
AUC_{inf} (ug.hr/mL)	15.24 (36)	15.06 (43)
AUC_{last} (ug.hr/mL)	14.97 (36)	14.86 (43)
CL/F (L/hr)	6.560 (36)	6.650 (43)
C_{max} (ug/mL)	1.886 (20)	1.923 (48)
$t_{1/2}$ (hr)	7.209 ± 2.0990	5.448 ± 1.5743
T_{max} (hr)	2.000 (0.550 - 2.08)	1.500 (1.00 - 2.00)
VZ/F (L)	65.51 (39)	50.37 (40)
Ae24 (mg)	35.66 (31)	54.23 (23)
CLr (L/hr)	2.509 (46)	3.738 (49)

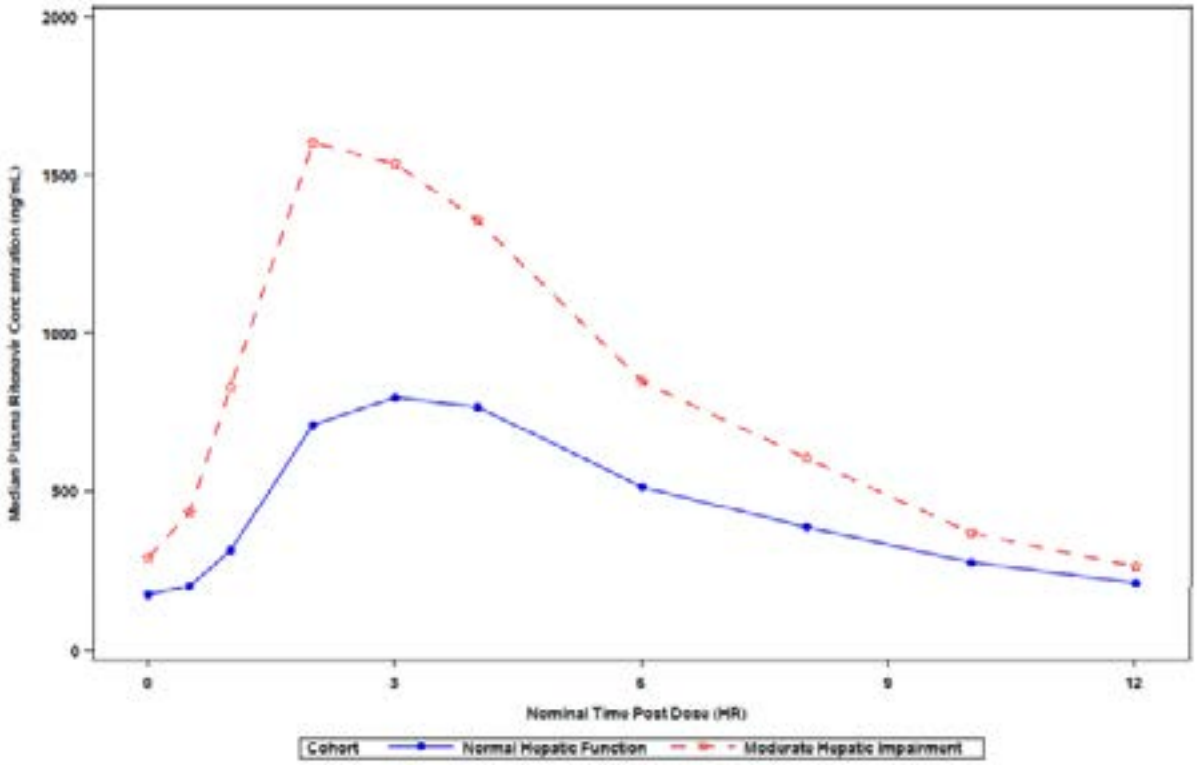
Source: Study 1010.
Note: Geometric Mean (Geometric %CV) for all: except Median (Range) for T_{max} and Arithmetic Mean ± SD for t1/2.
Abbreviations: Ae24, amount of unchanged drug excreted in urine at 24 hours; AUC_{inf}, area under the concentration-time curve to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing to the last measurable concentration; CL/F, apparent clearance; CLr, renal clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; N, total number of subjects; PK, pharmacokinetic; SD, standard deviation; t1/2, half-life; T_{max}, time for drug to reach maximum concentration; VZ/F, apparent volume of distribution

Table 91. Statistical Summary of Plasma Nirmatrelvir PK Parameters, Study 1010

Nirmatrelvir PK Parameter	Moderate Hepatic Impairment	Normal Hepatic Function	Ratio	90% CI
AUC_{inf} (ug.hr/mL)	15.06	15.24	0.99	(0.71,1.38)
C_{max} (ug/mL)	1.92	1.89	1.02	(0.74, 1.40)

Source: Study 1010.
Note: Values in table are the adjusted geometric means.
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; PK, pharmacokinetic

Figure 30. Median Plasma Ritonavir Concentration-Time Profiles Following Second Dose of Ritonavir, Study 1010



Source: Study 1010

Table 92. Descriptive Summary of Plasma Ritonavir PK Parameters, Study 1010

Parameter (Unit)	Normal Hepatic Function (N=8)	Moderate Hepatic Impairment (N=8)
AUC_{12} (ug.hr/mL)	5.912 (57)	9.929 (36)
C_{max} (ug/mL)	0.8768 (50)	1.611 (42)
T_{max} (hr)	3.000 (2.00 - 4.00)	2.000 (1.00 - 4.00)

Source: Study 1010.
Note: Geometric Mean (Geometric %CV) for all: except Median (Range) for T_{max}.
Abbreviations: AUC_{12}, area under the concentration-time curve to 12 hours; CI, confidence interval; C_{max}, maximum plasma concentration; N, number of total subjects; PK, pharmacokinetic; T_{max}, time for drug to reach maximum concentration

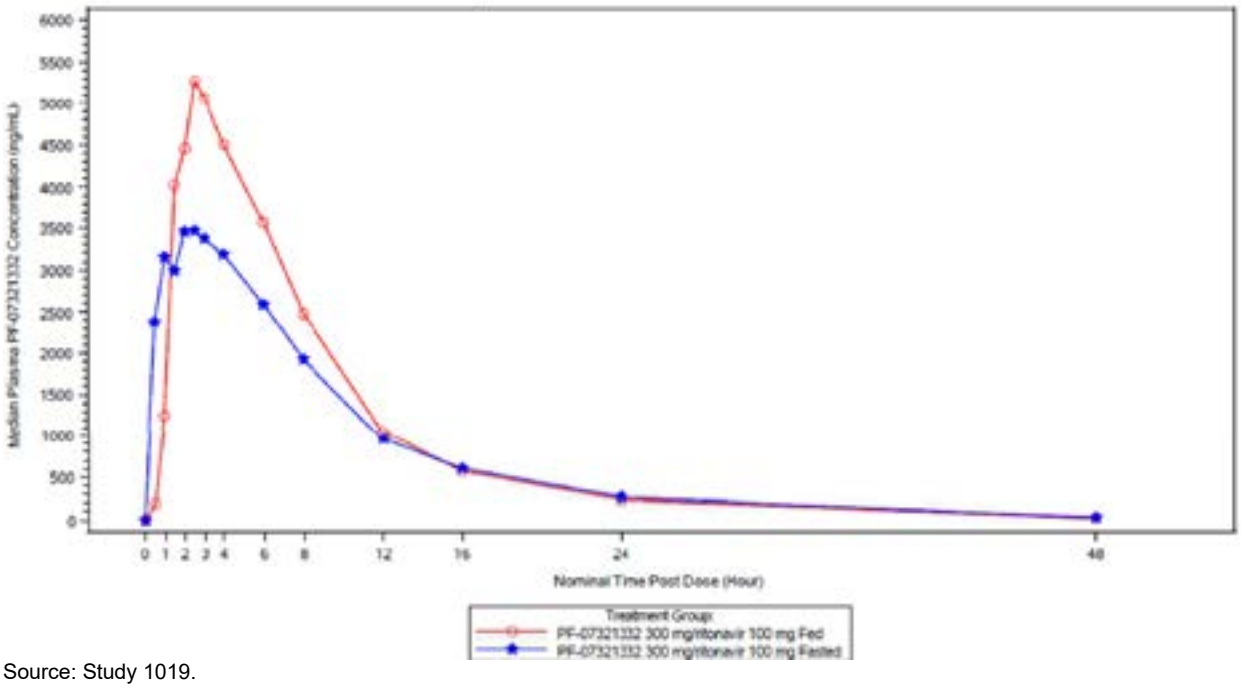
Food Effect Assessment with Commercial Tablet Formulation

The effect of a high-fat meal on the relative bioavailability of nirmatrelvir boosted with ritonavir was evaluated in 24 healthy adults in Study 1019. The study consisted of 2 treatments: a single oral dose of nirmatrelvir 300 mg (2x 150 mg tablets) under fasted conditions and 3 doses of

ritonavir 100 mg at -12-hour, 0 hour and 12 hour relative to nirmatrelvir dosing (Treatment A; n = 12), and a single oral dose of nirmatrelvir 300 mg (2 × 150 mg tablets) under fed conditions with 3 doses of ritonavir 100 mg at -12 hour, 0 hour and 12 hour relative to nirmatrelvir dosing (Treatment B; n=12). Subjects in Treatment B consumed a high-fat (approximately 50% of total caloric content of the meal), high-calorie (approximately 800 to 1000 calories) breakfast over a 20-minute interval with nirmatrelvir/ritonavir administered within 10 minutes of completion of the meal.

Blood samples were collected through 48 hours post dose for measurement of nirmatrelvir plasma concentrations. Overall, there was an increase in the systemic exposure of nirmatrelvir under fed conditions, with geometric mean values of approximately 20% higher nirmatrelvir AUC and 61% higher C_{max}. See Figure 31 and Table 93. The nirmatrelvir exposures changes in this study are higher than those noted in Study 1001, where coadministration of a nirmatrelvir suspension boosted with ritonavir resulted in 1.5% increase in AUC and 15% increase in C_{max} of nirmatrelvir. In addition, all subjects in the Phase 2/3 pivotal study, EPIC-HR, were dosed without regard to food based on the preliminary food effect results in the first in human study 1001. This was also the basis for the recommendation to take PAXLOVID without regard to food under the EUA, since the dedicated food effect study with the commercial formulation had not yet been conducted. Given nirmatrelvir/ritonavir demonstrated efficacy and was generally well tolerated in the pivotal Phase 2/3 study, PAXLOVID can be dosed without regard to food.

Figure 31. Median Plasma Nirmatrelvir Concentration-Time Profiles Following Nirmatrelvir/Ritonavir Administration Under Fed or Fasted Conditions



Source: Study 1019.

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Table 93. Statistical Summary of Plasma Nirmatrelvir PK Parameters, Study 1019

Parameter (unit)	Nirmatrelvir 300mg/ritonavir 100mg Fed (Test)	Nirmatrelvir 300 mg/ritonavir 100 mg Fasted (Reference)	Ratio (Test/Reference) of Adjusted Geometric Means	90% CI of Ratio
AUC_{inf} (ng.hr/mL)	44050	36810	1.20	(1.09, 1.32)
C_{max} (ng/mL)	5951	3696	1.61	(1.39, 1.86)

Source: Study 1019.
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; PK, pharmacokinetic

Effect of Itraconazole on Nirmatrelvir/Ritonavir

Study 1015 evaluated the PK of nirmatrelvir and ritonavir in eleven healthy adults with and without itraconazole (CYP3A and P-gp inhibitor) coadministration.

Subjects received the oral treatments described below.

Period 1

- Nirmatrelvir/ritonavir 300/100 mg administered orally q12h for a total of 5 doses, from Day 1 morning to Day 3 morning.

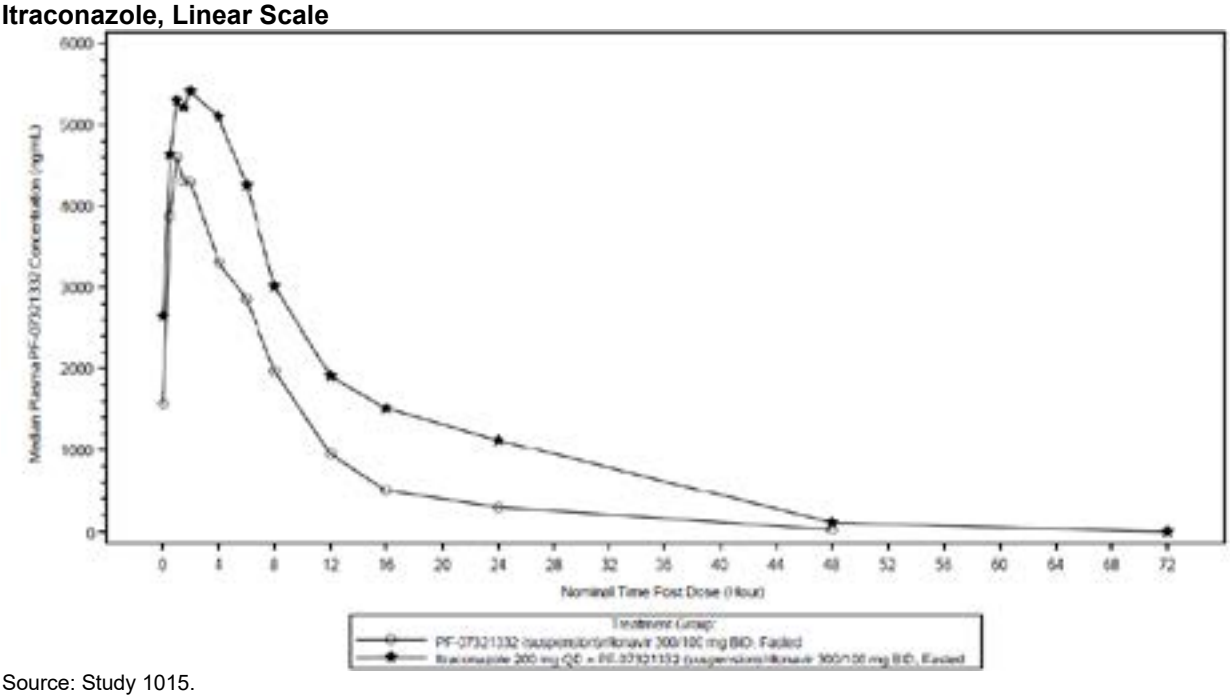
Period 2

- Itraconazole 200 mg orally once daily (using oral solution) from Days 1 through 8; and nirmatrelvir/ritonavir 300/100 mg administered orally q12h from Days 4 through 6, for a total of 5 doses, starting with the first dose on the morning of Period 2, Day 4 and the last dose administered on the morning of Period 2, Day 6.

For measurement of nirmatrelvir and ritonavir concentrations, intensive blood samples were collected at pre-dose and up to 48 hours post dose following the fifth dose on Day 3 of Period 1 and up to 72 hours post the fifth dose in Period 2.

In the presence versus absence of itraconazole, geometric mean nirmatrelvir AUCtau was increased 39% and C_{max} increased 19% (Figure 32, Table 94 and Table 95).

Figure 32. Median Plasma Nirmatrelvir Concentration-Time Profiles Following Multiple Oral BID Doses of Nirmatrelvir/Ritonavir Combination, Administered Alone or With Multiple QD Doses of Itraconazole, Linear Scale



Source: Study 1015.
Abbreviations: BID, twice daily; QD, once per day

Table 94. Descriptive Summary of Plasma Nirmatrelvir PK Parameters, Study 1015

Parameter (Unit)	Nirmatrelvir (suspension)/ritonavir 300/100 mg BID, Fasted (N=11)	Itraconazole 200 mg QD + Nirmatrelvir (suspension)/ritonavir 300/100 mg BID, Fasted (N=11)
N1, n[a,b]	11, 11	11, 10
AUC_{last} (ng.hr/mL)	41840 (21)	74430 (21)
AUC_{tau} (ng.hr/mL)	33350 (20)	46290 (18)
CL/F (L/hr)	8.990 (20)	6.478 (18)
C_{max} (ng/mL)	4678 (17)	5546 (15)
$t_{1/2}$ (hr)	8.255 ± 1.9465	7.793 ± 0.89019
T_{max} (hr)	1.020 (0.500 - 2.08)	1.700 (0.500 - 4.00)
VZ/F (L)	104.7 (33)	72.07 (16)

Source: Study 1015.
Note: Geometric mean (Geometric %CV) for all: except Median (Range) for T_{max} and arithmetic mean ± SD for $t_{1/2}$.
[a.] N1 = Number of participants contributing to the summary statistics.
[b.] n = Number of participants contr buting to the summary statistics for $t_{1/2}$ and VZ/F.
Abbreviations: AUC_{last}, area under the concentration-time curve from the time of dosing to the last measurable concentration; AUC_{tau}, area under concentration-time curve over dosing interval; BID, twice daily; CL/F, apparent clearance; C_{max}, maximum plasma concentration; N, total number of participants in the treatment group in the indicated population; PK, pharmacokinetic; QD, once per day; $t_{1/2}$, half-life; T_{max}, time for drug to reach maximum concentration; VZ/F, apparent volume of distribution

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Table 95. Statistical Summary of Plasma Nirmatrelvir PK Parameters, Study 1015

Parameter	Itraconazole 200 mg QD + nirmatrelvir (suspension)/ritonavir 300/100 mg BID, Fasted (Test)	Nirmatrelvir (suspension)/ritonavir 300/100 mg BID, Fasted (Reference)	Ratio (Test/Reference) of Adjusted Geometric Means	90% CI of Ratio
AUC_{tau} (ng.hr/mL)	46292	33346	1.39	(1.29,1.49)
C_{max} (ng/mL)	5546.1	4677.5	1.19	(1.13, 1.25)

Source: Study 1015.
Note: Natural log-transformed AUC_{tau} and C_{max} for PF-07321332 were analyzed using a mixed effect model with treatment as fixed effect and participant as a random effect.
Note: The ratios (and 90% CIs) were expressed as percentages.
Note: Values in table are the adjusted geometric means.
Abbreviations: AUC_{tau}, area under the concentration-time curve over the dosing interval; BID, twice daily; CI, confidence interval; C_{max}, maximum plasma concentration; QD, once per day

Effect of Carbamazepine on Nirmatrelvir/Ritonavir

Study 1014 evaluated the PK of nirmatrelvir and ritonavir in twelve healthy adults with and without carbamazepine (a strong CYP3A inducer) coadministration.

Participants received the oral treatments described below.

Period 1

- Nirmatrelvir 300 mg (as two 150-mg tablets), administered orally with ritonavir 100 mg (as one 100-mg tablet) as a single dose on Day 1 following an overnight fast.

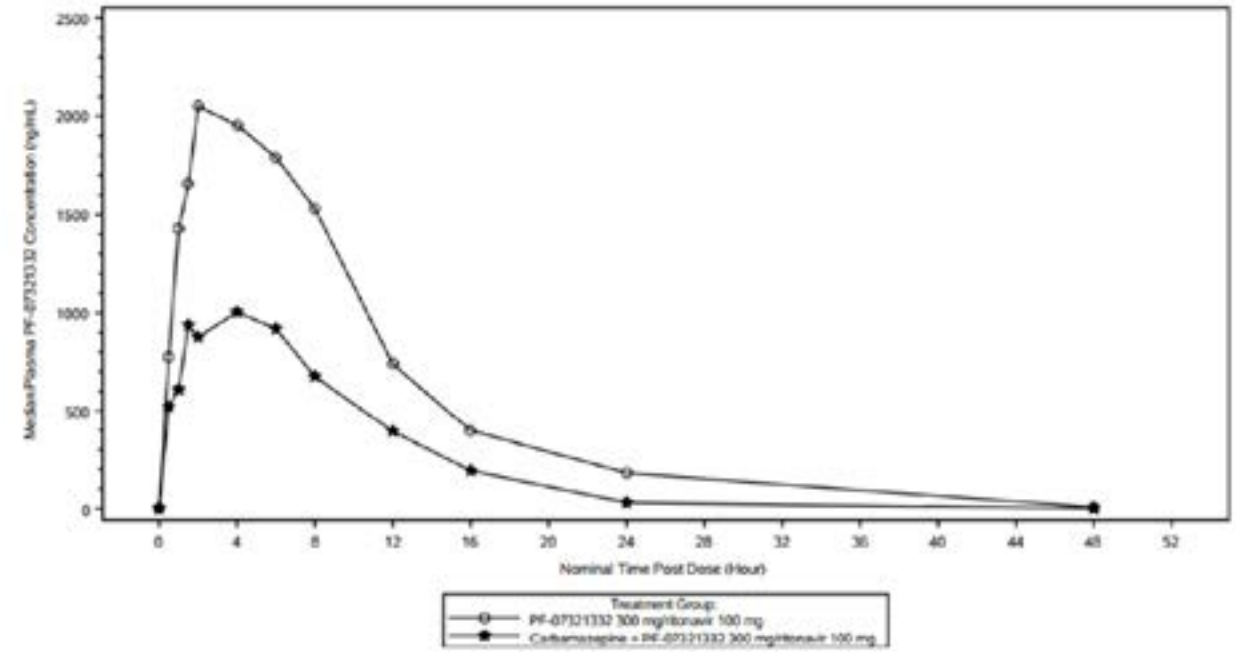
Period 2

- Carbamazepine 100 mg BID administered orally on Days 1, 2, and 3, and titrated up to 200 mg BID on Days 4, 5, 6, and 7. Carbamazepine was eventually titrated up to and maintained at 300 mg BID stably in the rest of Period 2 from Days 8 to 15. Carbamazepine was administered with or without food on all study days except on Study Day 14 when dosing was under fasting conditions. Approximately 15 to 30 min after the carbamazepine dose, on Period 2 Day 14, participants received a single dose of nirmatrelvir 300 mg (as two 150-mg tablets), administered orally with ritonavir 100 mg (as one 100-mg tablet).

For measurement of nirmatrelvir and ritonavir concentrations, intensive blood samples were collected at pre-dose and up to 48 hours post dose post-dose in Period 1, and at Day 14 pre-dose, and at up to 48 hours post-dose in Period 2.

Coadministration of multiple oral doses of carbamazepine titrated up to 300 mg BID decreased single dose nirmatrelvir AUC_{inf} and C_{max} by approximately 55% and 43%, respectively (Figure 33, Table 96 and Table 97). Carbamazepine titrated up to 300 mg BID decreased single dose ritonavir AUC_{inf} and C_{max} by approximately 83% and 74%, respectively (Figure 34, Table 98, and Table 99).

Figure 33. Median Plasma Nirmatrelvir Concentration-Time Profiles Following a Single Oral Dose of Nirmatrelvir/Ritonavir Administered Alone or With Multiple Oral Doses of Carbamazepine, Linear Scale



Source: Study 1014.

Table 96. Descriptive Summary of Plasma Nirmatrelvir PK Parameters, Study 1014

Parameter (unit)	Nirmatrelvir 300 mg/ Ritonavir 100 mg (N=12)	Carbamazepine + Nirmatrelvir 300 mg/ Ritonavir 100 mg (N=12)
N2, N3[a,b]	12, 12	10, 10
AUC_{inf} (ng.hr/mL)	23010 (23)	10280 (58)
AUC_{last} (ng.hr/mL)	22450 (23)	10050 (58)
CL/F (L/hr)	13.06 (23)	29.17 (58)
C_{max} (ng/mL)	2210 (33)	1300 (43)
$t_{1/2}$ (hr)	6.053 ± 1.7939	3.845 ± 0.99642
T_{max} (hr)	3.00 (1.02-6.00)	1.50 (0.500-4.00)
VZ/F (L)	109.4 (38)	157.2 (69)

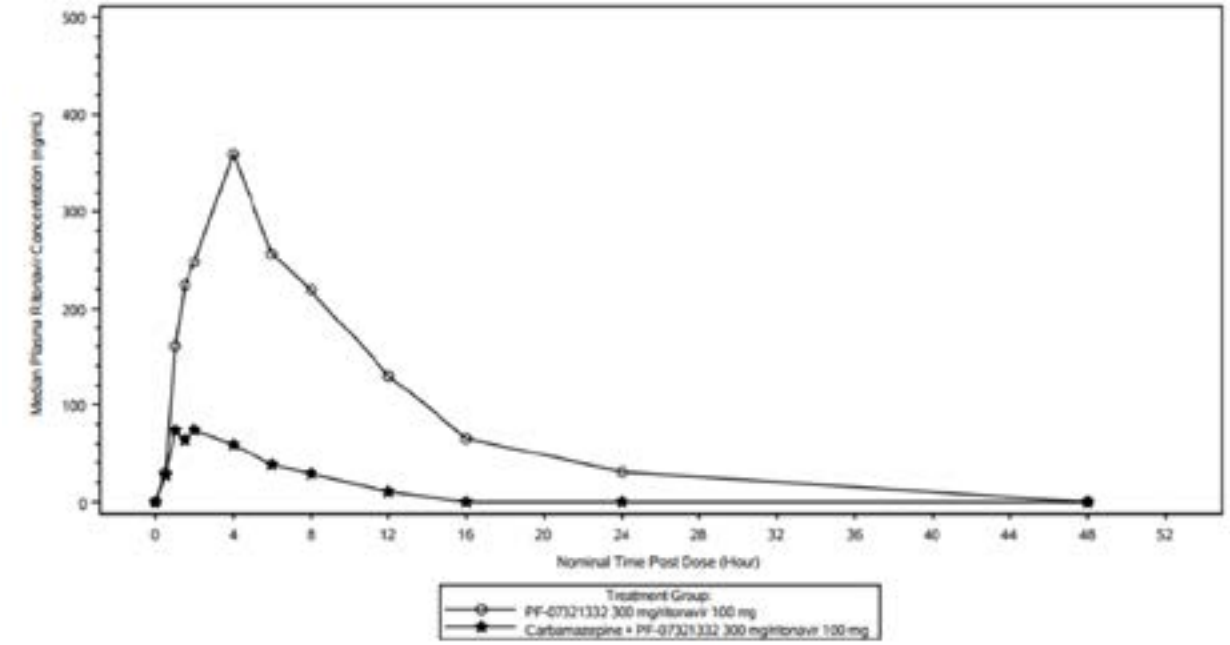
Source: Study 1014.
Note: Geometric mean (Geometric %CV) for all except Median (Range) for T_{max} and arithmetic mean ± SD for $t_{1/2}$.
[a] N2 = Number of participants contributing to the summary statistics
[b] N3 = Number of participants contributing to the summary statistics for AUC_{inf}, CL/F, $t_{1/2}$ and VZ/F.
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; AUC_{tau}, area under concentration-time curve over dosing interval; CL/F, apparent clearance; C_{max}, maximum plasma concentration; N, total number of participants in the treatment group in the indicated population; PK, pharmacokinetic; $t_{1/2}$, half-life; T_{max}, time for drug to reach maximum concentration; VZ/F, apparent volume of distribution

Table 97. Statistical Summary of Nirmatrelvir PK Parameters, Study 1014

Parameter (unit)	Carbamazepine + Nirmatrelvir 300 mg/ Ritonavir 100 mg (Test)	Nirmatrelvir 300 mg/ Ritonavir 100 mg (Reference)	Ratio (Test/Reference) of Adjusted Geometric Means	90% CI of Ratio
AUC_{inf} (ng.hr/mL)	10240	23010	0.45	(0.34, 0.59)
AUC_{last} (ng.hr/mL)	10010	22450	0.45	(0.34, 0.59)
C_{max} (ng/mL)	1256	2210	0.57	(0.47, 0.69)

Source: Study 1014.
Note: Natural log-transformed AUC_{inf}, AUC_{last} and C_{max} for PF-07321332 are analyzed using a mixed effect model with treatment as fixed effect and participant as a random effect.
Note: The ratio (and 90% CIs) are expressed as percentages.
Note: Values in table are the adjusted geometric means.
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing to the last measurable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; PK, pharmacokinetic

Figure 34. Median Plasma Ritonavir Concentration-Time Profiles Following a Single Oral Dose of Nirmatrelvir/Ritonavir Administered Alone or With Multiple Oral Doses of Carbamazepine, Linear Scale



Source: Study 1014.

Table 98. Descriptive Summary of Plasma Ritonavir PK Parameters, Study 1014

Parameter (unit)	Nirmatrelvir 300 mg/ Ritonavir 100 mg (N=12)	Carbamazepine + Nirmatrelvir 300 mg/ Ritonavir 100 mg (N=12)
N2, N3[a,b]	12, 12	10, 8
AUC_{inf} (ng.hr/mL)	3599 (47)	677.6 (61)
AUC_{last} (ng.hr/mL)	3414 (47)	466.2 (104)
CL/F (L/hr)	27.78 (48)	147.6 (61)
C_{max} (ng/mL)	359.3 (46)	96.07 (71)

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Parameter (unit)	Nirmatrelvir 300 mg/ Ritonavir 100 mg (N=12)	Carbamazepine + Nirmatrelvir 300 mg/ Ritonavir 100 mg (N=12)
$t_{1/2}$ (hr)	6.149 ± 2.2413	3.345 ± 0.79964
T_{max} (hr)	3.98 (1.48-4.20)	1.98 (0.983-4.00)
VZ/F (L)	234.0 (36)	697.5 (51)

Source: Study 1014.
[a.] N2 = Number of participants contributing to the summary statistics
[b.] N3 = Number of participants contributing to the summary statistics for AUC_{inf}, CL/F, $t_{1/2}$ and VZ/F.
Note: Geometric mean (Geometric %CV) for all except Median (Range) for T_{max} and arithmetic mean ± SD for $t_{1/2}$.
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing to the last measurable concentration; CL/F, apparent clearance; C_{max}, maximum plasma concentration; N, total number of participants in the treatment group in the indicated population; PK, pharmacokinetic; $t_{1/2}$, half-life; T_{max}, time for drug to reach maximum concentration; VZ/F, apparent volume of distribution

Table 99. Statistical Summary of Ritonavir PK Parameters, Study 1014

Parameter (unit)	Carbamazepine + Nirmatrelvir 300 mg/ Ritonavir 100 mg (Test)	Nirmatrelvir 300mg/ Ritonavir 100 mg (Reference)	Ratio (Test/Reference) of Adjusted Geometric Means	90% CI of Ratio
AUC_{inf} (ng.hr/mL)	596.4	3599	0.17	(0.13, 0.20)
AUC_{last} (ng.hr/mL)	441.1	3414	0.13	(0.09, 0.18)
C_{max} (ng/mL)	91.94	359.3	0.25	(0.19, 0.35)

Source: Study 1014.
Note: Natural log-transformed AUC_{inf}, AUC_{last} and C_{max} for PF-07321332 are analyzed using a mixed effect model with treatment as fixed effect and participant as a random effect.
Note: The ratio (and 90% CIs) are expressed as percentages.
Note: Values in table are the adjusted geometric means.
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing to the last measurable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; PK, pharmacokinetic

Effect of Nirmatrelvir/Ritonavir and Ritonavir on Dabigatran

Study 1012 evaluated the effect of nirmatrelvir/ritonavir and ritonavir on the PK of dabigatran (a P-gp substrate) in 24 healthy participants. Each participant received three treatments, each followed by a 3-day washout period.

Treatment 1

- Dabigatran 75 mg as a single oral dose.

Treatment 2

- Nirmatrelvir/ritonavir 300 mg/100 mg q12hours as a multiple oral dose over a period of 2 days. In the morning on Day 2, 75 mg of dabigatran was administered orally as a single dose.

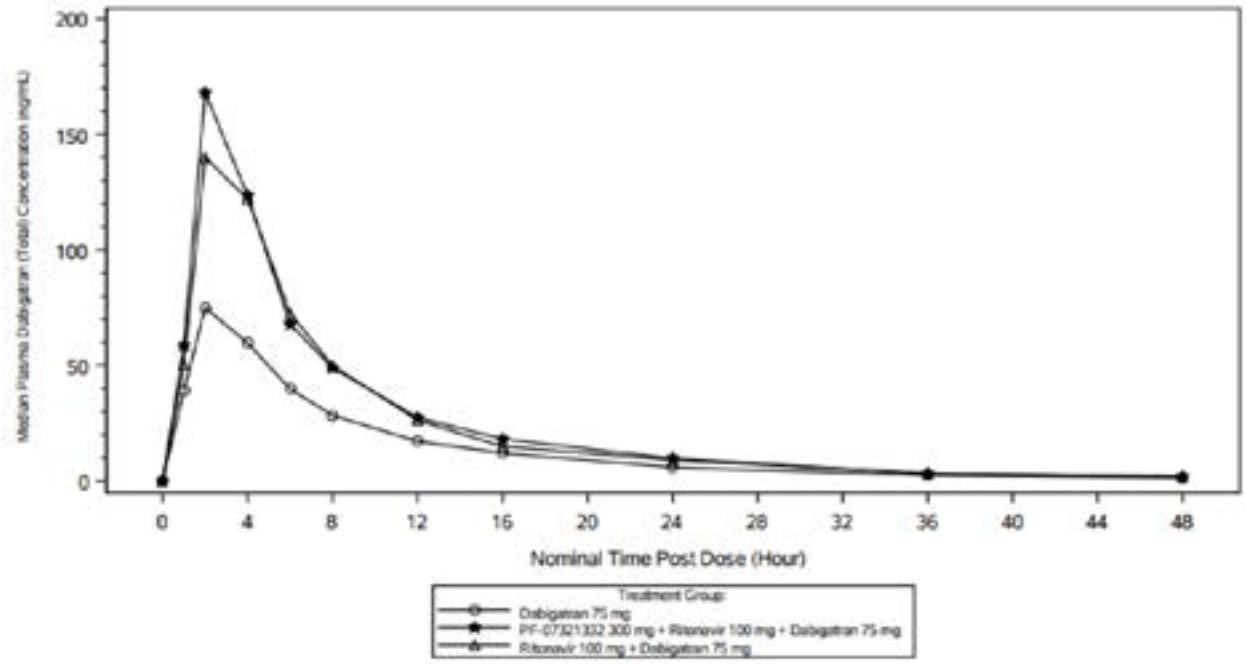
Treatment 3

- Ritonavir 100 mg q12h as a multiple oral dose over a period of 2 days. In the morning on Day 2, 75 mg of dabigatran was administered orally as a single dose.

Blood samples were collected pre-dose and up to 48 hours post-dose in each treatment group for PK assessments of nirmatrelvir, ritonavir and dabigatran.

The percent ratio of geometric means (90% CI) for dabigatran AUC_{inf} and C_{max} were 1.94 (1.55, 2.44) and 2.33 (1.72, 3.16) respectively, following dabigatran administration with multiple doses of nirmatrelvir/ritonavir combination as compared to administration alone (Figure 35 and Table 100).

Figure 35. Median Plasma Dabigatran Concentration-Time Profiles Following A Single Oral Dose Administered Alone and in Combination With Multiple Oral Doses of Nirmatrelvir/Ritonavir or Ritonavir



Source: Study 1012.

Table 100. Statistical Summary of Plasma Dabigatran PK Parameters, Study 1012

Parameter (Unit)	Test	Reference	Ratio (Test/Reference) of Adjusted Geometric Means	90% CI of Ratio
Nirmatrelvir 300 mg + Ritonavir 100mg + Dabigatran 75 mg vs. Dabigatran 75 mg				
AUC_{inf} (ng.hr/mL)	1221	627.9	1.94	(1.55, 2.44)
AUC_{last} (ng.hr/mL)	1201	558.3	2.15	(1.60, 2.90)
C_{max} (ng/mL)	158.3	67.91	2.33	(1.72, 3.16)
Ritonavir 100mg + Dabigatran 75 mg vs. Dabigatran 75 mg				
AUC_{inf} (ng.hr/mL)	1062	627.9	1.69	(1.35, 2.11)
AUC_{last} (ng.hr/mL)	893.5	558.3	1.60	(1.19, 2.15)
C_{max} (ng/mL)	116.7	67.91	1.72	(1.28, 2.32)

Source: Study 1012.
Note: Natural log-transformed AUC_{inf}, AUC_{last} and C_{max} for Dabigatran are analyzed using a mixed effect model with sequence, period and treatment as fixed effects and participant within sequence as a random effect.
Note: The ratio (and 90% CIs) are expressed as percentages.
Note: Reduced dataset excluded profiles where all concentrations were BLQ and C_{max} and AUC_{last}
Note: Values in table are the adjusted geometric means.
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing to the last measurable concentration; BLQ, below limit of quantitation; CI, confidence interval; C_{max}, maximum plasma concentration; PK, pharmacokinetic

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Effect of Nirmatrelvir/Ritonavir and Ritonavir on Midazolam

Study 1013 evaluated the effect of nirmatrelvir/ritonavir and ritonavir on the PK of midazolam (a CYP3A4 substrate) in 10 healthy subjects. Each subject received the treatments in the fasted state as described below.

Treatment A

- Single oral dose of 2 mg midazolam followed by a 2-day washout period.

Treatment B

- One hundred mg nirmatrelvir/100 mg ritonavir, administered orally, every 12 hours for 9 doses, with the last dose administered on the morning of Day 5. On Day 5, the nirmatrelvir/ritonavir dose was co-administered with a single oral dose of midazolam 2 mg followed by a 7-day washout period.

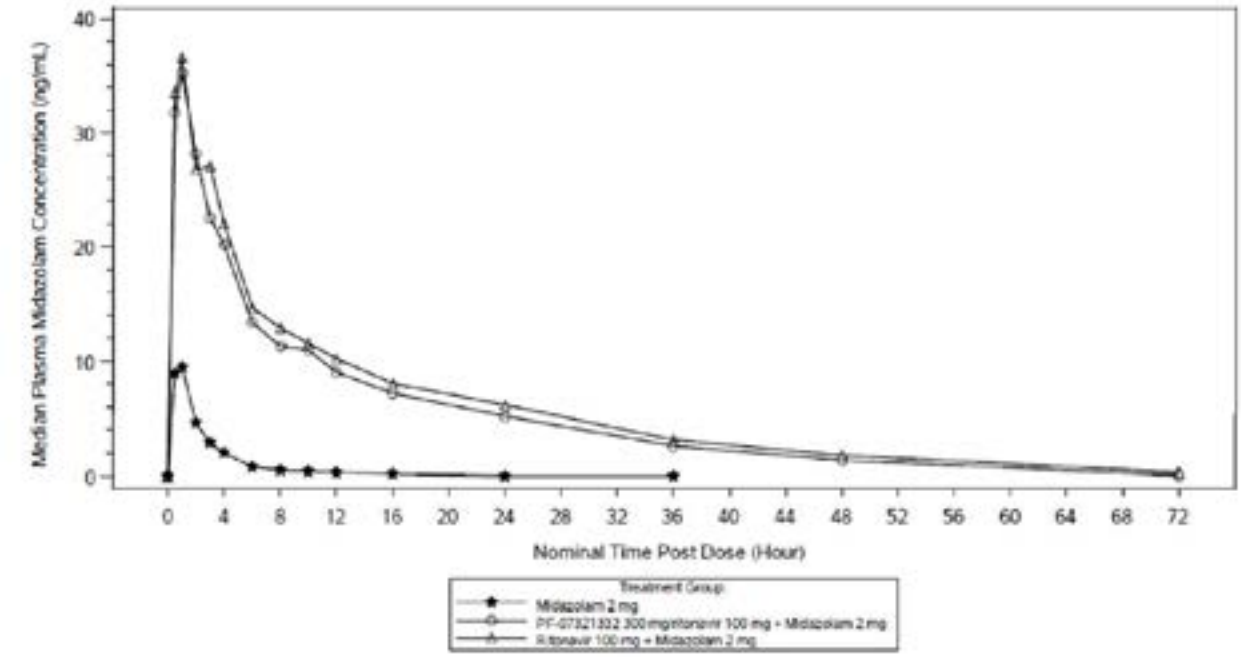
Treatment C

- One hundred mg ritonavir, administered orally, every 12 hours thereafter for a total of 9 doses, with the last dose administered on the morning of Day 5. On Day 5, the ritonavir dose was co-administered with a single oral dose of midazolam 2 mg followed by a 7-day washout period.

Blood samples were collected pre-dose and up to 36 hours post-dose for midazolam concentrations in Treatment group A and up to 72 hours post-dose for nirmatrelvir, ritonavir and midazolam concentrations in Treatment groups B and C.

The percent ratio of the geometric mean (90% CI) for midazolam AUC_{inf} and C_{max} were 14.30 (12.04, 17.00) and 3.68 (3.19, 4.25) respectively, following midazolam administration with multiple doses of nirmatrelvir/ritonavir as compared to administration alone (Figure 36 and Table 101).

Figure 36. Median Plasma Midazolam Concentration-Time Profiles Following A Single Oral Dose Administered Alone and in Combination With Multiple Oral Doses of Nirmatrelvir/Ritonavir or Ritonavir



Source: Study 1013

Table 101. Statistical Summary of Plasma Midazolam PK Parameters, Study 1013

Parameter (Unit)	Test	Reference	Ratio (Test/Reference) of Adjusted Geometric Means	90% CI of Ratio
Nirmatrelvir 300 mg/Ritonavir 100mg + Midazolam 2 mg vs. Midazolam 2 mg				
AUC_{inf} (ng.hr/mL)	362.5	25.35	14.30	(12.04, 17.00)
AUC_{last} (ng.hr/mL)	353.4	24.35	14.51	(12.24, 17.21)
C_{max} (ng/mL)	36.29	9.852	3.68	(3.19, 4.25)
Ritonavir 100mg + Midazolam 2 mg vs. Midazolam 2 mg				
AUC_{inf} (ng.hr/mL)	417.1	25.35	16.45	(13.86, 19.53)
AUC_{last} (ng.hr/mL)	408.3	24.35	16.77	(14.14, 19.89)
C_{max} (ng/mL)	38.15	9.852	3.87	(3.35, 4.47)

Source: Study 1013.
Note: Natural log-transformed AUCinf, AUC_{last} and C_{max} for Midazolam are analyzed using a mixed effect model with sequence, period, and treatment as fixed effects and participant within sequence as a random effect.
Note: The ratio (and 90% CIs) are expressed as percentages.
Note: Values in table are the adjusted geometric means.
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing to the last measurable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; PK, pharmacokinetic

14.3. Bioanalytical Method Validation and Performance

Bioanalytical methods used to measure nirmatrelvir and ritonavir concentrations in human plasma, urine and dried blood were fully validated and met precision and accuracy acceptance criteria (±15%, ±20% at the lower limit of quantification (LLOQ), see Table 102).

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Method C4679002 supported the Pivotal Phase 2/3 Study 1005 (Table 102). Validated bioanalytical methods used in the clinical drug-drug interaction (DDI) studies also met precision and accuracy acceptance criteria and are summarized in Table 103.

Table 102. Bioanalytical Methods Used to Quantify Nirmatrelvir and Ritonavir in Plasma, Urine, and Dried Blood

Method Number	Analytical Technique	Analyte Measured	Calibration Range (ng/mL)	Matrix/ Anticoagulant	Long-Term Stability	Supported Clinical Studies
071459	LC-MS/MS	Nirmatrelvir	10.0-50,000	Human Plasma/K2EDTA	51 days at -20°C and 70°C	1001
C4679002	LC-MS/MS	Nirmatrelvir and Ritonavir	Nirmatrelvir: 10.0-10,000 Ritonavir: 5,00-5,000	Human Plasma/K2EDTA	200 days at 20°C and -80°C	1005 1006 1010 1011 1012 1013 1014 1015 1019
074112	LC-MS/MS	Nirmatrelvir	10.0-50,000	Human Urine	63 days at -20°C and -70°C	1001
C4679003	LC-MS/MS	Nirmatrelvir	100-200,000	Human Urine	92 Days 20°C and 80°C	1011 1010
C4679008	LC-MS/MS	Nirmatrelvir and Ritonavir	Nirmatrelvir: 10.0-10,000 Ritonavir: 5,00-5,000	Human Dried Blood/K2EDTA	29 days at -20°C and -80°C	1026

Source: Validation reports 071459, C4679002, 074112, C4679003, C4679008.
Abbreviations: K2EDTA, anticoagulant; LC, liquid chromatography; MS/MS, tandem mass spectrometry

Table 103. Bioanalytical Methods Used in Clinical DDI Studies

Method Number	Analytical Technique	Analyte Measured	Calibration Range (ng/mL)	Matrix/ Anticoagulant	Long-Term Stability	Supported Clinical Studies
B7459007	HPLC-MS/MS	Total Dabigatran	1.00 - 800	Human Plasma/K2EDTA	95 days at -20°C and -80°C	1012
C4679007	LC-MS/MS	Midazolam	0.100-100	Human Plasma/K2EDTA	63 days at -20°C	1013

Source: Validation report B7459007 and C4679007.
Abbreviations: HPLC, high-performance liquid chromatography; K2EDTA, anticoagulant; LC, liquid chromatography; MS/MS, tandem mass spectrometry

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Not applicable.

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14.5. Pharmacometrics Assessment

14.5.1. Review Summary

This review aims to 1) evaluate appropriate treatment duration in immunocompromised patients based on QSP modeling, 2) provide pharmacometrics perspective in support of the dose in the indicated population.

Applicant's quantitative systems pharmacology (QSP) modeling suggests that the treatment duration of 5 days, as indicated in the current EUA fact sheet and proposed label, might not be sufficient for immunocompromised patients. A longer treatment duration might be potentially beneficial to further manage viral RNA shedding in this patient subgroup, thus providing additional support for the need of the ongoing EPIC-IC trial.

The QSP model is designed to include the current mechanistic understanding of the interplay between viral infection/replication and immune response in the absence or presence of antiviral products with calibration/validation using longitudinal data from observational study of biomarkers (e.g., SARS-CoV-2 RNA levels, circulating cytokines/chemokines, and immune cells signature), and aggregate virology data from several randomized control trials of antiviral products. While the calibration with full EPIC-HR data inclusive of immune markers is not currently available, the current version of QSP model aligned with the aggregate virology data and is deemed qualitatively acceptable to depict viral dynamics of SARS-CoV-2 in patients with mild-to-moderate COVID-19 (PAXLOVID-eligible population) in the absence and presence of PAXLOVID.

The immunocompromised (IC) virtual populations were generated from the virtual population representative of the PAXLOVID-eligible population. In combination with QSP model, the proposed immunocompromised virtual populations reproduced the prolonged viral shedding profile and are acceptable to inform the dose proposal in EPIC-IC trial based on the predicted efficacy of viral suppression (Aydillo et al. 2020; Caillard et al. 2021). Even with uncertainty, the QSP analysis suggests that a prolonged treatment duration beyond 5 days may be beneficial for this patient population.

Applicant's population pharmacokinetics (PopPK) model is generally acceptable to characterize nirmatrelvir (NIR) PK profiles in patients with COVID-19 who received multiple doses of PAXLOVID that support the labeling language with regards to intrinsic factors (age, weight, gender, race/ethnicity, renal impairment). Parameters were generally estimated with acceptable precisions. The derived individual exposure metrics is not expected to be credible for exposure-response analyses since ETA shrinkages are moderate to high (>50%). There is no unacceptable bias in goodness-of-fit plots and the prediction corrected visual predictive check plots generally captures the central tendency and variability of the observed concentrations.

For dosage in adolescents and severe renal impaired patients, PK matching approach extrapolated with population PK model was employed. The conclusions from modeling perspective were in-line with those drawn from the analysis using the preliminary model documented in the EUA review. The data for model validation are very limited during the current review cycle.

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14.5.2. Applicant's QSP Modeling and Analysis

14.5.2.1. Objectives

The primary objectives of Applicant's analysis were to:

- Support EPIC-HR dose selection for intent-to-treat population
- Evaluate an appropriate treatment duration in immunocompromised population from viral suppression perspective

14.5.2.2. Overview of Studies Included in QSP Analysis

The Applicant developed a QSP model to describe SARS-CoV-2 viral dynamics on a population scale and to subsequently use the model to support selection of treatment duration in target population, and specific population such as immunocompromised patients. Clinical data used in calibration of the model parameters are listed in Table 104.

Table 104. Clinical Data Used in QSP Modeling Calibration

Study	Description	Drug and Data Used
Curated data	Observational studies in moderate to severe patients with COVID-19	• Drug: None • Data: Individual viral RNA shedding, cytokine and chemokine, and PBMCs data in mainly hospitalized patients*
Blaze-1	A Phase 3 study to assess the PK, safety, and tolerability of NIR/RTV in adult participants with moderate hepatic impairment and healthy participants with normal hepatic function	• Drug: Bamlanivimab and etesevimab • Data: Mean viral RNA shedding data and disease severity**
COV-2067	A Phase 1-3 study to assess the safety, tolerability, and efficacy of anti-spike SARS-CoV-2 monoclonal antibodies for the treatment of ambulatory adult and pediatric patients with COVID-19 (only Phase 2/3 data were used)	• Drug: Casirivimab and imdevimab, • Data: Mean viral RNA shedding data and disease severity**
MK-4422	A Phase 2 study to assess the safety, tolerability, and efficacy of molnupiravir to eliminate infectious virus detection in persons with COVID-19	• Drug: Molnupiravir • Data: Mean viral RNA shedding data
EPIC-HR	A Phase 2/3 study to assess the safety and efficacy to PAXLOVID for the treatment of non-hospitalized symptomatic adults with COVID-19.	• Drug: PAXLOVID • Data: Mean viral RNA shedding data

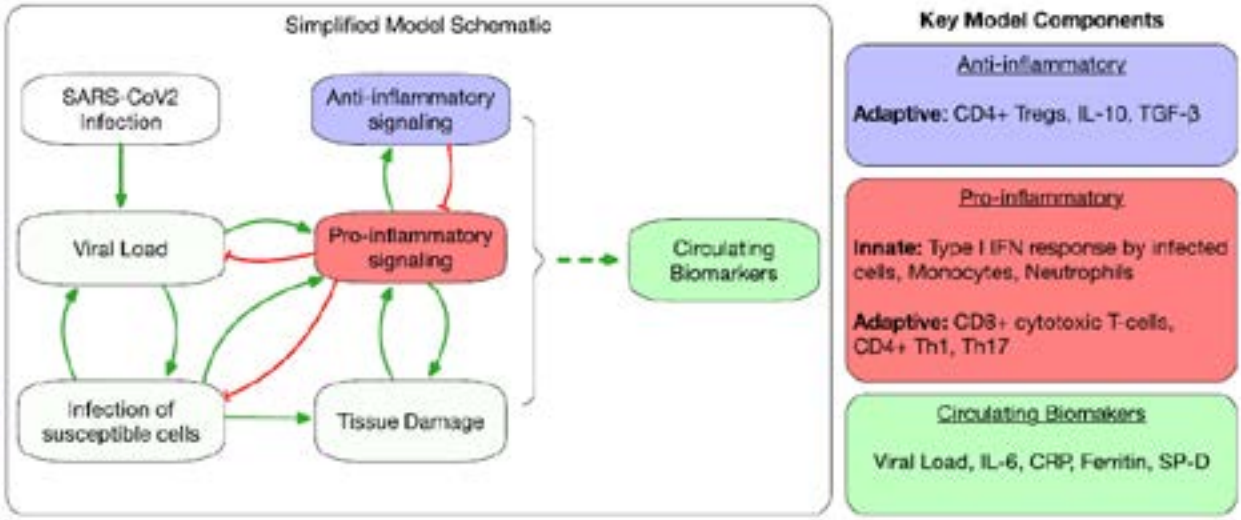
Source: Adapted from Applicant's PK report, Table 1.
* (Lucas et al. 2020; Mann et al. 2020; Mudd et al. 2020; Gastine et al. 2021)
** Plasma IL-6 threshold of 40 pg/mL was used as the primary biomarker for clinical endpoint in the model for disease severity classification.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; IL, interleukin; PBMC, peripheral blood mononuclear cells; QSP, quantitative system pharmacology; RNA, ribonucleic acid

14.5.2.3. QSP model

The QSP modeling and simulation was conducted using MATLAB 2019b.

QSP model leverages existing mechanistic knowledge to describe the disease pathophysiology of viral dynamics and the innate and adaptive immune response with a set of ordinary differential equations (ODEs) in alveolar and plasma compartments (Figure 37). The pharmacodynamic effects of anti-viral products were added to the model according to their mechanism of action.

Figure 37. Simplified Model Schematic



Source: Applicant's EPIC-IC QSP model summary, Figure 1.
Abbreviations: CD, cluster of differentiation; CRP, C-reactive protein; IFN, interferon; IL, interleukin; SP-D, surfactant protein D; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; TGF, transforming growth factor; Th, T helper cell

Model parameters were informed by literature and experimental data or calibrated by unit test and/or clinical data. There are over 200 parameters included in the QSP model, the specific breakdown relating to their attributes is as follows:

- Calibrated with unit tests: 140 parameters involved in immune/alveolar cell differentiation, regeneration, maturation, or clearance, immune cell activation by cytokines, and cytokine induced tissue damage
- From literature: 28 parameters describing cell death rate or cytokine clearance, and dynamics of circulating biomarkers
- Calibrated with observational clinical data and randomized control trials: 50 parameters involved in viral infectivity or shedding, death of infected cells, immune cell activation, and basal production of cytokines

14.5.2.4. Virtual Population Development

Twenty-eight parameters in the last category with high sensitivity and uncertainty (Table 105) were selected to form virtual population comprised of sets of parameters which imitate pathophysiological heterogeneity in patient population. The virtual population was generated and refined in a stepwise fashion (Dai et al. 2021; Rao et al. 2023): 1) confining the distribution of parameter sets using various observed markers (e.g., viral RNA shedding, circulating cytokines) from curated observational studies on COVID-19 to obtain a plausible population, and 2) selecting a subset of plausible subjects whose simulated responses conform to interventional data

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from a published randomized control trial (Blaze 1 study) to form a virtual population that represents symptomatic outpatient COVID-19 population (n = 502).

The important assumptions for modeling and simulation are listed below, which are informed by the clinical findings, literatures, or rational premise from analysis standpoint:

1. Symptom onset coincides with the peak viral RNA shedding to translate "day of symptom onset" to "day of infection" for calibration
2. A homogenous initial inoculum of 10 viral RNA copies/mL
3. Endogenous Ab response on Day 20 post infection
4. Innate immune cells behave as log sensors to pathogen levels rather than having saturable maturation kinetics
5. Post peak, virus can no longer infect new susceptible cells within the host when the viral load declines below 10^4 viral RNA copies/mL (10^3 copies/mL threshold investigated in a sensitivity analysis that showed no obvious difference in viral dynamics (Rao et al. 2023)) to avoid unphysiological rebound at later time points when viral RNA is close to the lower limit of quantification for SARS-CoV-2 real-time, reverse transcription-polymerase chain reaction (RT-PCR) assay
6. The effects of nirmatrelvir were only captured as a suppression of net viral production and shedding from infected cells despite of the intracellular life cycle of SARS-CoV-2

The plausible population is composed of subjects exhibiting viral dynamics that are physiologically realistic (Figure 38).

Figure 39 shows the distribution of parameters for the refined virtual population, where the median of the parameters in virtual population in generally aligns with the nominal value. The viral dynamics of this virtual population was validated against viral RNA shedding data of two other published randomize control trials (COV-2067 study, MK-4422 study) which showed good agreement (Rao et al. 2023). The agreement in viral dynamics was also observed for different baseline viral RNA shedding levels (Figure 40).

14.5.2.5. Application of QSP Modeling to Inform Treatment Duration in Target Populations

The QSP model together with preliminary population PK model (refer to EUA review for the PK model) were used to inform selection of treatment duration for EPIC-HR. In this model, the E_{max} of the therapeutic is fixed to one, the in vivo potency of nirmatrelvir (EC_{50}) was estimated from preclinical data and subsequently updated to align with the observed experimental virology data for simulating treatment with PAXLOVID. Assuming 4 days post peak viral RNA shedding/symptom onset, the viral dynamics of two dosing durations (i.e., 5-day and 10-day) were assessed. The model predicted that a longer dosing regimen would not provide meaningful difference in viral RNA shedding lowering efficacy at Day 7 or Day 10 regardless of clinical potency (Figure 41).

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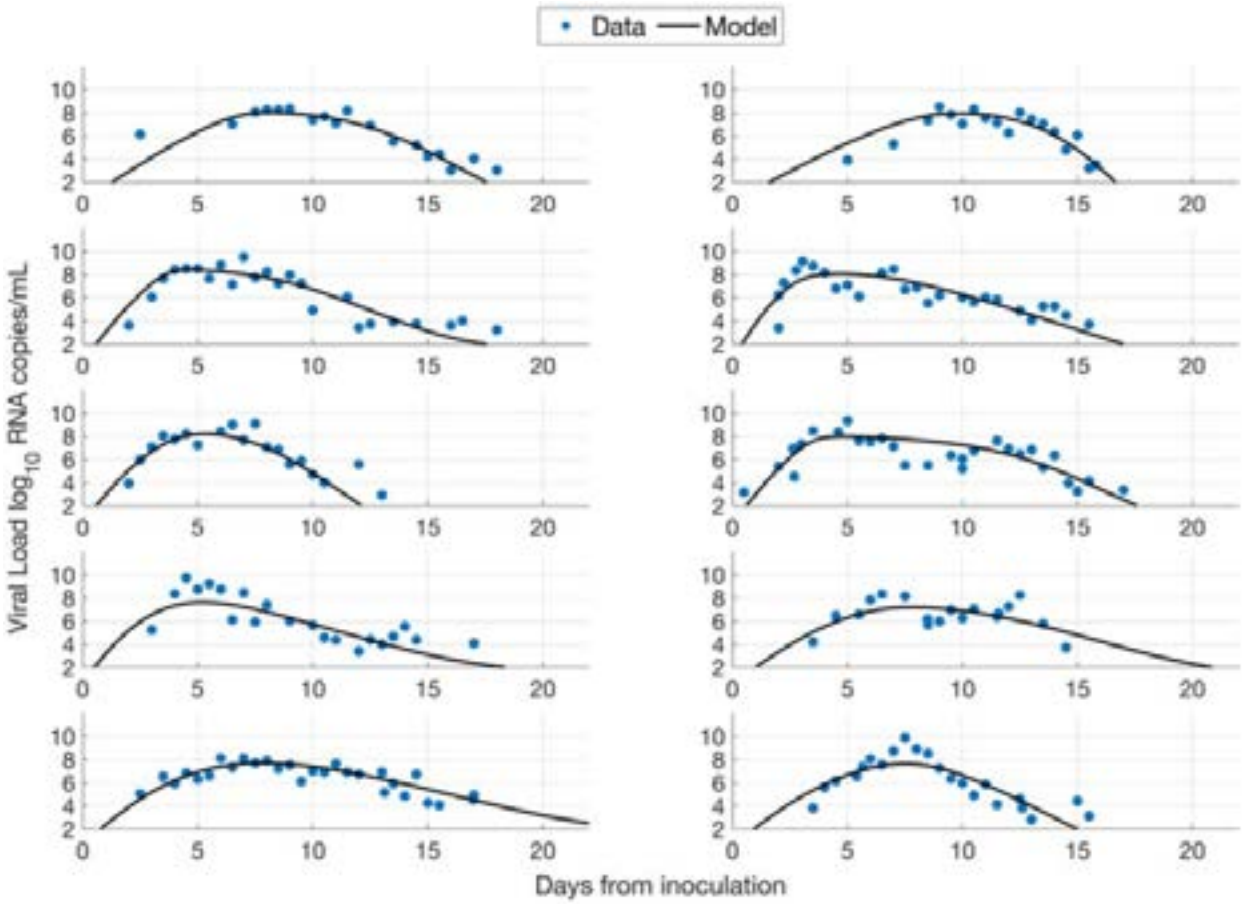
Table 105. Parameters Varied to Generate Plausible and Virtual Population

Parameter	Description
A_V	viral shedding by infected cells
b_V	endogenous viral clearance
b_I	death rate for infected cells
a_DC	rate constant for production of mature dendritic cells
km_DC_IL10	IC_{50} for inhibition of DC activation by IL-10
a_Th1	rate constant for activation of Th1 cells
a_Th17	rate constant for activation of Th17 cells
a_Treg	rate constant for Treg activation
a_M1	rate constant for activation of macrophages
a_CTL	rate constant for CTL activation
a_ifnb	basal induction of Type I IFN
b_dAT1	death rate for damaged AT1 cells
km_int_IFNb	IC_{50} for anti-viral effects of Type I IFN
k_v	rate constant for viral activation of innate immune cells
k_I	rate constant for innate immune activation by infected cells
k_dAT	rate constant for innate immune activation by damaged cells
k_kill	rate constant for infected cell clearance by $CD8^+$ cell clearance
k_damage_cyt	rate constant overall cytokine damage
k_int	viral endocytosis by AT2
basal_tnfa	basal production rate of TNF
basalil6	basal production rate of IL-6
basalil1	basal production rate of IL-1
basalifng	basal production rate of IFNg
basalifnb	basal production rate of Type I IFN
basalil2	basal production rate of IL-2
basalil12	basal production of IL-12
basalgmcsf	basal production of GM-CSF
basalil10	basal production rate of IL-10

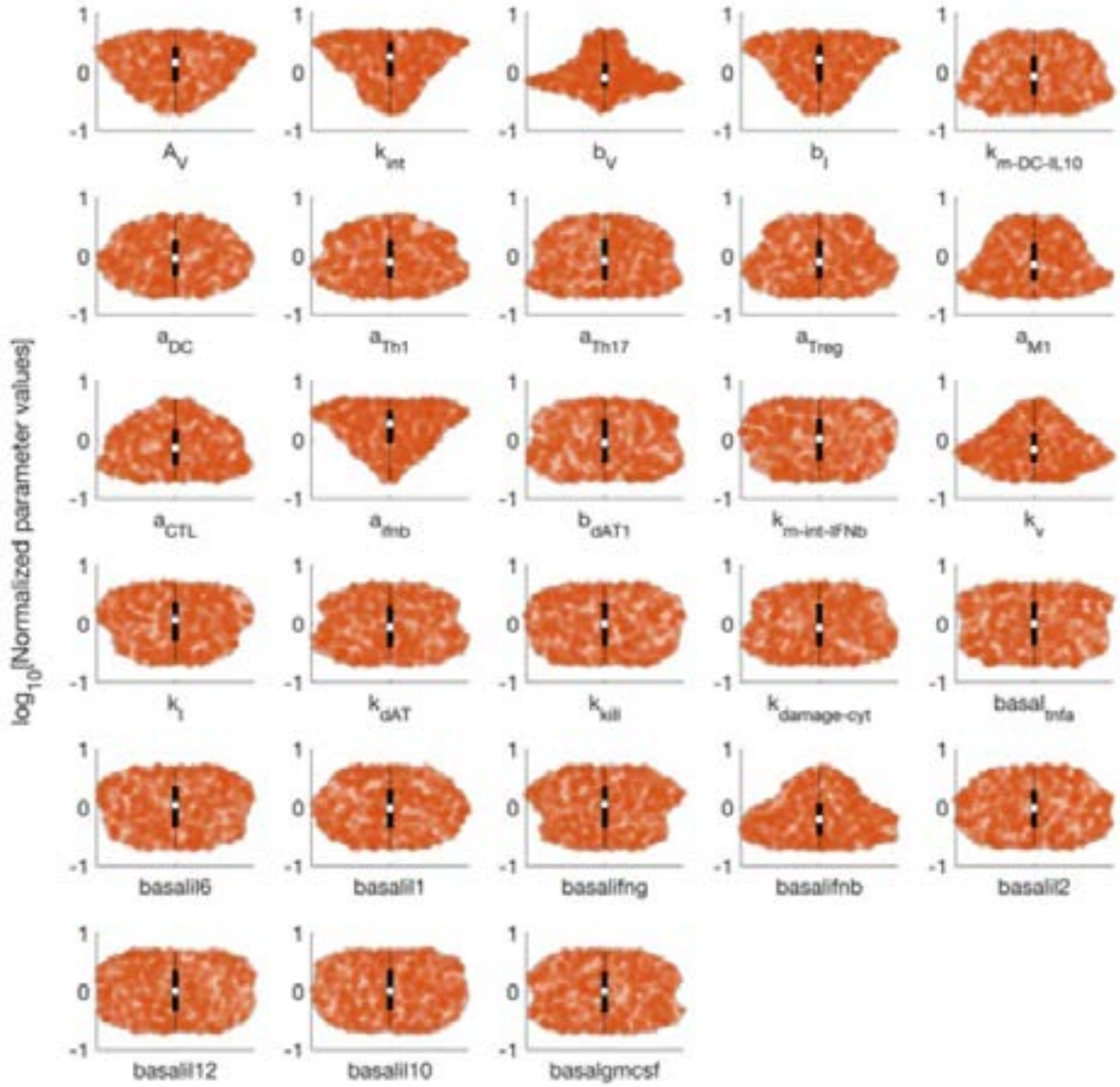
Source: Applicant's EPIC-IC QSP model summary, Appendix 3.
Abbreviations: AT2, angiotensin 2 receptor; CD, cluster of differentiation; CTL, cytotoxic T lymphocytes; DC, dendritic cells; EC_{50}, median effective concentration; GM-CSF, granulocyte macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; SP-D, surfactant protein D; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; Th, T helper cell; TNF, tumor necrosis factor

Figure 38. Viral Dynamics in Selected Virtual Subjects From the Plausible Population That Matched Individual Data in a Published SARS-CoV-2 Human Challenge Study



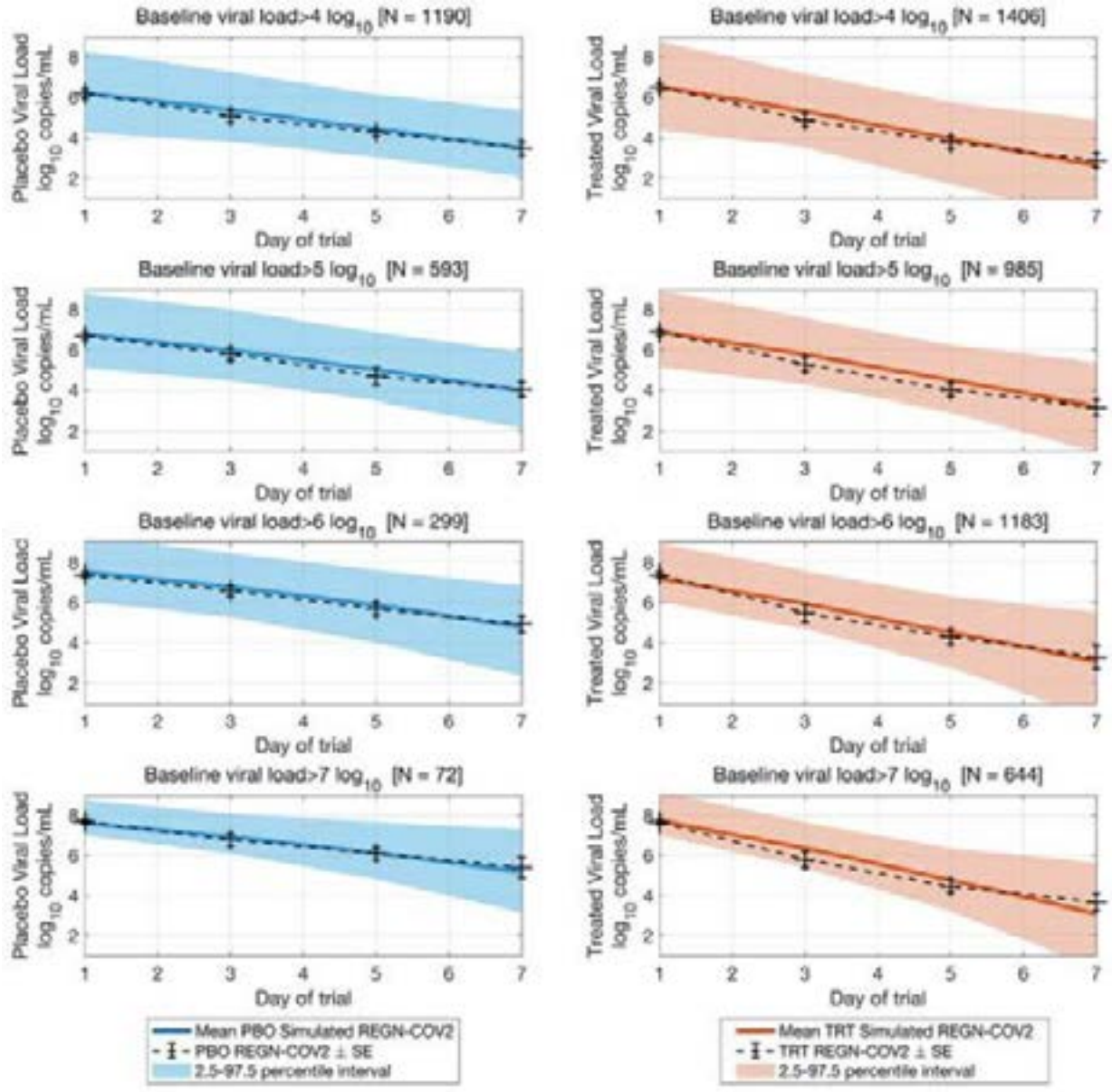
Source: Applicant's EPIC-IC QSP model summary, Figure 3.
Note: Data is extracted for subjects with confirmed symptomatic SARS-CoV-2 Infection with above LOQ PCR assay measurements upon viral inoculation from Killingley et al (Killingley et al. 2022).
Abbreviations: log, logarithm; LOQ, limit of quantification; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; QSP, quantitative systems pharmacology; RNA, r bonucleic acid

Figure 39. Distribution of Parameters for the Virtual Population Matching the Blaze-1 Clinical Data



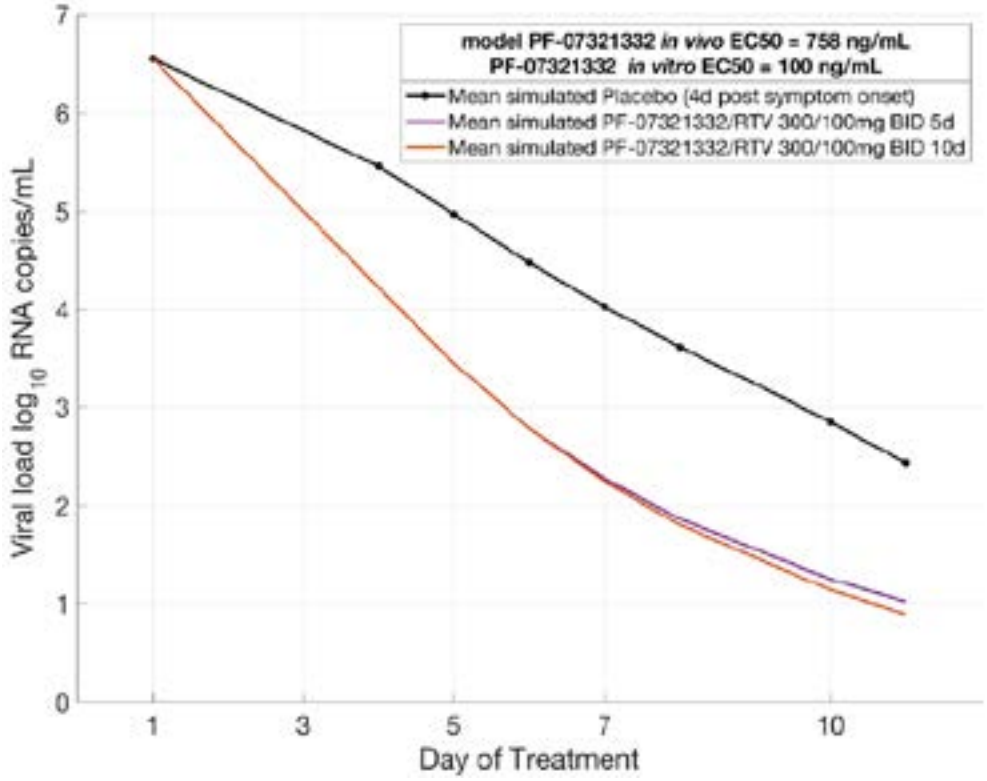
Source: Applicant's EPIC-IC QSP model summary, Figure 2.
Note: Parameters normalized by the nominal value of each parameter.
Abbreviations: log, logarithm; QSP, qualitative systems pharmacology

Figure 40. Viral Dynamics Selected From the Plausible Population Grouped by Baseline Viral Loads That Match the Strata in Subgroup Analysis of Viral Dynamics in REGEN-COV Phase 2 Study



Source: Applicant's EPIC-IC QSP model summary, Figure 4.
Note: Mean viral RNA shedding trajectories for each subgroup is extracted from Weinreich et al (Weinreich et al. 2021). The shaded regions represent the 95% intervals for the simulated viral RNA shedding. The virtual subject was selected from the plaus ble population to match the subgroup by baseline viral RNA shedding.
Note: The above virtual populations are obtained by selecting virtual subjects from the plaus ble population to independently match each subgroup in the placebo and treated conditions, therefore representing different virtual populations from those selected from the virtual population calibrated by Blaze 1 (n=502). The graph of the latter virtual population for the purpose of validation in REGEN-COV was reported in Rao R et al.'s paper (Rao et al. 2023).
Abbreviations: log, logarithm; N, total number of subjects; n, number of subjects in sample; QSP, quantitative systems pharmacology; RNA, ribonucleic acid; SE, standard error

Figure 41. QSP Model Predictions for Symptomatic COVID-19 Patients



Source: Applicant's QSP model summary, Figure 2.
Abbreviations: BID, twice daily; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; EC_{50}, median effective concentration; QSP, quantitative systems pharmacology; RNA, ribonucleic acid

Clinical data are not available to calibrate the viral dynamics for Omicron viral variants. According to the reported viral dynamics of Omicron relative to Delta, Applicant stated that the difference is within the variability contained in the plausible and virtual population. The parameter K_int that describes viral infectivity may be sensitive to viral variant, for instance, Omicron is known for a higher infectivity than Delta, the viral RNA shedding could be subsequently shifted, which may impact the observable difference between placebo and treatment.

14.5.2.6. QSP Analysis in Immunocompromised Population

Virtual Population Development for Immunocompromised Patients

QSP model is being calibrated iteratively throughout the development. When EPIC-HR data became available, the Applicant adjusted the parameters of virtual population as well as IC_{50} to match the aggregate virology data (Figure 42). The resulting virtual population is termed the nominal virtual population (n = 739). This nominal virtual population corresponds to the overall PAXLOVID eligible population and was used to generate immunocompromised patients who are expected to mount an inadequate innate and adaptive immune response to SARS-CoV-2 infection. Notably in this nominal virtual population, the model overpredicts the viral RNA shedding at early time points primarily due to an under-representation in virtual population of the proportion of participants that are tested positive for COVID-19 RT-PCR with viral RNA shedding under LLOQ at baseline in EPIC-HR.

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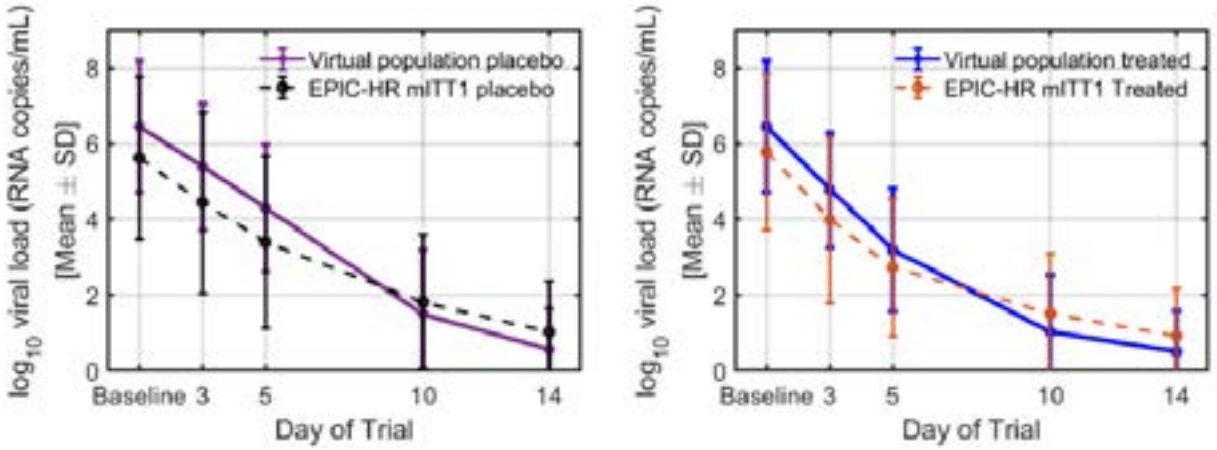
The immunocompromised patients are expected to exhibit a significantly longer viral RNA shedding than immunocompetent high-risk outpatient population. The immunocompromised virtual population was formulated using two approaches (bottom-up and top-down) to reproduce the expected viral dynamics mechanistically or phenotypically:

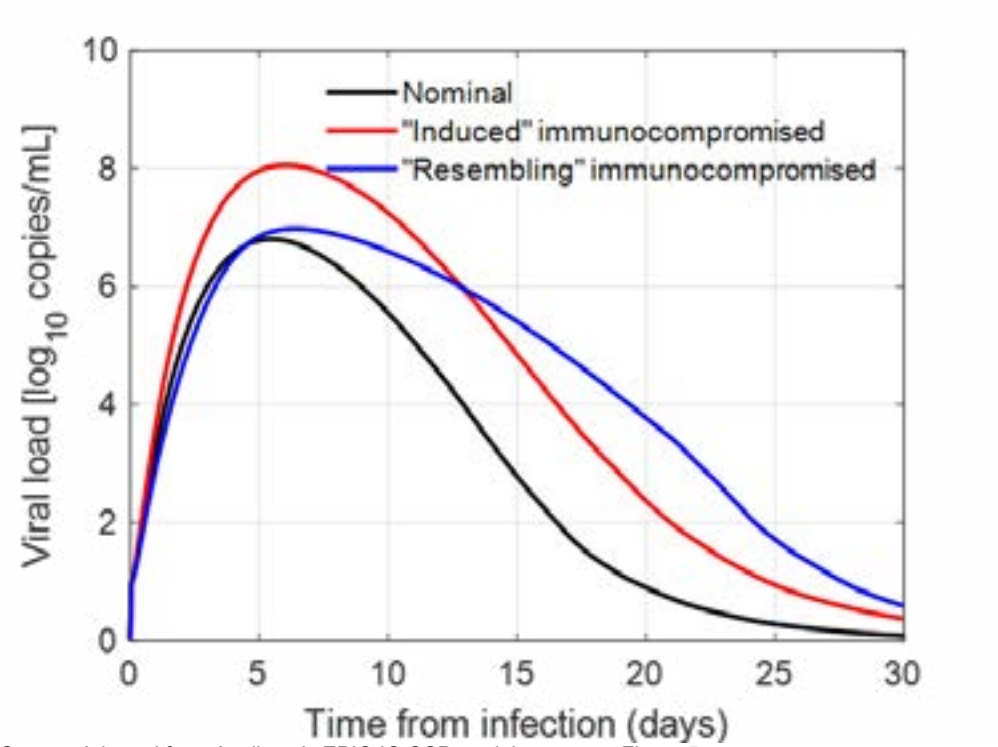
- Bottom-up approach: The bottom-up approach refers to an induced immunosuppression based on the mechanistical understanding of key components (i.e., Type I IFN, $CD8^+$ T cells) critical in mounting an effective immune response. For each subject in the nominal population, the values of the three parameters relating to the anti-viral effects was decreased by a factor of 2 (km_int_IFNb: IC_{50} of Type I IFN, k_IFNb_kill: rate constant for induction of infected cell clearance by Type I IFN, k_kill: rate constant for infected cell clearance by $CD8^+$ cell). The virtual population was then trimmed to exclude those with viral RNA shedding >10^3 copies/mL by day 75 of the initial viral inoculum. The resulting virtual patients (n = 505), also referred to as "induced" immunocompromised patients, exhibit a higher peak viral RNA shedding and a prolonged viral shedding upon infection (Figure 43).
- Top-down approach: The top-down approach refers to the selection or enrichment of a subset from virtual population that presents a prolonged viral shedding. The selection criterium is the subjects with duration of viral RNA shedding (from viral RNA shedding peak to <10^2 copies/mL) in the top 85th percentile of the nominal virtual population. The selected virtual patients, also referred to as "resembling" immunocompromised patients, naturally exhibit a longer viral shedding than the overall virtual patients (Figure 43).

Figure 42. Aggregate Viral Load Time Course for Placebo (Left) and Treatment (Right) of the Virtual Population and EPIC-HR mITT1 Study Population.



Source: Applicant's IR response submitted on February 1, 2023, Figure 1.
Note: The spanning bar represents SD of viral load at each nominal time point.
Abbreviations: log, logarithm; mITT, modified intent to treat; RNA, ribonucleic acid; SD, standard deviation

Figure 43. Example Mean Viral Dynamic in Immunocompromised Virtual Patients Using Two Independent Approaches



Source: Adapted from Applicant's EPIC-IC QSP model summary, Figure 5.
Note: The top-down approach to preferentially select a cohort of virtual subjects [blue line, N=110] with prolonged viral shedding that resembles viral dynamics in immunocompromised patients, and a bottom-up approach [red line, N = 505] that mechanistically induces immunosuppression by diminishing the effect of the immune response in a nominal virtual population [Solid Black Line]
Abbreviations: log, logarithm; N, total number of subjects; QSP, quantitative systems pharmacology

Evaluation of Treatment Duration in Immunocompromised Patients

To identify the appropriate treatment duration in immunocompromised patients, QSP model was applied to predict viral dynamics in the two immunocompromised virtual populations. Viral RNA shedding reduction across different durations of treatment was graphically explored by the Reviewer and showed a maximal viral suppression on average around Day 10 in both immunocompromised virtual populations (Figure 44). Applicant summarized viral RNA shedding rebound with the lower and upper bound informed by the more extreme values of pooled event rates from the two immunocompromised virtual populations. The odds ratio relative to the nominal virtual population (high-risk immunocompetent population) treated with 5-day PAXLOVID was calculated using the equation below:

Equation 1. Odds Ratio Relative to the Nominal Virtual Population Following 5 Days of Paxlovid Treatment

$$Odds\ ratio = \frac{\%\ VLR\ of\ X\ days\ treatment\ in\ immunocompromised}{\%\ VLR\ of\ 5\ days\ treatment\ in\ immunocompetent}$$

Source: FDA reviewer.
Abbreviations: VLR, viral load rebound

The viral RNA shedding rebound in the Applicant's analysis is defined as positive slope post treatment termination (see example of viral RNA shedding rebound in individual virtual subjects

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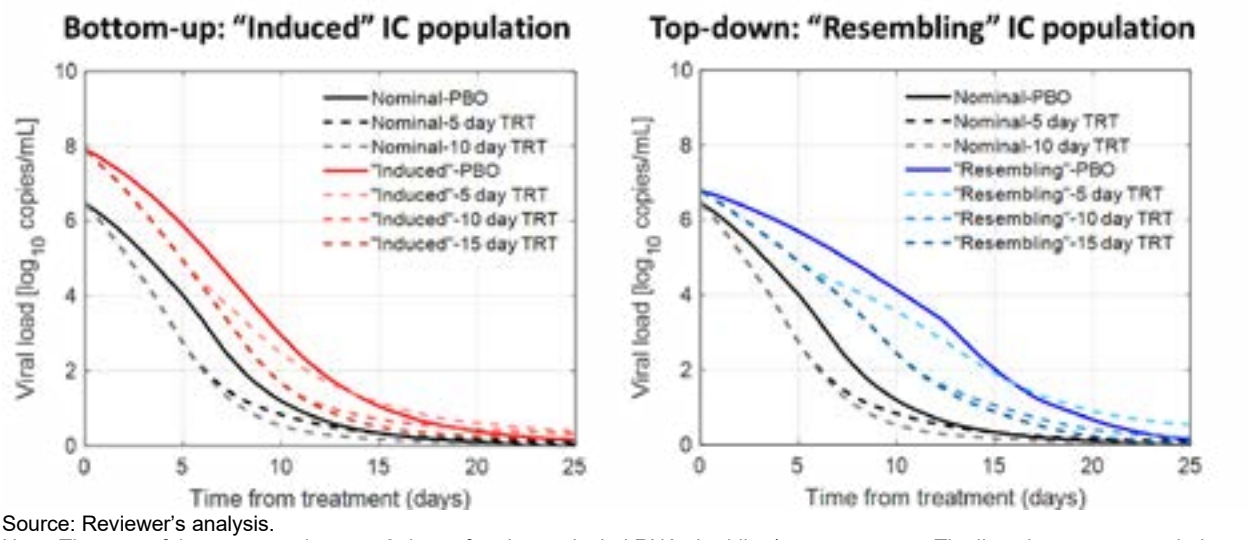
in Figure 45). As shown in Figure 46, the risk of rebound upon treatment termination is substantially reduced with 10 days of treatment and is predicted to be more comparable to that in a high-risk immunocompetent population. Extending the treatment to 15 days is not predicted to lead to further benefit in mitigating the risk of viral RNA shedding rebound.

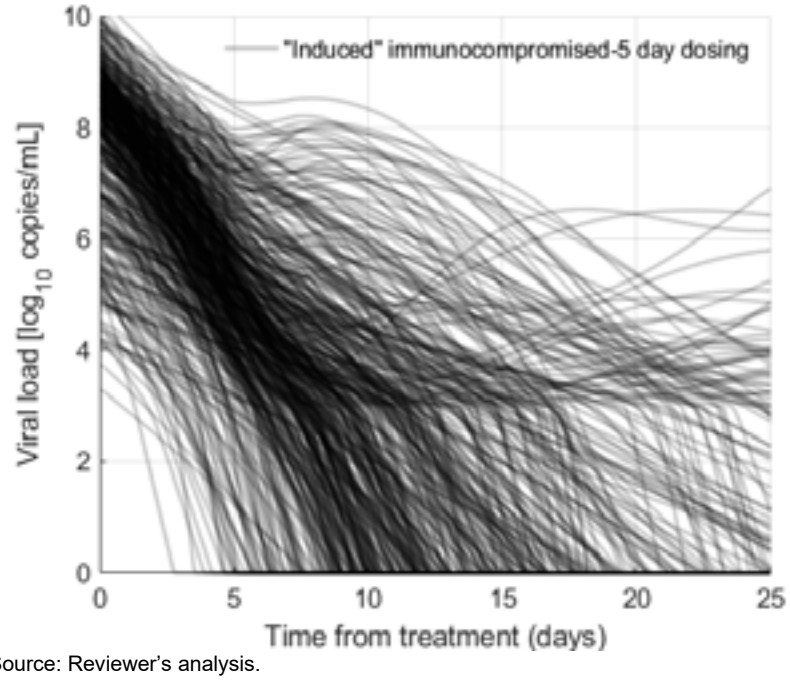
It is worth noting that the nominal virtual population was only calibrated to the observed rate of post-treatment viral RNA shedding rebound in the treatment arm with no regards to the observed rate of viral RNA rebound in the placebo arm. Therefore, the comparison for viral RNA rebound is only interpreted under the treatment condition. Another caveat is the inconsistent time frame to capture viral RNA rebound between the numerator and denominator of odds ratio. As noted in the viral RNA rebound definition, the event is captured post treatment termination, therefore, for treatment longer than 5 days in the numerator, the effect on viral RNA rebound is a combined effect of time elapse and treatment, despite that few viral RNA rebound events are expected during treatment. In order to minimize the time dependent effect on viral RNA rebound, a consistent time frame instead of post treatment (i.e., 5 days after the treatment) was used to recalculate odds ratio for different duration of treatment in immunocompromised virtual patients in a sensitivity analysis by Reviewer. The result agrees with Applicant's result that the risk of viral RNA rebound with 10 days of treatment in immunocompromised virtual populations is comparable to that with 5 days of treatment in a high-risk immunocompetent population (Figure 46).

Figure 44. Predicted Mean Viral Dynamic With Longer Treatment Duration in the Two Immunocompromised Virtual Patients



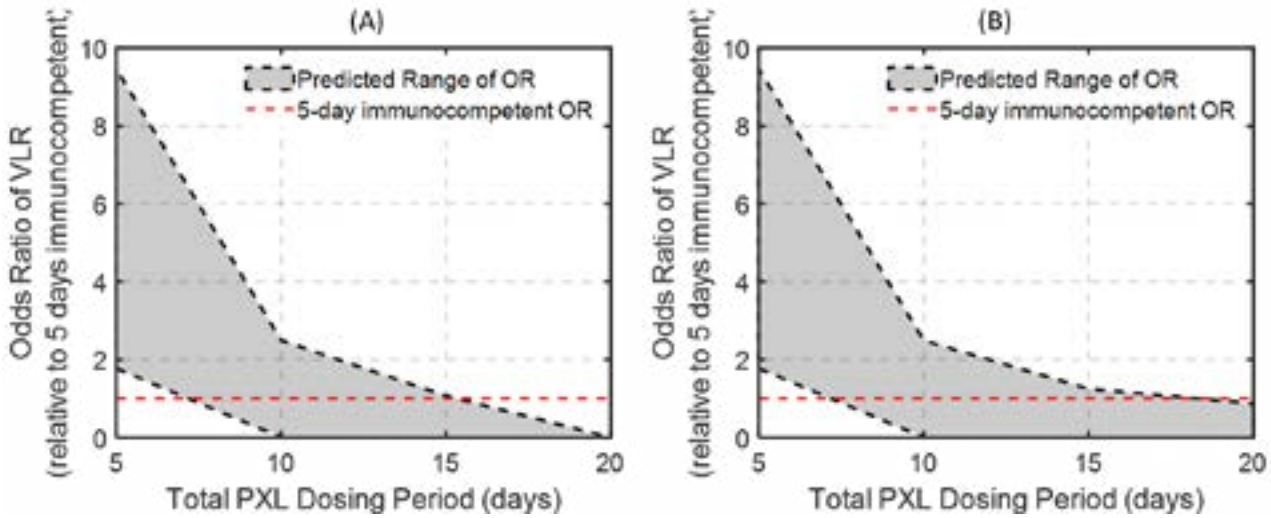
Source: Reviewer's analysis.
Note: The start of the treatment is set at 3 days after the peak viral RNA shedding/symptom onset. The line shows average viral RNA shedding over time.
Abbreviations: IC, immunocompromised; log, logarithm; PBO, placebo; RNA, r bonucleic acid; TRT, treatment

Figure 45. Viral Dynamics in Immunocompromised Virtual Patients With 5 Days of Dosing



Source: Reviewer's analysis.
Abbreviations: log, logarithm

Figure 46. Predicted Risk of Viral Load Rebound in Immunocompromised Patients for Increasing PAXLOVID Dosing Duration Relative to the Risk of Rebound Upon 5 Days of Dosing in a High-Risk Immunocompetent Population



Source: Adapted from Applicant's EPIC-IC QSP model summary, Figure 6.
Note: (A) Applicant's analysis, (B) Reviewer's analysis that differs in the time frame for capturing viral RNA rebound event.
Abbreviations: OR, odds ratio; PXL, paxlovid; QSP, quantitative systems pharmacology; RNA, ribonucleic acid; VLR, viral load rebound

The submitted QSP models were calibrated and validation with various sources of observational and interventional clinical data. The prospective simulations with the submitted QSP models were used to inform the treatment duration of PAXLOVID in EPIC-HR. Efficacy of PAXLOVID was later demonstrated in this trial, and the data were used to refine the QSP model

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such that it better captures the aggregate viral RNA shedding time course profiles in target population with or without treatment. Thus, the proposed QSP modeling as well as parameters sampled in virtual population are appropriate for depicting an average viral dynamics profile in mild-to-moderate COVID-19 outpatient population. To select the treatment duration for immunocompromised patients, the same modeling approach was adapted by developing a virtual population for immunocompromised patients. Results of QSP simulations showed that the treatment duration of 5 days, as indicated in the current EUA fact sheet and proposed label, might not be optimal for immunocompromised patients. Reviewer concluded that QSP modeling approach is appropriate in support of selecting treatment duration for the clinical trials in the overall PAXLOVID-eligible population (EPIC-HR trial) as well as immunocompromised patients (ongoing EPIC-IC trial).

14.5.2.7. Assessment of Model Risk

Table 106. Assessment of Model Risk

Assessment	Description[1]	Comments
Context of use	Describe the specific issue(s) that the QSP analyses will be used to address	Using QSP modeling approach to evaluate the optimal treatment duration for immunocompromised patients being tested in clinical trial, EPIC-IC.
Model influence	Describe the model influence, i.e., what is the weight of model predictions in decision-making considering the totality of evidence	Medium: QSP analyses provide predictions of viral dynamics under various exposure scenarios. Simulations results were used to support the selection of treatment duration in EPIC-IC. Clinical data from EPIC-HR are also used to inform the trial design of EPIC-IC.
Decision consequence	Discuss your decision consequence based on all available evidence i.e., potential safety or efficacy risk to patients if an incorrect decision is made.	Low: The efficacy and safety have been established by EPIC-HR, EPIC-SR, and EPIC-PEP, and PAXLOVID is used widely in real-world. Risks of therapeutic failure or unknown adverse effects in immunocompromised patients receiving PAXLOVID, based on current and upcoming information from EPIC-IC, are considered low.

Source: Reviewer's analysis.
1. (Kuemmel et al. 2020).
Abbreviations: QSP, quantitative system pharmacology

14.5.3. Applicant's Population PK Analysis

14.5.3.1. Objectives

The primary objectives of the Applicant's analysis were to:

- Characterize the PK of nirmatrelvir in healthy adults and mild-to-moderate COVID-19 patients.
- Evaluate time- and dose-dependent change in PK.

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14.5.3.2. Overview of Studies Included in Population PK Analysis

Applicant conducted a population PK analysis to characterize the PK of nirmatrelvir in the presence of ritonavir (RTV) which is used to inhibit CYP3A-mediated metabolism of nirmatrelvir, identified covariate factors that could affect disposition, and exported the individual exposure estimates for subsequent exposure-response (E-R) analysis. Population PK analysis included the studies listed in Table 107.

Table 107. Clinical Studies Used in Population PK Analysis

Study (n)	Description	Dose and Sampling Time
C4671001 (n=43)	A Phase 1 randomized, single- and multiple-dose escalation study to evaluate the safety, tolerability, and PK of NIR in healthy adult participants	Single Dose • 250 mg, 300 mg, 750 mg Multiple Doses • Repeated: 75 mg/250 mg/500 mg q12h • Intense: 750 mg at 0,2, & 4 hours PK Sampling • Rich sampling up to 72 hours for single dose, up to 12 hours on Days 1, 5, & 10 for multiple repeated doses, up to 96 hours for multiple intense doses.
C4671010 (n=16)	A Phase 1 study to assess the PK, safety, and tolerability of NIR/RTV in adult participants with moderate hepatic impairment and healthy participants with normal hepatic function	Dose • Single 100 mg dose PK Sampling • Rich sampling up to 48 hours
C4671010 (n=34)	A Phase 1 study to assess the PK, safety, and tolerability of NIR/RTV in adult participants with renal impairment and in healthy participants with normal renal function	Dose • Single 100 mg dose PK Sampling • Rich sampling up to 48 hours
C4671012 (n=23)	A Phase 1 crossover study to estimate the effect of NIR/RTV and RTV on the PK of dabigatran (a P-gp substrate) in healthy participants	Dose: • 300 mg q12h for 3 doses PK Sampling: • Rich sampling up to 48 hours on Day 2
C4671013 (n=11)	A Phase 1 crossover study to estimate the effect of NIR/RTV and RTV on the PK of midazolam (a CYP3A substrate) in healthy participants	Dose • 300 mg q12h for 9 doses PK Sampling • Rich sampling up to 72 hours on Day 5
C4671014 (n=12)	A Phase 1 crossover study to estimate the effect of carbamazepine (a strong CYP3A inducer) on the PK of NIR/RTV in healthy participants	Dose • Single dose: 300 mg PK Sampling • Rich sampling up to 48 hours

Study (n)	Description	Dose and Sampling Time
C4671015 (n=11)	A Phase 1 crossover study to estimate the effect of itraconazole (a strong CYP3A inhibitor) on the PK of NIR/RTV in healthy participants	Multiple Dose • 300 mg q12h for 5 doses PK Sampling • Rich sampling up to 72 hours on the last day of dosing
C4671005 EPIC-HR (n=1087)	A Phase 2/3 study to investigate orally administered NIR/RTV compared with placebo in non-hospitalized symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illness	Multiple Dose • 300 mg q12h for 10 doses PK Sampling • 1 sample collected 30-90 min post-dose on Day 1, 1 predose sample on Day 5.

Source: Applicant's PK report, Table 1.
Note: Synopsis of clinical data that only included the cohorts/treatment arms with 100 mg ritonavir co-administration.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; CYP3A, cytochrome P450, family 3, subfamily A; n, number of subjects in sample; NIR, nirmatrelvir; P-gp, P-glycoprotein; PK, pharmacokinetic; q12h, every 12 hours; RTV, ritonavir

14.5.3.3. Population PK Model

The population PK analysis was conducted via nonlinear mixed-effects modeling with the *NONMEM* software, version 7.5.0 using first-order conditional estimation with *INTERACTION* option (*FOCEI*).

Baseline patient characteristics of the population PK dataset are summarized in Table 108. A total of 2408 samples from healthy participants and 1996 ambulatory COVID-19 patients (EPIC-HR) were included for the population PK analysis. BLQ accounts for 14% of PK samples in the pooled data and 20% of PK samples in EPIC-HR study. Majority of BLQ samples are post-dose and within 24 hours of dosing. Post-dose BLQ after single dose of NIR/RTV co-administration was not observed in Phase 1 studies when the drug was taken at full compliance. In EPIC-HR, the large proportion of BLQ samples could be due to the nature of this study design that non-compliance or inaccurate documentation of dosing and/or sampling time is plausible. Concentrations collected before the first dose were excluded from the PK analysis as well as post-dose observations that were below the limit of quantification (BLQ).

Covariates explored included age, body weight, sex, race, GMI, creatinine clearance, disease status (heathy, coronavirus disease [COVID], hepatic impaired), CYP3A inhibitors/inducers, dose, and formulation.

The final population PK parameters for nirmatrelvir with RTV co-administration are presented in the Table 109. The final PK models were parameterized in terms of Ka, CL, V2, Q, and V3. Covariates including COVID-19 disease, CYP3A inducer/inhibitor, formulation, dose, age were statistically significant.

Estimated fixed and random effect parameters were estimated with good precision (percent relative standard error [%RSE] <30%) with the exception of IIV of CL (35.9% RSE). The magnitude of the IIV was moderate to high except IIV of V2 which was 27.3%. Residual variability was small for phase 1 data, but high for phase 2/3 data which are exclusively from EPIC-HR. ETA shrinkages are moderate to high (>50%) for all parameters.

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The diagnostic plots showed no obvious bias in prediction relative to observations across the time range, however, there appears to be some bias across concentrations (Figure 47). The bias is primarily observed for concentrations from EPIC-HR (C4671005) which might be due to the inaccuracy of dosing/sampling and other reasons related to compliance of the trial (Figure 48). Visual predictive check for the final PK models were stratified by dose (Figure 49). There was bias between prediction and observations observed in EPIC-HR for high and low concentrations but not for median concentrations. Overall, the prediction corrected visual predictive check plots generally captures the central tendency and variability of the observed concentrations.

Table 108. Patient Characteristics in NIR PK Analysis Dataset

Characteristics	All (n=1237)	COVID-19 (n=1087)	Healthy (n=150)
Race			
White	865 (69%)	777 (62%)	88 (7%)
Black	105 (8%)	56 (4%)	49 (4%)
Asian	162 (13%)	152 (12%)	10 (1%)
American Indian	95 (8%)	95 (8%)	0
Other/unknown	10 (1%)	7 (1%)	3 (0%)
Intrinsic Factors			
Female, n (%)	580 (46%)	541 (43%)	39 (3%)
Body weight (kg), median (range)	79 (42-158)	80 (42-158)	77 (53-114)
Age (years), median (range)	45 (18-86)	45 (18-86)	49 (20-76)
Baseline Values			
Baseline BSA, normalized CLCR (mL/min/1.73m^2), median (range)	119 (16-318)	124 (23-318)	96 (16-247)
Baseline BMI (kg/m^2), median (range)	28 (17-58)	28 (17-58)	27 (20-40)

Source: Applicant's PK report, Table 6.
Abbreviations: BMI, body mass index; BSA, bovine serum albumin; CLCR, creatinine clearance; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; n, number of subjects in sample; NIR, nirmatrelvir; PK, pharmacokinetic

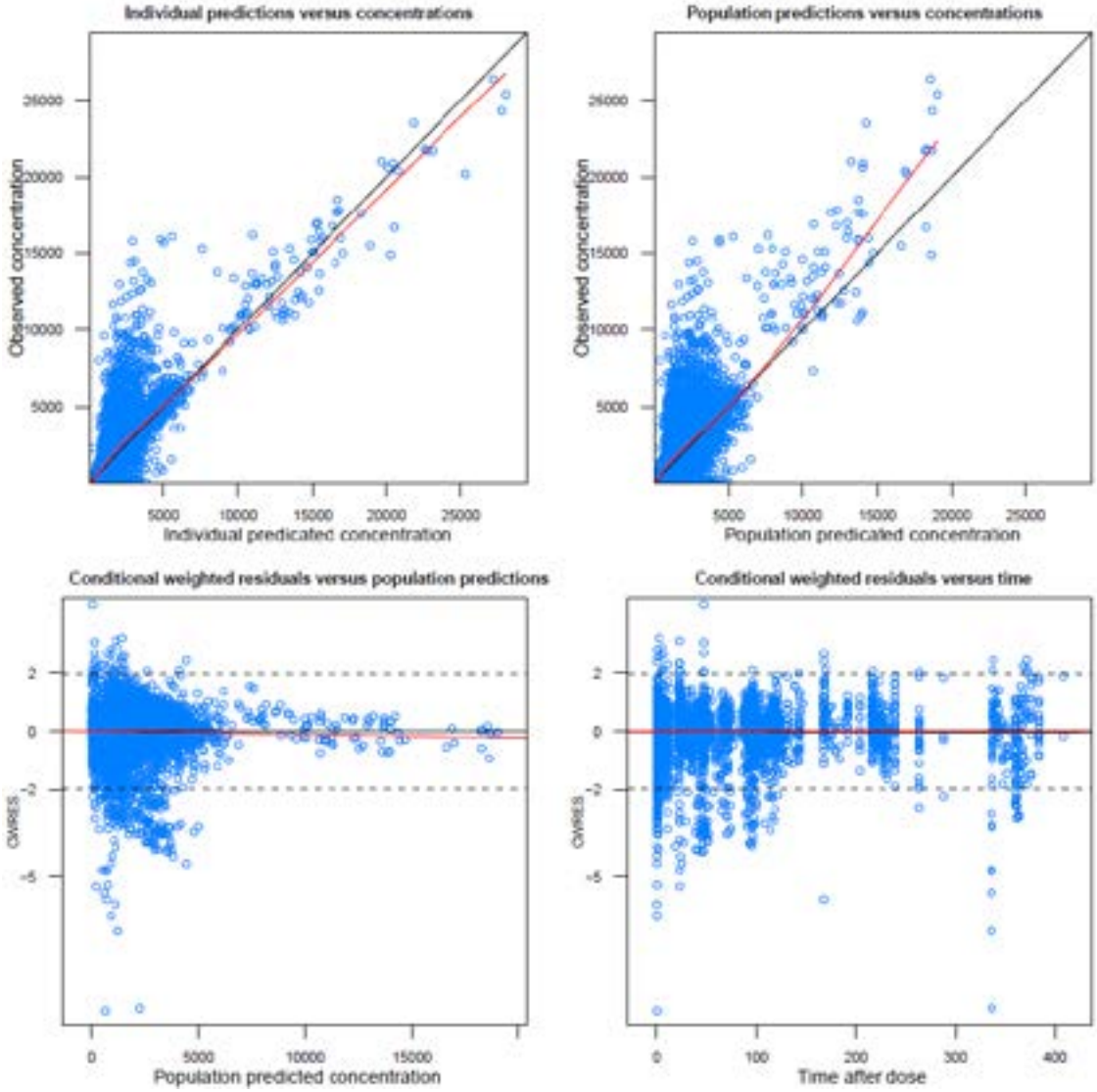
Table 109. Population Pharmacokinetic Model Parameters for NIR With RIT Co-Administration

	Final Run			Sampling Importance Resampling Run
Parameter	Estimate	% RSE	Shrinkage (%)	Median (2.5th, 97.5th percentile)
CL (L/h)	9.09	3.6		8.98 (8.53, 9.42)
V2 (L)	56.9	4.3		57.5 (53.6, 62.6)
Q (L/h)	1.28	14.2		1.02 (0.704, 1.36)
V3 (L)	12.8	11.1		10.1 (8.22, 12.7)
Ka (1/h)	0.873	8.9		0.908 (0.791, 1.03)
$nCLCR_{breakpoint}$ (mL/min/1.73m^2)	70.1	0.03		70.1 (70.0, 70.1)
$nCLCR_{power}$ for <$nCLCR_{breakpoint}$	1.05	8.4		0.907 (0.748, 1.09)
$F1_{power}$	-0.409	8.7		-0.401 (-0.458, -0.341)
Effect of COVID-19 on CL	-0.341	10.7		-0.348 (-0.410, -0.288)
Effect of Carbamazepine on CL	0.74	27.1		0.740 (0.583, 0.939)
Effect of Itraconazole on CL	-0.308	7.2		-0.303 (-0.332, -0.272)
Power of age effect on V2	-0.425	17.6		-0.416 (-0.553, -0.285)
Effect of 150 mg tablet on F1	-0.379	10.1		-0.391 (-0.454, 0.331)
IIV-CL (%CV)	35.9	48.8	55.9	35.7 (30.5, 42.9)
IIV-V2 (%CV)	27.3	17.6	68.8	31.2 (27.5, 34.1)
IIV-V3 (%CV)	58.7	26.6	79.2	59.2 (44.9, 71.6)
IIV-Ka (%CV)	60.7	20.9	63.1	60.5 (51.7, 68.6)

Parameter	Final Run Estimate	% RSE	Shrinkage (%)	Sampling Importance Resampling Run Median (2.5th, 97.5th percentile)
Proportional error Phase 1 (%)	32.4	5.7	6.28	31.9 (30.7, 33.4)
Proportional error Phase 2/3 (%)	139	3.8		136 (131, 142)
Additive error (ng/mL)	10 fixed			

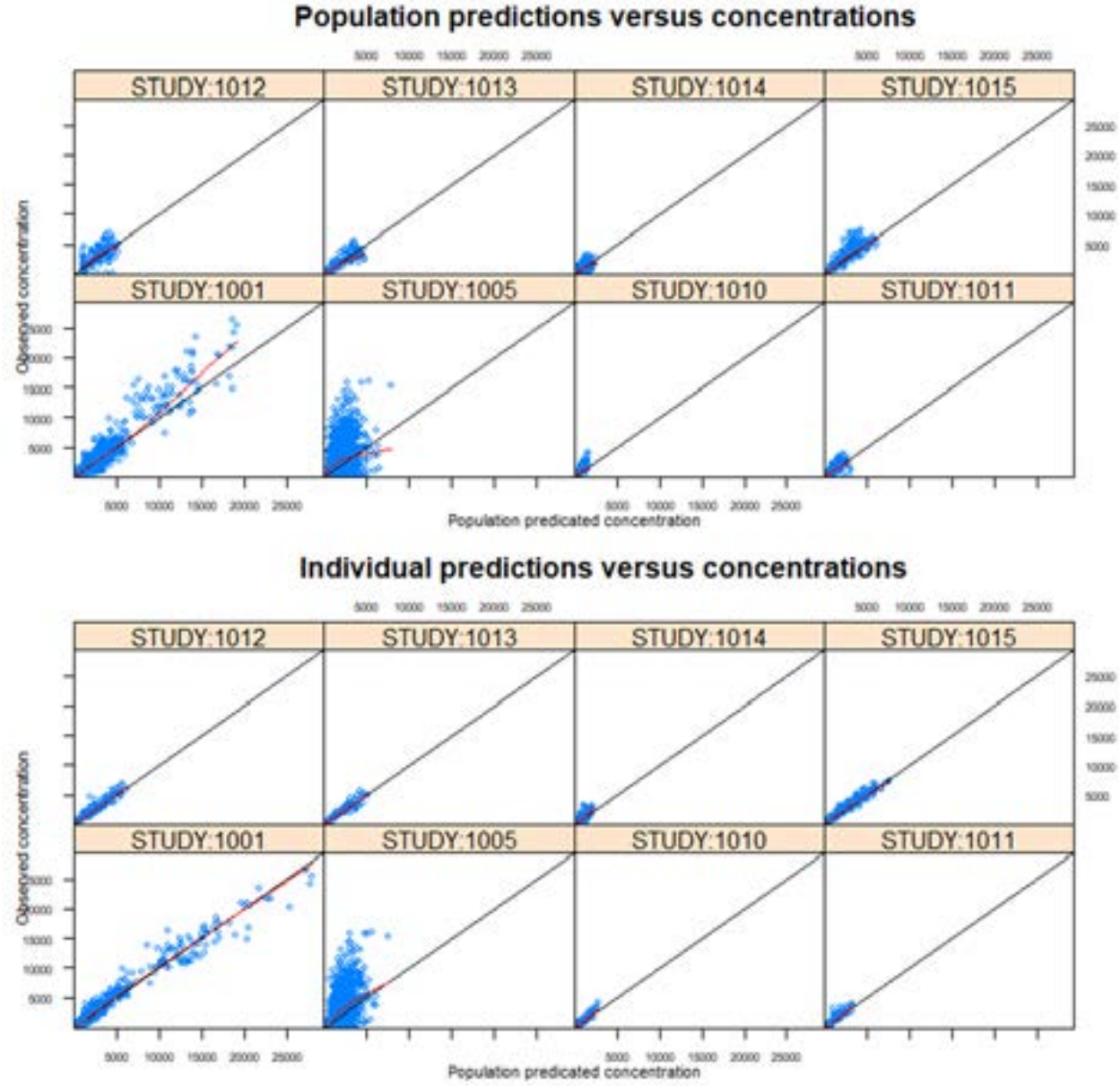
Source: Applicant's PK report, Table 12.
Note: Weight effect is parameterized as (Weight/70 kg)^0.75 on CL and Q, and (Weight/70 kg)^1 on V2 and V3
Note: Effect of COVID-19, Carbamazepine, or itraconazole was parameterized as a proportional shift of (1+THETA) on CL.
Note: Power of age effect = exponent for (Age/45 years) on V2.
Abbreviations: CL, apparent clearance of NIR; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; CV, coefficient of variation; F1, relative bioavailability; $F1_{power}$, exponent of power function for (Dose/300 mg) on F1; IIV, interindividual variability; Ka, first-order absorption rate constant; nCLCR: body surface area-normalized creatinine clearance; $nCLCR_{breakpoint}$, breakpoint for nCLCR effect on CL; $nCLCR_{power}$, exponent of power function for (nCLCR/70.1 mL/min/1.73m^2) on CL; NIR, nirmatrelvir; PK, pharmacokinetic; Q, inter-compartmental clearance; RIT, ritonavir; %RSE, percent relative standard error; V2, central volume of distr bution; V3, peripheral volume of distr bution

Figure 47. Goodness-of-Fit for NIR Population PK Model



Source: Reviewer's analysis.
Abbreviations: CWRES, conditional weighted residuals; NIR, nirmatrelvir; PK, pharmacokinetic

Figure 48. Prediction vs. Concentrations by Study



Source: Reviewer's analysis.

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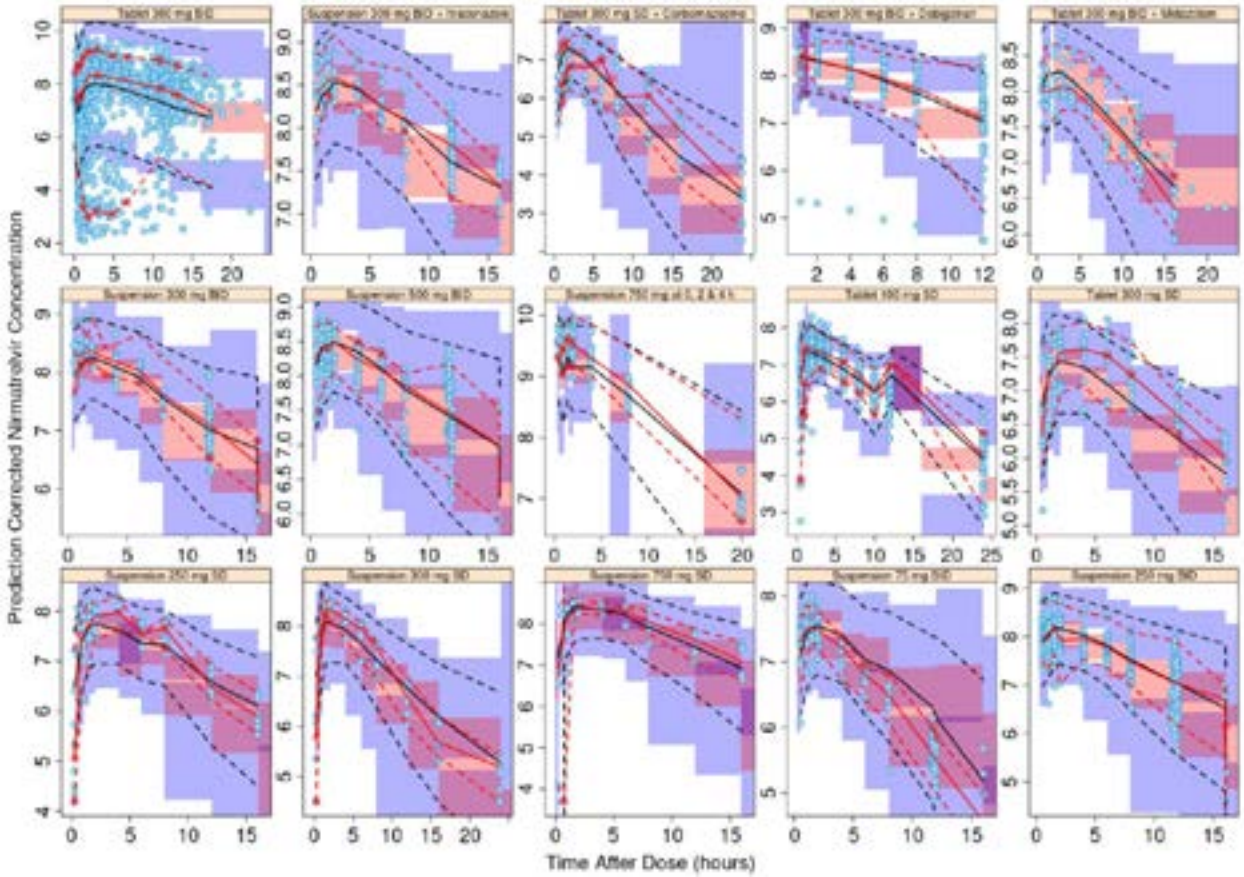
Figure 49. Visual Predictive Check for NIR Population PK Model Stratified by Treatment



Source: Applicant's PK report, Figure 4.
Note: Symbols = observed NIR concentrations; Red solid and broken lines = median, 5th & 95th confidence intervals of the observed data; Black solid and broken lines = median, 5th & 95th confidence intervals from 1000 simulations with surrounding 95% shaded area in pink and blue. Excluded observations with time after dose ≥24 hours.
Abbreviations: BID, twice daily; NIR nirmatrelvir; PK, pharmacokinetic; SD, single dose

The PK model appropriately described the data for both PK/pharmacodynamic (PD) modeling and descriptive labeling purposes. A large proportion of post-dose BLQ is observed which is unlikely to be related to the property of drug disposition. The evaluable concentrations were quantifiable for reliable estimation of PK parameters in the two-compartment model with first-order absorption. The Applicant indicated that there is bias between the observed and predicted concentrations in EPIC-HR (C4671005) only. It is because that PK sampling/dosing schedule in this trial was inaccurate. We notice that the dosing schedule is obtained through subject log only in this trial, not for others. It might provide a possible explanation on the bias. ETA shrinkage is high and would not generate credible individual parameter estimates in E-R analysis.

14.5.4. Applicant's Exposure-Response Analyses

14.5.4.1. Overview of Studies Included in the E-R Analysis

Efficacy and safety data from the EPIC-HR was utilized for the E-R analyses. Exploratory analyses were conducted using R version 3.6.1 or later.

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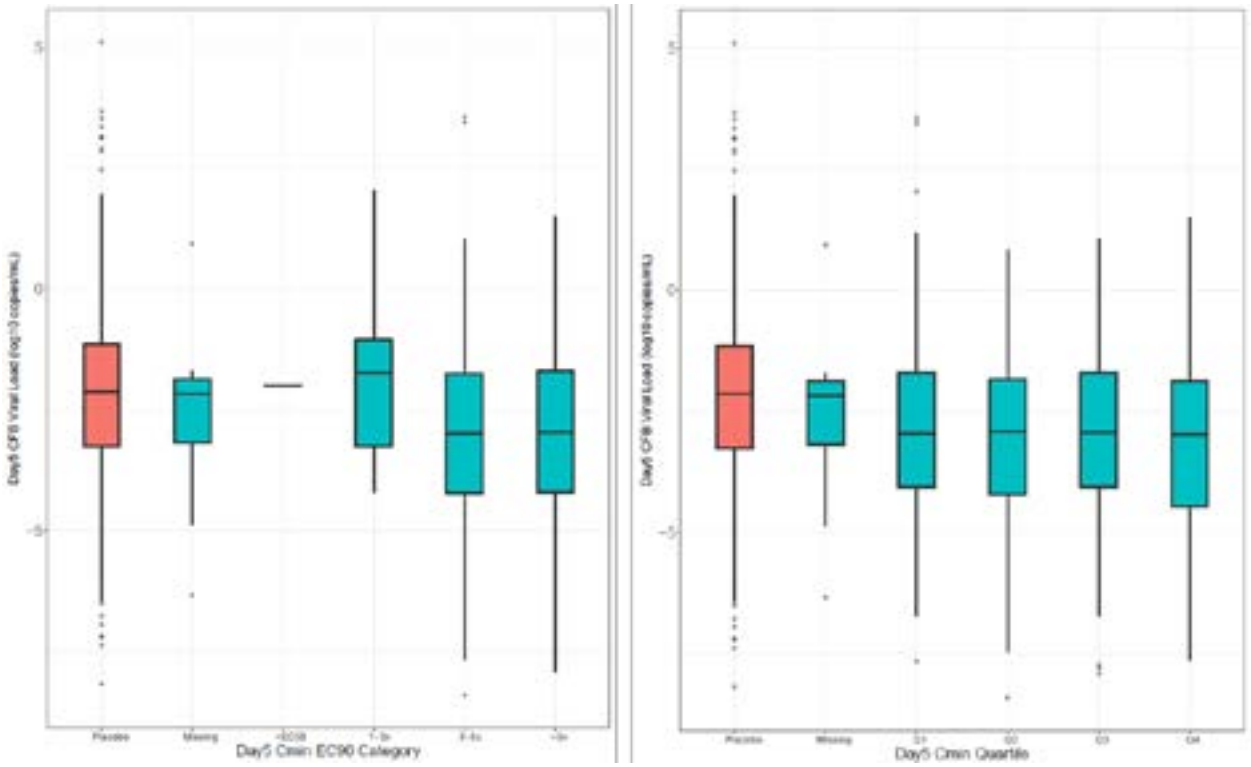
14.5.4.2. E-R for Efficacy

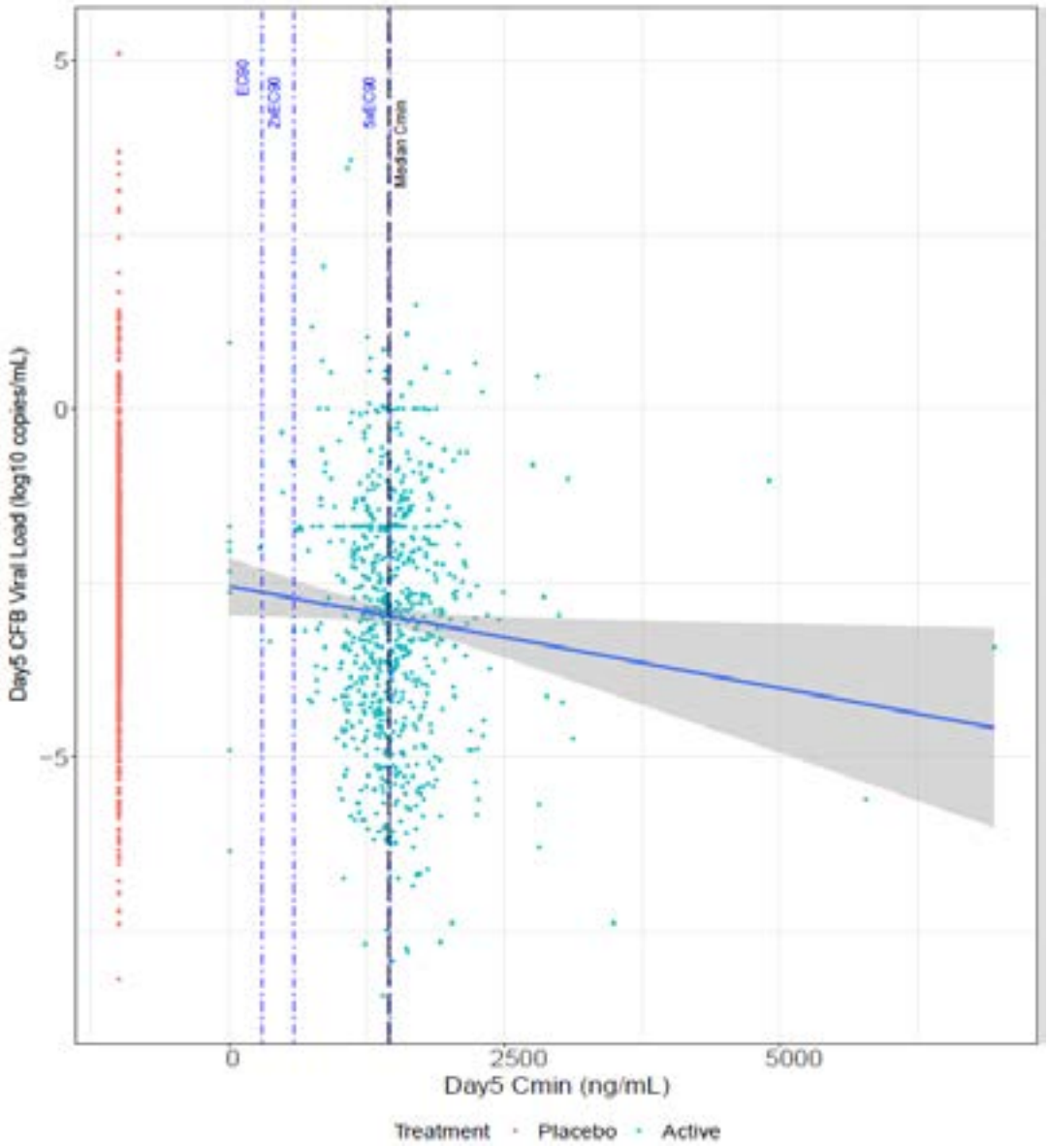
E-R relationship between the change from baseline in viral RNA shedding and C_{min} at Day 5 of treatment was explored by categorizing C_{min} relative to nirmatrelvir in vivo EC_{90} value (i.e., <EC_{90}, 1-3x EC_{90}, 3-5x EC_{90}, and >5x EC_{90} values) or in quartiles (Figure 50). Linear regression was also conducted which predicted a small slope for C_{min}, which predicts to a 0.08 reduction in viral RNA shedding (in Log_{10} copies/mL) for an increase of 1 EC_{90} (Figure 51). This seemingly suggests an enhanced viral clearance with an increased concentration; however, the variability is very large across concentrations and few concentrations in PAXLOVID treated patients were under 3x EC_{90} value. By comparison across quartiles, there was no obvious difference in the change from baseline in viral RNA shedding.

Figure 50. Day 5 Change From Baseline in Viral Load by D5 NIR C_{min} Relative to EC_{90} Value or in Quartiles



Source: Applicant's ER-efficacy report, Figure 1 and 2.
Note: Placebo participants represented in red, active PAXLOVID treatment participants represented in blue. Boxes extend from 25th to 75th percentiles with center line representing median; whiskers extend to 1.5 times the inter-quartile range with individual dots representing outlying points.
Abbreviations: CFB, change from baseline; C_{min}, minimum plasma concentration; D5, Day 5; EC90, 90% maximal effective concentration; ER, exposure-response; log, logarithm; NIR, nirmatrelvir; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4

Figure 51. Day 5 Change From Baseline in Viral Load by D5 NIR C_{min}



Source: Applicant's ER-efficacy report, Figure 3.
Note: Linear regression line shown in solid blue with associated 95% confidence interval in gray. Median predicted Day 5 C_{min} shown with black dashed line; EC90 value reference lines shown with blue dot-dash lines. Placebo participants represented in red, active PAXLOVID treatment participants represented in blue.
Abbreviations: CFB, change from baseline; C_{min}, minimum plasma concentration; D5, Day 5; EC90, 90% maximal effective concentration; ER, exposure-response; log, logarithm; NIR, nirmatrelvir

14.5.4.3. E-R for Safety

E-R relationship between major safety events and observed/suspected lab abnormalities and exposures at Day 5 of treatment (i.e., C_{max}, C_{min}, AUC_{tau}) was explored by categorizing the exposure in quartiles.

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The analysis included the following AE/lab abnormalities:

- Safety events
  - Grade ≥1 dysgeusia
  - Grade ≥1 diarrhea, headache
  - Grade ≥1 vomiting
  - Grade ≥1 nausea
  - Grade ≥1 hypertension
- Lab abnormalities
  - Activated partial thromboplastin time (aPTT) >1.1x upper limit of normal (ULN)
  - Prothrombin time (PT) >1.1x ULN
  - Platelets <0.5x lower limit of normal (LLN)
  - Platelets >1.75x ULN
  - Leukocytes <0.6x LLN
  - Leukocytes >1.5x ULN
  - Glucose >1.5x ULN
  - Creatinine kinase >2.0x ULN
  - Fibrinogen >1.25x Baseline
  - D-Dimer >1.5x ULN

Univariate logistic regression was conducted for the selected safety endpoints. Table 110 summarizes the event number, exposure in the final model (selected by the largest deviance and smallest p-value among the exposure metrics), p-value for logistic regression, and AUC of receiver-operating characteristic curve. The significant E-R relationships were identified for Grade ≥1 dysgeusia, Grade ≥1 diarrhea, leukocytes <0.6x LLN, and fibrinogen >1.25x baseline. Among them, all expect dysgeusia had either few events or AUC_{ROC} close to 0.5 which indicates poor model predictive performance. For dysgeusia, a positive relationship was observed but the slope was relatively flat for 95% of predicted C_{max} (Figure 52). The predicted probability of Grade ≥1 dysgeusia at the maximal predicted C_{max} with an event is 13%.

Table 110. E-R Analysis for Safety Events in EPIC-HR

AEs	Grade Assessed	Event Number (%)[a]	Exposure in Final Model	Slope	p-value for E-R	AUC_{ROC}
Dysgeusia	≥ Grade 1	63 (2.86%)	C_{max} (ng/mL)	0.000502	p<0.0001	0.742 (0.697-0.788)
Headache	≥ Grade 1	30 (1.36%)	C_{min} (ng/mL)	3.47E-05	p=0.8765	0.514 (0.411-0.616)
Diarrhea	≥ Grade 1	52 (2.36%)	C_{min} (ng/mL)	0.000369	p=0.0158	0.593 (0.518-0.668)
Nausea	≥ Grade 1	34 (1.54%)	C_{max} (ng/mL)	1.93E-05	p=0.8424	0.512 (0.408-0.617)
Vomiting	≥ Grade 1	21 (0.95%)	C_{max} (ng/mL)	0.000119	p=0.3216	0.564 (0.434-0.694)
Hypertension	≥ Grade 1	8 (0.36%)	C_{max} (ng/mL)	0.000324	p=0.0899	0.693 (0.494-0.892)

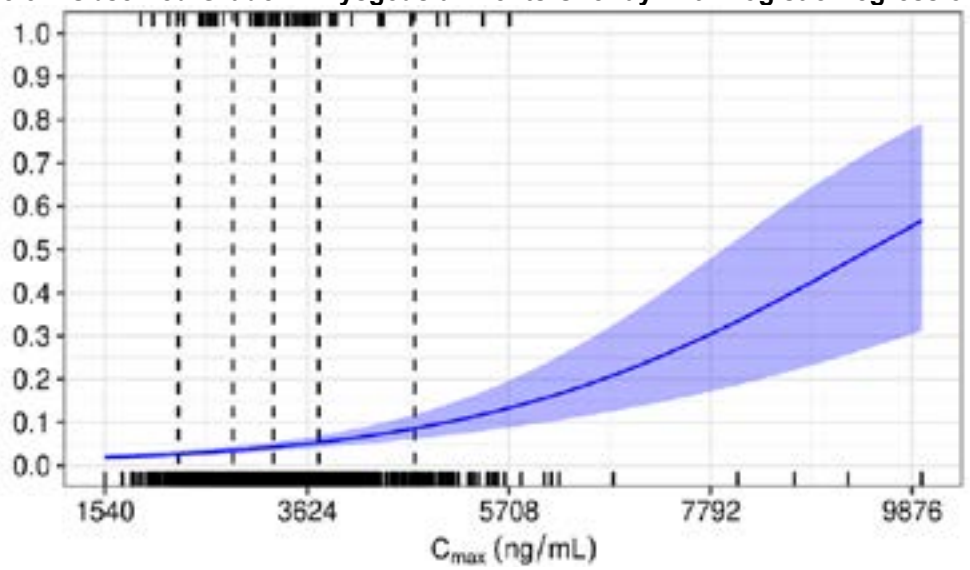
Source: Applicant's clinical pharmacology IR response on August 30, 2022, Table 1 and 2; Synopsis from Applicant's ER-safety report.
[a.] Event numbers includes all participants regardless of treatment group. % = % total of study participants.
Abbreviations: AE, adverse event; AUC_{ROC}, area under the receiving operating characteristic curve; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; E, exponentiation with base 10; E-R, exposure-response

Table 111. E-R Analysis for Lab Abnormalities in EPIC-HR

Lab Test (Unit)	Clinical Cut-Off	Event Number (%)[a]	Exposure in the Final Model	Slope	p-value for E-R	AUC_{ROC}
aPTT (sec)	> 1.1 x ULN	366 (16.62%)	C_{max} (ng/mL)	-1.61E-05	p=0.6203	0.507 (0.477-0.537)
Prothrombin time (sec)	> 1.1 x ULN	202 (9.17%)	C_{min} (ng/mL)	-7.91E-05	p=0.3922	0.515 (0.473-0.554)
Platelets (10^9/L)	<0.5 x LLN	5 (0.23%)	AUC_{tau} (ng*hr/mL)	0.000876	p=0.9928	0.747 (0.737-0.758)
Platelets (10^9/L)	> 1.75 ULN	15 (0.68%)	C_{min} (ng/mL)	0.000361	p=0.3079	0.56 (0.417-0.703)
Leukocytes (10^9/L)	< 0.6 x LLN	10 (0.45%)	AUC_{tau} (ng*hr/mL)	-6.70E-05	p=0.0493	0.68 (0.548-0.813)
Leukocytes (10^9/L)	>1.5 x ULN	25 (1.14%)	C_{max} (ng/mL)	7.59E-05	p=0.4949	0.528 (0.428-0.627))
Glucose (mg/dL)	>1.5 x ULN	156 (7.08%)	C_{min} (ng/mL)	-4.58E-05	p=0.6576	0.482 (0.442-0.523)
Creatinine Kinase (U/L)	> 2.0 x ULN	116 (5.27%)	C_{min} (ng/mL)	0.00012	p=0.2912	0.516 (0.467-0.564)
Fibronogen (mg/dL)[b]	> 1.25 x baseline	413 (18.76%)	AUC_{tau} (ng*hr/mL)	-1.50E-05	p<0.0001	0.558 (0.53-0.587)
D-Dimer[b]	> 1.5 x ULN	325 (14.76%)	C_{min} (ng/mL)	0.000169	p=0.0274	0.551 (0.519-0.583)

Source: Applicant's clinical pharmacology IR response on August 30, 2022, Table 1 and 2; Synopsis from Applicant's ER-safety report.
[a.] Event numbers includes all participants regardless of treatment group. %=% total of study participants.
[b.] Treatment-emergent AEs.
Abbreviations: AE, adverse event; aPTT, activated partial thromboplastin time; AUC_{ROC}, area under the receiving operating characteristic curve; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; E, exponentiation with base 10; E-R, exposure-response

Figure 52. Observed Grade ≥1 Dysgeusia Events Overlay With Logistic Regression Model



Source: Applicant's ER-safety report, Figure A2.2.
Note: The vertical dashed lines represent the observed 0.05, 0.25, 0.5, 0.75 and 0.95 quantiles of the dependent variable.
Abbreviations: C_{max}, maximum plasma concentration; E-R, exposure-response

In the Applicant's analyses for efficacy and safety based on the data from EPIC-HR, a flat relationship was generally observed across the exposure range (or substantial part if not all) for viral RNA shedding reduction from baseline and safety endpoints. The analysis is considered exploratory with caveats of narrow exposure range and inaccurate individual exposures due to moderate to high ETA shrinkages in population PK analysis. The results/conclusions thus require further evaluation with the clinical data.

14.6. Physiologically Based Pharmacokinetic Modeling Review

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's physiologically based pharmacokinetic (PBPK) analyses to:

- Evaluate the drug-drug interaction (DDI) potential of nirmatrelvir, in the nirmatrelvir/ritonavir combination product, as a victim of moderate and weak CYP3A inducers.

The Division of Pharmacometrics has reviewed the PBPK reports (032551, 083028 and 074428), the responses to Food and Drug Administration's (FDA's) information requests (resp-fda-clin-

pharm-ir-05oct2022, resp-fda-ir-pbpk-01-nov-2022, response-30-oct-22-ir-alt-dosage, resp-13dec2022-ir-clin-pharmacology), and the modeling supporting files to conclude that:

- The ritonavir model used by the Applicant is inadequate to predict the effects of CYP3A inducers on the exposure of nirmatrelvir/ritonavir combination.
- The reviewer used an alternative ritonavir model and predicted that weak and moderate CYP3A inducers are expected to have minimal effects on nirmatrelvir exposure in the nirmatrelvir/ritonavir 300/100 mg product.

Background

Nirmatrelvir (also known as PF-07321332) is a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) main protease (M^{pro}: also referred to as 3CLpro or nsp5 protease) inhibitor, currently being developed for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults (b) (4) who are at high risk for progression to severe COVID-19, including hospitalization or death. PAXLOVID is 300 mg nirmatrelvir (two 150 mg tablets) co-packaged with 100 mg ritonavir (one 100 mg tablet). Ritonavir is not active against SARS-CoV-2 M^{pro}. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir. These three tablets must be taken together twice daily for 5 days with or without food.

Following oral administration of nirmatrelvir/ritonavir, the increase in systemic exposure of nirmatrelvir was less than dose proportional up to 750 mg as a single dose and up to 500 mg twice daily as multiple doses (C4671001). Twice-daily dosing over 10 days achieved steady state on Day 2 with approximately 2-fold accumulation (C4671001). After a standardized FDA high-fat meal, the mean C_{max} and AUC of nirmatrelvir increased approximately 61% and 20%, compared to the fasted state, following administration of a 300 mg nirmatrelvir (2x 150 mg)/100 mg ritonavir tablets (C4671019).

Nirmatrelvir is extensively metabolized in vitro, and fraction metabolized by CYP3A4 was estimated to be 99% (084546 and 072016). In the presence of 100-mg ritonavir, the mean AUC and C_{max} of nirmatrelvir increased approximately 8- and 3.3-fold, respectively, confirming that nirmatrelvir is a sensitive CYP3A substrate (C4671001). Following coadministration of 300/100 mg nirmatrelvir/ritonavir twice daily with 200 mg itraconazole once daily, nirmatrelvir AUC and C_{max} increased 38.8% and 18.6%, respectively, suggesting that majority of the CYP3A pathway in nirmatrelvir elimination was blocked by ritonavir (C4671015). The results from the human ADME study, conducted with a single 300 mg nirmatrelvir co-administered with 100-mg ritonavir given at -12, 0, 12 and 24 hours relative to nirmatrelvir dosing, showed that approximately 49.6% and 35.3% of radioactivity dose were recovered in the urine (46.7% unchanged parent) and the feces (23.3% unchanged parent), respectively and none of the metabolites formed in the in vitro metabolism studies were observed (C4671001).

Based on in vitro drug interaction studies, nirmatrelvir is determined to be a competitive and time-dependent inhibitor and an inducer of CYP3A (Table 112). Nirmatrelvir is a substrate of P-gp, but not a substrate of BCRP, OATP1B1/3, OATP2B1, NTCP, OCT1/2, OAT1/2/3, MATE1/2K, PEPT1 and OATP4C1 (Study PF-07321332_24Nov20_114514 and_110227, Studies PF-07321332_23Jul21_124535, PF-07321332_14Jul21_013448, and PF-07321332_10Aug21_124557). Nirmatrelvir has low potential to inhibit various efflux and uptake

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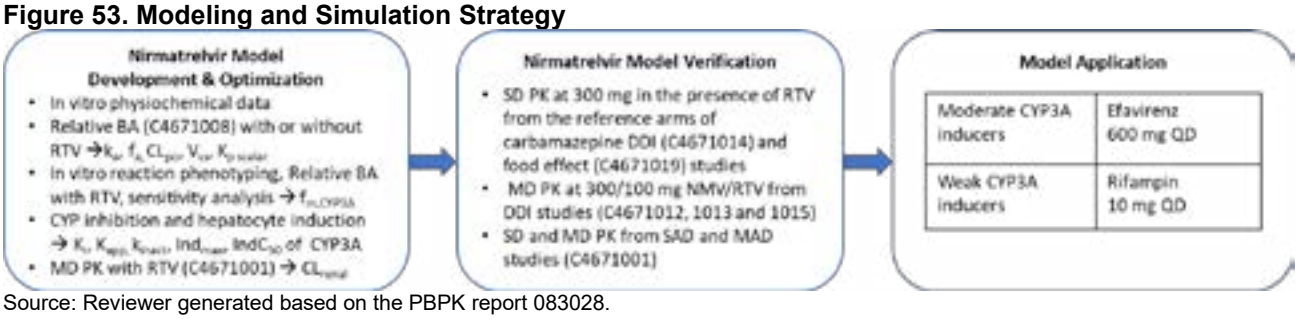
transporters except for P-gp and OATP1B1 (Table 112). In addition to the interaction studies with itraconazole and ritonavir, the Applicant conducted clinical DDI studies with carbamazepine (C4671014), dabigatran (C4671012) and midazolam (C4671013) to evaluate some of the in vitro findings. Refer to the Clinical Pharmacology review section for detail information on nirmatrelvir regarding ADME properties, in vitro and clinical studies used in the PBPK modeling.

Methods

Simulations were performed using the PK/PD Profiles mode in the Simcyp® Simulator (Versions 21, Certara, Sheffield, UK). Schemes of the PBPK modeling and simulation strategy are shown in Figure 53, which summarizes the studies used for nirmatrelvir model development and verification, and model applications in predicting DDI with weak and moderate CYP3A inducers. The final model input parameters were summarized in Table 112. The nirmatrelvir PBPK model consists of a first-order absorption model, a full PBPK model (method 2) for distribution, and an enzyme kinetics model and renal clearance for elimination. The Simcyp library files ritonavir first-order compound file (SV-ritonavir_FO), itraconazole and metabolite (SV-Itraconazole_Fasted Soln and SV-OH-Itraconazole), carbamazepine and metabolite (SV-Carbamazepine and SV-Carbamazepine-10,11-epoxide), and midazolam (Sim-Midazolam) were used without any modification unless otherwise noted. Simulations were performed in a virtual healthy subject population (sim-Healthy Volunteers).

Figure 53. Modeling and Simulation Strategy



Source: Reviewer generated based on the PBPK report 083028.
Abbreviations: BA, bioavailability; CL_{renal}, renal clearance; CL_{po}, oral clearance; CYP, cytochrome P450; DDI, drug-drug interaction; f_a, fraction absorbed; $f_{m,CYP3A}$, fraction metabolized by CYP3A; IndC50, concentration at the half of maximal fold induction; Ind_{max}, maximum fold induction; k_a, absorption rate constant; K_i, reversible inh bition rate constant; k_{inact}, maximal enzyme inactivation rate constant measured for a time-dependent inhibitor; K_{app}, unbound inhibitor concentration at 50% k_{inact}; ; MAD, multiple ascending dose; MD, multiple dose; NMV, nirmatrelvir; PBPK, physiological-based pharmacokinetics; PK, pharmacokinetics; QD, once per day; RTV, ritonavir; SAD, single ascending dose; SD, single dose; V_{ss}, steady-state volume of distribution; K_p, tissue:plasma partition coefficients;

Table 112. Final Input Parameters in the Nirmatrelvir Model

Category	Parameters	Value	Reference
PhysChem Properties	MW	499.5	General Pharmaceutics Profile
	LogP	1.84	General Pharmaceutics Profile
	Compound type	Neutral	General Pharmaceutics Profile
	B/P	0.6	PF-07321332_18Nov20_100444
	f_{up}	0.31	PF-07321332_23Nov_010657
Elimination	$CL_{int,CYP3A4}$ (µl/min/pmol)	0.148	Retrograde with (b) (4) C4671008
	Additional HLM CL_{int} (µl/min/mg)	3.23	Retrograde with C4671008
	$f_{u,mic}$	1	Default
	CLR (L/h)	3.4	C4671001 (Section 4.2)
Distribution	Kp Scalar	0.48	Parameter estimated with (b) (4) (C4671008) Full PBPK method 2
Absorption	k_a (h^{-1}) (b) (4)	2.63	Parameter estimation
	f_a (b) (4)	1	Assumed
	k_a (h^{-1}) (tablet)	0.55	Parameter estimation
	f_a (tablet)	0.73	C4671008 (Section 4.1)
	$f_{u,gut}$, Q_{gut} (L/h)	1, 10	Default
CYP3A4 Interaction	K_i (µM)	22.6	PF-07321332_04Nov_1139907
	K_{app} (µM)	13.9	PF-07321332_09Nov20_122202
	k_{inact} (h^{-1})	0.99	
	Ind_{max} (fold)	9.74	PF-07321332_18Oct20_102559 (Lot BNA, calibrated with rifampin)
	IndC50 (µM)	19.04	
	γ	1.63	
Transporter Interaction	Gut Apical P-gp K_i (µM)	55.2	PF-07321332_18Nov20_020944
	Gut Apical OCT1 K_i (µM)	138.1	
	Liver Sinusoidal OATP1B1 K_i (µM)	44.4	
	Liver Sinusoidal OATP1B3 K_i (µM)	283.2	
	Liver Sinusoidal OCT1 K_i (µM)	138.1	
	Liver Canalicular P-gp K_i (µM)	55.2	
	Liver Canalicular MATE1 K_i (µM)	111.7	
	Kidney Apical P-gp K_i (µM)	55.2	
	Kidney Apical MATEs K_i (µM)	111.7	
	Kidney Basal OCT2 K_i (µM)	954.5	
	Kidney Basal OAT3 K_i (µM)	520.6	

Source: Table 1 in PF-07321332_31May22_083028
Abbreviations: f_a, fraction absorbed; IndC50, concentration at the half of maximal fold induction; Ind_{max}, maximum fold induction; k_a, absorption rate constant; K_i, reversible inhibition rate constant; k_{inact}, maximal enzyme inactivation rate constant measured for a time-dependent inh bitor; K_I, unbound inh bitor concentration at 50% k_{inact}; $f_{u,gut}$, unbound fraction escaping gut metabolism; f_{up}, unbound fraction in the plasma; $f_{u,mic}$, unbound fraction in the microsomal incubation; B/P, blood to plasma concentration ratio; CL_{int}, intrinsic clearance; CL_R, renal clearance; MW, molecular weight; LogP, octanol-water partition coefficient; HLM, human liver microsome; Q_{gut}, nominal blood flow in the small intestine; K_p, tissue:plasma partition coefficients; (b) (4).

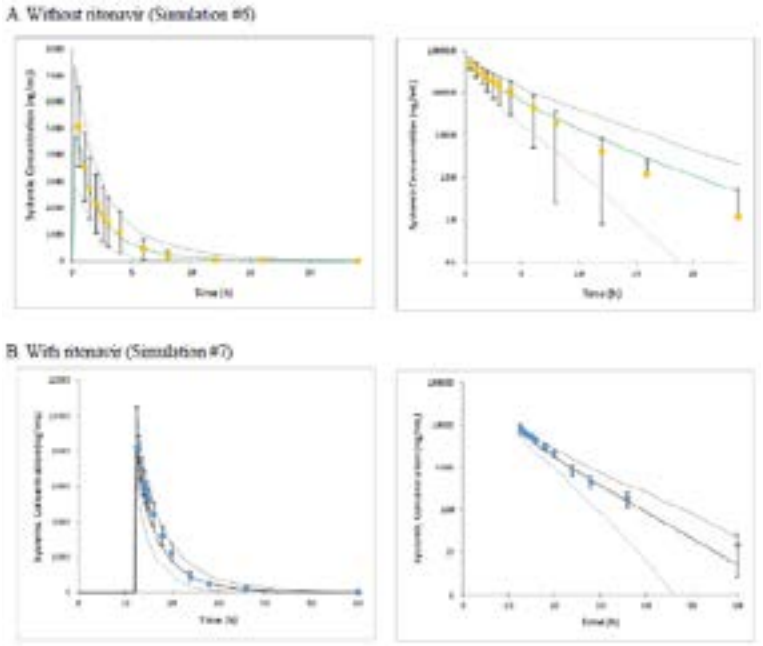
Results

Can the PBPK Model Adequately Describe the PK Profiles of Nirmatrelvir?

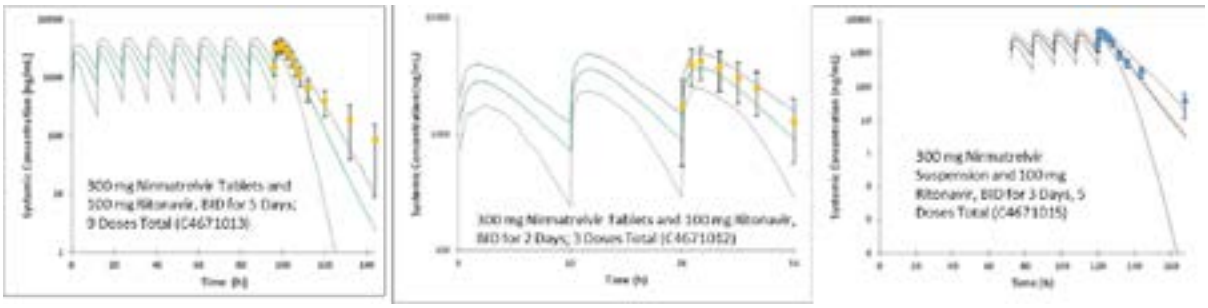
Yes. The nirmatrelvir PBPK model could reasonably well describe the PK of nirmatrelvir when ritonavir was present. Simulated and observed nirmatrelvir PK profiles and parameters following administration of single and multiple doses of 300/100 mg nirmatrelvir/ritonavir and different doses of nirmatrelvir co-administered with 100 mg ritonavir are summarized in Figure 54 and Table 113.

Figure 54. Simulated and Observed Nirmatrelvir PK Profiles Following Oral Administration of Single and Multiple Doses of Nirmatrelvir in Healthy Subjects

(A) Single Dose of 300 mg Nirmatrelvir (b) (4) Suspension Formulation Without or With Three Doses of 100 mg Ritonavir at -12, 0 and 12h



(B) Multiple Doses of Nirmatrelvir/Ritonavir (300/100 mg) Twice Daily



Source: (A) Figure 1 in the PBPK report 083028. (B) Figures 3 - 5 in the PBPK report 083028.
Note: In (A) Observed data from C4671008 the green and black line represents the predicted mean concentration the gray lines represent 5th and 95th percentile' the colored circles represent data points from participants. Vertical lines represent standard deviation.
Note: In (B) Depicted are simulated (lines) and observed data (circles). The green or black lines represent the mean data of the simulated population, and the grey lines represent 5% and 95% percentiles. Error bars represent standard deviation.
Abbreviations: BID, twice daily; PBPK, physiological-based pharmacokinetics; PK, pharmacokinetics

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Table 113. Simulated and Observed PK Parameters Following Oral Administration of Single and Multiple Doses of Nirmatrelvir/Ritonavir in Healthy Subjects

Simulation purposes	Dosing Regimen	Observed		Simulated		Simulated/Observed		Clinical studies
		C_{max} ng/mL	AUC_{inf} ng•h/mL	C_{max} ng/mL	AUC_{inf} ng•h/mL	C_{max}	AUC_{inf}	
Model development	Nirmatrelvir (b) (4)	4871	10580	4670	11111	0.96	1.05	C4671008
	NMV (b) (4) 300 mg SD+ RTV 100 mg q12h, 3 doses	8840	48680	8157	42399	0.92	0.87	C4671008
	NMV (tablet) 300 mg SD+ RTV 100 mg q12h, 3 dose	3347	35540	3260	31348	0.97	0.88	C4671008
Model verificaton	NMV (tablet)/RTV 300/100 mg SD	3696	36810	3404	33226	0.92	0.90	C4671019
	NMV (tablet)/RTV 300/100 mg q12h, 5 days	3875	30680	3815	29129	0.98	0.95	C4671013
	NMV (tablet)/RTV 300/100 mg q12h, 3 doses	4065	30080	3788	28707	0.93	0.95	C4671012
	NMV (suspension)/RTV 300/100 mg q12h, 5 doses	4678	33350	3921	30611	0.84	0.92	C4671015
	NMV (tablet)/RTV 300/100 mg SD	2210	23010	2768	25527	1.25	1.11	C4671014

Source: Tables 5 and 6 in the PBPK report 083028.
Note: Geometric means are reported.
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; C_{max}, maximum plasma concentration; NMV, nirmatrelvir; q12h, every 12 hours; PBPK, physiological-based pharmacokinetics; RTV, ritonavir; SD, single dose; (b) (4) suspension formulation

Can PBPK Analyses Predict the Effects of CYP3A Inducers on the PK of Nirmatrelvir?

The ritonavir model used by the Applicant is inadequate to predict the effects of CYP3A inducers on the exposure of nirmatrelvir/ritonavir combination. The reviewer developed and verified an alternative ritonavir model for this intended purpose. The reviewer's analysis predicted that weak and moderate CYP3A inducers are expected to have minimal effects on nirmatrelvir exposure in the nirmatrelvir/ritonavir combination product. The reviewer's assessment is detailed below.

FDA's Assessment

Nirmatrelvir is predominantly metabolized by CYP3A. The main function of the ritonavir component in PAXLOVID is to boost the plasma exposure of nirmatrelvir through its strong inhibitory effect on CYP3A enzyme. The clinical DDI study with carbamazepine showed that the strong CYP3A inducer carbamazepine decreased plasma AUC of ritonavir by 83% (C4671014), presumably via CYP3A induction because ritonavir is also a CYP3A substrate. Consequently, the plasma AUC of nirmatrelvir reduced by 55% (C4671014) due to decrease in CYP3A inhibition by ritonavir and increase in CYP3A-mediated elimination of nirmatrelvir. Therefore, besides evaluating the adequacy of the nirmatrelvir PBPK model, whether the ritonavir PBPK model could reproduce the effects of CYP perpetrators on ritonavir will be one of the key factors to determine the adequacy of the modeling analysis for predicting effects of moderate and weak CYP3A inducers on nirmatrelvir exposure in the nirmatrelvir/ritonavir product.

Ritonavir PBPK Model

The default SV-ritonavir_FO model the Applicant used has not been verified for its use as a victim of DDI. FDA requested the Applicant to (1) demonstrate the ability of the ritonavir model could adequately simulate the ritonavir PK profiles and exposure at different doses, especially doses lower than 100 mg, following administration of single- and multiple-dose of ritonavir, and (2) simulate the DDI studies with itraconazole (C4671015) and carbamazepine (C4671014) to verify that the PBPK models of nirmatrelvir and ritonavir could simulate the observed effects of

CYP3A perpetrators on nirmatrelvir and ritonavir, respectively (FDA information request issued on December 13, 2022).

The simulation results are summarized in Table 114, Table 115 and Figure 55. Ritonavir exposure was reasonably well predicted for the doses ranging from 100 mg to 300 mg, but its exposure was underpredicted for doses above 400 mg and was overpredicted for doses less than 100 mg (Table 114). Therefore, the nonlinear PK of ritonavir was not well characterized by the default SV-ritonavir_FO model. Moreover, PBPK analyses could not reproduce the results from the carbamazepine DDI study. The PBPK simulation overpredicted ritonavir plasma concentrations and underpredicted the effect of carbamazepine on ritonavir exposure following co-administration of nirmatrelvir/ritonavir with carbamazepine (Table 115 and Figure 55). As a result of overprediction of ritonavir exposure, minimal effects of carbamazepine on nirmatrelvir PK were predicted, which is inconsistent with the 55% reduction in nirmatrelvir AUC observed in the study (C4671014). Therefore, the default SV-ritonavir_FO model was considered not suitable for predicting the effects of CYP3A inducers on ritonavir as a booster in a combination product.

Table 114. Simulated and Observed Ritonavir Exposure Following Single or Multiple Doses of Ritonavir

Ritonavir Dosing Regimen	Observed mean		Simulated mean		Simulated / Observed		References of observed data	Sources of simulated results
	C_{max} (ng/mL)	AUC (ng•h/mL)	C_{max} (ng/mL)	AUC (ng•h/mL)	C_{max}	AUC		
20 mg SD	44.7	235	63.5	461	1.42	1.96	PMID: 23381882	Tables 9 and 10 in PBPK report 083028
50 mg SD	94	862	164	1651	1.74	1.92		
50 mg QD 11 days [a]	257	2650	334	3466	1.30	1.31	PMID: 29302721	
100 mg BID 5 doses [b]	1440	7185	978	7550	0.68	1.05	C4671015	
100 mg SD [b]	359	3599	446	4338	1.24	1.21	C4671014	
20 mg QD 10 days [c]	20	134	111	930	5.71	6.94	PMID: 18815591	Reviewer's analysis
50 mg QD 10 days [c]	130	1120	362	3399	2.78	3.03		
100 mg QD 10 days [c]	807	6530	818	7904	1.01	1.21		
200 mg QD 10 days [c]	2460	16000	1734	17131	0.70	1.07		
100 mg BID 16 days	890	6200	1073	8966	1.21	1.45	PMID: 16338282	
200 mg BID 16 days	2300	17100	2216	18538	0.96	1.08	PMID: 9145841	
300 mg BID 16 days	3200	22600	3371	28335	1.05	1.25		
400 mg BID 16 days	7400	48400	4533	38217	0.61	0.79		
500 mg BID 16 days	11500	79900	5700	48162	0.50	0.60		

Source: PBPK report 083028, Reviewer's independent analysis and literature references(details in the table).
Note: AUC = $AUC_{0\text{-}inf}$ for SD. AUC_{24h} for QD. AUC_{12h} for BID.
[a.] Co-administered with venetoclax.
[b.] Co-administered with nirmatrelvir.
[c.] Co-administered with elvitegravir.
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; C_{max}, maximum plasma concentration; PBPK, physiological-based pharmacokinetics; PMID, PubMed unique identifier; QD, once per day; SD, single dose

Table 115. Geometric Means of Simulated and Observed PK Parameters of Ritonavir and Nirmatrelvir in the Presence of Carbamazepine

Paxlovid	$C_{max,ind}$ (ng/mL)	$AUC_{0\text{-}inf,\ ind}$ (ng*h/mL)	C_{max} Ratio	$AUC_{0\text{-}inf}$ Ratio	Trials
Ritonavir				(b) (4)	Observed Simulated Sim/obs

Paxlovid	$C_{max,ind}$ (ng/mL)	$AUC_{0\text{-}inf,\ ind}$ (ng*h/mL)	C_{max} Ratio	$AUC_{0\text{-}inf}$ Ratio	Trials
Nirmatrelvir	(b) (4)				Observed Simulated Sim/obs

Source: Applicant's response to FDA IR (seq0105) simulation output files c4671014-cbz-300mg-bid-plv-300mg-sd.xlsx, c4671014-control-plv-300mg-sd.xlsx.
Note: For carbamazepine DDI, carbamazepine was given orally 100 mg BID from Days 1 -3, 200 mg BID from Days 4 -7 and 300 mg BID from Days 8 -15, and a single dose of nirmatrelvir/ritonavir 300/100 mg was given on Day 14. Ind, in the presence of carbamazepine.
Abbreviations: $AUC_{0\text{-}inf}$, area under the concentration-time curve to infinity; $AUC_{0\text{-}inf,ind}$, area under the concentration-time curve to infinity during induction; BID, twice daily; C_{max}, maximum plasma concentration; $C_{max,ind}$, maximum plasma concentration during induction; DDI, drug-drug interaction; Ind, induction; PK, pharmacokinetic Sim, simulated

Figure 55. Simulated and Observed PK Profiles of Ritonavir and Nirmatrelvir in the Presence of Carbamazepine

(b) (4)

Source: Applicant's response to FDA IR (seq0105), simulation output file c4671014-cbz-300mg-bid-plv-300mg-sd.xlsx
Note: Depicted are simulated (lines) and observed data (circles). The green lines represent the mean data of the simulated population (n = 120), and the grey and black lines represent 5% and 95% percentiles, respectively. Error bars represent standard deviation.
Abbreviations: log, logarithm; n, number of subjects in sample; PK, pharmacokinetic

Nirmatrelvir PBPK Model

The intrinsic clearance of CYP3A in the nirmatrelvir model was optimized by using sensitivity analysis of $f_{m,\ CYP3A}$ to recover the nirmatrelvir PK in the presence and absence of a single dose of 100 mg ritonavir in the relative bioavailability study (C4671008, Figure 54 and Table 113). However, ritonavir not only strongly inhibits CYP3A but also increases the AUC of fexofenadine, a P-gp substrate, up to 2.2-fold following a single dose of 100 mg ritonavir (PubMed 16809801). Nirmatrelvir is a substrate of both CYP3A and P-gp. Thus, the differences observed in nirmatrelvir PK in the presence and absence of ritonavir in the abovementioned study could be the net effect of ritonavir inhibition and/or induction on CYP3A and P-gp. The

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Applicant performed verification of the nirmatrelvir model using multiple clinical studies (Table 113 and data from the PBPK report 074428 not shown), but these verifications were considered insufficient because all nirmatrelvir PK were simulated in the presence of 100 mg ritonavir. At this dose, ritonavir almost completely inhibits CYP3A activity rendering the contribution of CYP3A to the elimination of nirmatrelvir minimal (C4671001).

Despite insufficient verification of $f_{m,\ CYP3A}$ in the nirmatrelvir PBPK model, the model may still be useful for estimating the effects of CYP3A inducers on nirmatrelvir exposure because the current $f_{m,\ CYP3A}$ determination may be a conservative estimate as all the effects of ritonavir on nirmatrelvir was attributed to CYP3A inhibition. To test this possibility, the reviewer used this nirmatrelvir model to simulate the effect of carbamazepine on nirmatrelvir exposure by using the ritonavir exposure observed in the presence of carbamazepine. The ritonavir exposure was simulated using the SV-ritonavir-FO model with the following modifications. The "In Vivo Clearance model" was used for its elimination model, instead of "Enzyme kinetics model", and the clinically observed value of oral clearance of ritonavir (=16.4 L/h) was applied for the dose of 100-mg ritonavir (Mathias et al. 2010). This 'modified ritonavir model' could reproduce the observed ritonavir exposure following multiple-dose administration of 100-mg ritonavir and the effects of ritonavir on intravenous (IV) and oral midazolam. The predicted values were mostly within the bioequivalent bounds of the observed values (Table 116). This 'modified ritonavir model' was considered verified for the intended purpose, thus used for subsequent simulations. To simulate the effect of carbamazepine, ritonavir dose was reduced from 100 mg to 9 mg so that the simulated AUC of ritonavir matched the observed ritonavir AUC of 596.4 ng*h/mL in the presence of carbamazepine. This was needed since the mechanistic effect of CYP3A induction on ritonavir elimination was not considered in the modified ritonavir model. The simulations reasonably well reproduced the effects observed in the carbamazepine DDI study (Table 117), therefore the nirmatrelvir/modified ritonavir models could be used to estimate the effects of moderate CYP3A inducers on nirmatrelvir exposure.

Table 116. Prediction of Ritonavir Exposure and the Effects of Ritonavir on IV and Oral Midazolam PK Using the Modified SV-Ritonavir-FO Model

Dosing Regimens	PK Parameters	Ritonavir Exposure			Midazolam AUC or C_{max} Ratio		
		Observed	Predicted	Pred./Obs.	Observed	Predicted	Pred./Obs.
RTV 100 mg QD 10d + 1 mg *MDZ IV* D10	AUC (mg*h/L)	6.53	6.77	1.04	6.8	6.62	0.97
	C_{max} (mg/L)	0.807	0.75	0.93	1	1	1
RTV 100 mg BID 3d + 5 mg *MDZ PO* D3	AUC (mg*h/L)	6.2	6.77	1.09	23.9	27.1	1.13
	C_{max} (mg/L)	0.89	0.9	1.01	4.03	4.94	1.23

Source: Reviewer's analyses.
Note: Mean values are reported. Observed data from Aarnoutse et al. and Mathias et al.; Simulations were performed using SV-ritonavir-FO_in vivo CL (Aarnoutse et al. 2005; Mathias et al. 2010).
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; CL, clearance; C_{max}, maximum plasma concentration; d or D, day; FO, first-order absorption; IV, intravenous; MDZ, midazolam; Obs, observed; PK, pharmacokinetic; PO, oral; Pred, predicted; QD, once per day; RTV, ritonavir..

Table 117. Simulated Effects of Carbamazepine on Nirmatrelvir in the Presence of Carbamazepine Following a Single Dose of PAXLOVID

Treatment	Control		Carbamazepine		Ratio		
Nirmatrelvir PBPK Model	C_{max} (ng/mL)	AUC (ng*h/mL)	$C_{max,inh}$ (ng/mL)	$AUC_{0-inf, inh}$ (ng*h/mL)	C_{max}	AUC_{0-inf}	Trials
Full model	2210	23010	1256	10240	0.57	0.45	observed
	3009	27708	1907	14085	0.63	0.51	simulated
	1.36	1.20	1.52	1.38	1.11	1.13	Sim/obs
Full model with no CYP3A inhibition parameters	2998	27562	1829	12449	0.61	0.45	Simulated
	1.36	1.20	1.46	1.22	1.07	1.00	Sim/obs
Full model with CYP3A IndC50/10 but no CYP3A inhibition parameters	2979	26873	1776	11305	0.60	0.42	Simulated
	1.35	1.17	1.41	1.10	1.05	0.93	Sim/obs
Full model with CYP3A IndC50/100 but no CYP3A inhibition parameters	2959	25291	1713	9655	0.58	0.38	Simulated
	1.34	1.10	1.36	0.94	1.02	0.85	Sim/obs

Source: Reviewer's analyses.
Abbreviations: AUC, area under the concentration-time curve; AUC_{0-inf}, area under the concentration-time curve to infinity; $AUC_{0-inf,inh}$, area under the concentration-time curve to infinity during inhibition; C_{max}, maximum plasma concentration; $C_{max,inh}$, maximum plasma concentration during inhibition; CYP, cytochrome P450; $IndC_{50}$, concentration at the half of maximal fold induction; Obs, observed; Sim, simulated

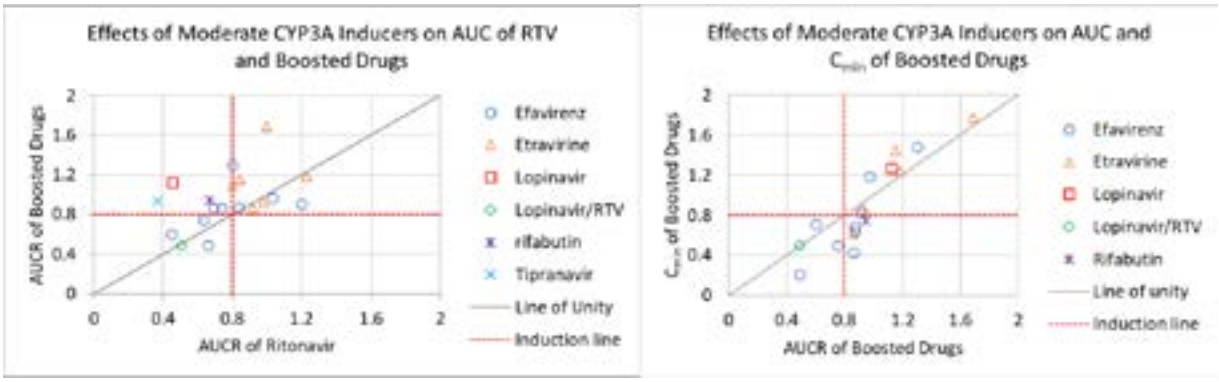
Model Application: Estimation of the Effects of Moderate CYP3A Inducers on Nirmatrelvir Exposure

The reviewer collected and analyzed publicly available data of clinical DDI studies of moderate CYP3A inducers with ritonavir-boosted anti-infective products. Figure 56 summarizes the effects of known moderate CYP3A inducers on the exposure of the components in ritonavir combinations. The maximal reduction in the AUC of ritonavir was 63%. In most cases, lesser reduction was observed in AUCs of the corresponding boosted drugs. The trough concentrations (C_{min}) of the boosted drugs, which are often the more relevant PK metrics to the efficacy of these anti-infectives, were more vulnerable to the induction than their AUCs. Whether a moderate CYP3A inducer reduces the C_{min} of the boosted drugs may depend on the dose of each co-administered components, the combination of co-administered components, and drug interaction potentials of the boosted drugs.

To simulate the effects of moderate CYP3A inducers on nirmatrelvir exposure, the reviewer reduced the dose of ritonavir of the 'modified ritonavir model' from 100 mg to 37 mg so that the AUC of ritonavir was reduced by 63%, the maximal reduction in ritonavir AUC observed so far. Moderate CYP3A inducers were predicted to have little effects on nirmatrelvir PK (Table 118), assuming ritonavir AUC was reduced up to 63% by moderate CYP3A inducers. As mentioned above, reduction in the C_{min} of the boosted drugs depends on drug interaction potentials of the boosted drugs. Nirmatrelvir is a time-dependent inhibitor and an inducer of CYP3A in vitro. The DDI potential of nirmatrelvir alone as a perpetrator of CYP3A has not been well characterized because its effect on midazolam was only evaluated together with 100-mg ritonavir. Therefore, the CYP3A inhibition and induction parameters in the nirmatrelvir model have not been sufficiently verified. To explore the effects of these CYP3A interaction parameters on the prediction, the reviewer performed additional simulations using the nirmatrelvir model but with the following modifications: (1) no CYP3A inhibition parameters (2) no CYP3A inhibition

parameters and the CYP3A induction parameter $IndC_{50}$ reduced by 10-fold (3) no CYP3A inhibition parameters and the CYP3A induction parameter $IndC_{50}$ reduced by 100-fold. These simulations examine the potential underprediction of the effects of moderate CYP3A inducers due to overprediction of CYP3A inhibition and underprediction of CYP3A induction by nirmatrelvir. The modified nirmatrelvir models (1) and (2) could reasonably well reproduce nirmatrelvir PK both following coadministration of carbamazepine with a single dose of nirmatrelvir/ritonavir 300/100 mg (C4671014) (Table 117) and following nirmatrelvir/ritonavir 300/100 mg twice daily for 5 days (C4671015) (Table 118). Using the same modified models, minimal changes were predicted on nirmatrelvir exposure when nirmatrelvir/ ritonavir 300/100 mg are co-administered with moderate CYP3A inducers (Table 118), confirming the previous predicted results. Based on these data, little changes are expected for weak CYP3A inducers.

Figure 56. Effects of Moderate CYP3A Inducers on the Exposure of the Components in Ritonavir Combinations



Source: Reviewer's analysis.
Abbreviations: AUCR, area under the concentration-time curve ratio; C_{min}, minimum plasma concentration; CYP3A, cytochrome P450, family 3, subfamily A; RTV, ritonavir

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Table 118. Predicted Effects of Moderate CYP3A Inducers on Nirmatrelvir Exposure Following 5 Days of PAXLOVID Twice Daily Assuming Ritonavir AUC is Reduced by 63%

Nirmatrelvir PBPK Model	Interaction State	C_{max} (ng/mL)	AUC_{tau} (ng*h/mL)	C_{min} (ng/mL)
Observed in Itraconazole DDI	Control	3875	30680	900
Full model	Control	3843	29258	927
	induced	3751	28250	854
	Induced/control	0.98	0.97	0.92
Full model except for no CYP3A inhibition parameters	Control	3839	29209	923
	induced	3722	27940	833
	Induced/control	0.97	0.96	0.90
Full model with CYP3A IndC50 reduced 10-fold but no CYP3A inhibition parameters	Control	3781	28507	869
	induced	3507	25408	676
	Induced/control	0.93	0.89	0.78
Full model with CYP3A IndC50 reduced 100-fold but no CYP3A inhibition parameters	Control	3686	27392	755
	induced	3224	22446	473
	Induced/control	0.87	0.82	0.63

Source: Reviewer's analysis.
Abbreviations: AUC, area under the concentration-time curve; AUC_{tau}, area under the concentration-time curve over dosing interval; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; CYP3A, cytochrome P450, family 3, subfamily A; DDI, drug-drug interaction; $IndC_{50}$, concentration at the half of maximal fold induction; PBPK, physiological-based pharmacokinetics

Conclusions

Weak and moderate CYP3A inducers are expected to have minimal effects on nirmatrelvir exposure in the nirmatrelvir/ ritonavir 300/100 mg product.

14.7. Pharmacogenetics

Not applicable.

15. Study/Trial Design

15.1. Applicant's Protocol Synopsis for EPIC-HR

Title

An Interventional Efficacy And Safety, Phase 2/3, Double-Blind, 2-Arm Study To Investigate Orally Administered PF-07321332/Ritonavir Compared With Placebo In Nonhospitalized Symptomatic Adult Participants With Covid-19 Who Are At Increased Risk Of Progressing To Severe Illness.

Rationale

The purpose of this trial is to evaluate the efficacy and safety of PF-07321332/ritonavir for the treatment of nonhospitalized, symptomatic adult subjects with COVID-19 who are at increased risk of progressing to severe illness.

Objectives, Endpoints, and Estimands

Table 119. Objectives, Endpoints, and Estimands for EPIC-HR

Objectives	Endpoints	Estimands
Primary		
• To compare the efficacy of PF-07321332/ritonavir to placebo for the treatment of COVID-19 in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease	• Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28.	• The difference in proportions of patients experiencing COVID-19-related hospitalization or death from any cause through Day 28 in nonhospitalized adult patients with symptomatic COVID-19 who are at increased risk of progression to severe disease, who did not receive COVID-19 therapeutic mAb treatment and were treated ≤3 days after COVID-19 symptom onset. This will be estimated without regard to adherence to randomized treatment.
Secondary		
• To describe the safety and tolerability of PF-07321332/ ritonavir relative to placebo in the treatment of nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Incidence of TEAEs. • Incidence of SAEs and AEs leading to discontinuations.	• Not applicable.
• To compare the efficacy of PF-07321332/ritonavir to placebo for the treatment of COVID-19 in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28	• The difference in proportions of patients experiencing COVID-19-related hospitalization or death from any cause through Day 28 in nonhospitalized adult patients with symptomatic COVID-19 who are at increased risk of progression to severe disease and who did not receive COVID-19 therapeutic mAb treatment. This will be estimated without regard to adherence to randomized treatment.

Objectives	Endpoints	Estimands
• To compare PF-07321332/ritonavir to placebo for the duration and severity of signs and symptoms in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Time (days) to sustained alleviation of all targeted signs/symptoms through Day 28. • Proportion of participants with severe signs/symptoms attributed to COVID-19 through Day 28. • Time (days) to sustained resolution of all targeted signs/symptoms through Day 28. • Duration of each targeted COVID-19 sign/symptom. • Progression to a worsening status in 1 or more self-reported COVID-19-associated symptoms through Day 28. • Proportion of participants with a resting peripheral oxygen saturation ≥95% at Days 1 and 5.	• The absolute difference in median time to sustained alleviation or resolution of symptoms for all nonhospitalized adult patients with COVID-19 who are at increased risk of progression to severe disease. This will be estimated irrespective of adherence to randomized treatment
• To compare PF-07321332/ritonavir to placebo for all-cause mortality in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Proportion of participants with death (all cause) through Week 24.	• Not applicable.
• To determine the PK of PF-07321332 in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• PF-07321332 PK in plasma and whole blood (if feasible).	• Not applicable.
• To describe the viral load in nasal samples over time in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Viral titers measured via RT-PCR in nasal swabs over time.	• Not applicable.
• To compare PF-07321332/ritonavir to placebo for COVID-19-related medical visits in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Number of COVID-19 related medical visits through Day 28.	• Not applicable.

Objectives	Endpoints	Estimands
• To compare PF-07321332/ritonavir to placebo for COVID-19-related hospitalizations in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Number of days in hospital and ICU stay in participants with COVID-19 related hospitalization.	• Not applicable.

Source: EPIC-HR final protocol amendment 4.
Abbreviations: AE, adverse event; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; ICU, intensive care unit; mAb, monoclonal antibodies; PK, pharmacokinetic; RT-PCR, real-time, reverse transcription-polymerase chain reaction; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Overall Design

Brief Summary

This phase 2/3, randomized, double-blind, placebo-controlled study in nonhospitalized, symptomatic adult subjects with COVID-19 who are at increased risk of progressing to severe illness will determine the efficacy, safety, and tolerability of PF-07321332/ritonavir compared with placebo. Eligible subjects with a confirmed diagnosis of SARS-CoV-2 infection will be randomized (1:1) to receive PF-07321332/ritonavir or placebo orally q12h for 5 days (10 doses total). Randomization will be stratified by geographic region and whether subjects have received/are expected to receive COVID-19 therapeutic mAb treatment (yes/no) based on the site investigator's assessment at the time of randomization.

Enrollment of subjects who have received/are expected to receive COVID-19 therapeutic mAb treatment is expected to be approximately 20% and will be limited to approximately 25% of subjects. Enrollment of subjects that had COVID-19 symptom onset >3 days prior to randomization is expected to be approximately 25% and will be limited to a total of approximately 1000 subjects.

Number of Subjects

Approximately 3000 subjects will be randomly assigned to study intervention.

"Enrolled" means a subject's, or his or her legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and screening. A subject will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential subjects who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration

Subjects will be screened within 48 hours of randomization. Eligible subjects will receive PF-07321332 plus ritonavir or placebo orally q12h for 5 days. The total study duration is up to 24 weeks, study intervention through Day 5 or Day 6, efficacy assessments through Day 28, a safety follow-up period through Day 34, and long-term follow-up at Weeks 12 and 24.

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Data Monitoring Committee or Other Independent Oversight Committee

An independent, external data monitoring committee (E-DMC) will review unblinded data to ensure the safety of subjects on an ongoing basis throughout the duration of the study, as specified in the E-DMC Charter. In addition to up to weekly reviews of safety, the E-DMC will review the following:

- Sentinel cohort safety review: The E-DMC will review unblinded safety data after approximately the first 60 subjects have completed Day 10 of the study, at which point enrollment will be paused pending E-DMC review of the safety data. After review of the sentinel cohort, the frequency of safety reviews may be reduced subsequently based on E-DMC recommendations.
- Proof-of-concept assessment: The E-DMC will review viral load data when approximately 200 subjects in the primary analysis set with evaluable data complete the Day 5 assessments. Enrollment will not be paused during review of these data but may be paused or stopped following E-DMC review.
- Interim analysis: A planned interim analysis for efficacy and futility will be done after approximately 45% of participants in the modified intent-to-treat (mITT) analysis set complete the Day 28 assessments (i.e., 28 days after randomization).

Statistical Methods

The cumulative proportion of participants hospitalized for the treatment of COVID-19 or dying during the first 28 days of the study will be estimated for each treatment group using the Kaplan-Meier method to take account of losses to follow-up and summarized graphically for each treatment group. The estimand is then the difference of the proportions in the 2 groups and its 95% CI will be presented as well as the associated Wald test. For the 95% CI, the corresponding estimate of the standard error is computed using Greenwood's formula. The Greenwood's formula to estimate the variance of the difference of proportions at Day 28 is [Var(SPF(28)) + Var(SPlacebo(28))]. Instead of dealing with S(ti) the log-log approach to CI will be used. The 95% CI will be computed for the estimate of L(t)= log(-log(S(t))), the log hazard function.

The above primary analysis will also be conducted for the planned interim analysis. Two-sided 95% CI (adjusted for the planned interim analysis) and associated p-value for the null hypothesis of no difference between treatment groups will be presented. Significance level will be determined using the O'Brien-Fleming approach at the interim analysis and the final analysis. The overall significance level is set at 5% (2 sided).

The estimate of required sample size is based on data from the BLAZE-1 phase 2/3 trial among participants with mild to moderate COVID-19 who were at high risk for progressing to severe COVID-19 and/or hospitalization at enrollment. During the 29-day period following enrollment, the proportion of placebo-treated subjects with a COVID-19-related hospitalization/emergency department visit was 7% in the phase 3 portion of the trial.

This trial is designed to have 90% statistical power to show a difference of 3.5% in the proportion of subjects hospitalized/dying that did not receive COVID-19 therapeutic mAb between the treatment arms (PF-07321332/ritonavir versus placebo), using a 2-sided Type I error

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rate of 5%. Based on the above study, the proportion of hospitalization/death in the placebo arm is assumed to be 7%.

For a 2-sample proportion test, the sample size needed to detect this difference with 90% power at a 2-sided significance level of 5% was determined to be 1717 randomized subjects.

Enrollment of subjects who have received/are expected to received COVID-19 therapeutic mAb treatment is expected to be approximately 20% of subjects, and will be limited to approximately 25% of subjects. Enrollment of subjects that had COVID-19 symptom onset >3 days prior to randomization is expected to be approximately 25%, and will be limited to a total of approximately 1000 subjects. Assuming a 5% dropout rate, the total sample size for this study will be approximately 3000 subjects.

Study enrollment will be stopped after approximately 1717 subjects are available for the primary analysis.

The primary estimand is the difference in proportions of patients experiencing COVID-19 related hospitalization or death from any cause through Day 28 in nonhospitalized adult participants with COVID-19 who are at increased risk of progression to severe disease, who did not receive COVID-19 therapeutic mAb treatment and were treated ≤3 days after COVID-19 symptom onset. This will be estimated without regard to adherence to randomized treatment.

Complete Eligibility Criteria

Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

1. Subjects ≥18 years of age (or the minimum country-specific age of consent if >18) at the time of the Screening Visit
   - WOCBP may be enrolled
   - All fertile participants must agree to use a highly effective method of contraception
2. Confirmed SARS-CoV-2 infection as determined by RT-PCR in any specimen collected within 5 days prior to randomization
3. Initial onset of signs/symptoms attributable to COVID-19 within 5 days prior to the day of randomization and at least 1 of the specified signs/symptoms attributable to COVID-19 present on the day of randomization. The specified signs/symptoms for study entry include:
   - cough
   - shortness of breath or difficulty breathing
   - fever (documented temperature >38˚C [100.4˚F]) or subjective fever (e.g., feeling feverish), chills or shivering
   - fatigue (low energy or tiredness)
   - muscle or body aches
   - diarrhea (loose or watery stools)
   - nausea (feeling like you wanted to throw up)
   - vomiting (throw up)
   - headache
   - sore throat
   - stuffy or runny nose

4. Has at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19 including:
   - ≥60 years of age
   - Body mass index (BMI) >25
   - Current smoker (cigarette smoking within the past 30 days) and history of at least 100 lifetime cigarettes.
   - Immunosuppressive disease (e.g., bone marrow or organ transplantation or primary immune deficiencies) OR prolonged use of immune-weakening medications:
     - Has received corticosteroids equivalent to prednisone ≥20 mg daily for at least 14 consecutive days within 30 days prior to study entry
     - Has received treatment with biologics (e.g., infliximab, ustekinumab), immunomodulators (e.g., methotrexate, 6MP, azathioprine) or cancer chemotherapy within 90 days prior to study entry
     - HIV infection with CD4 cell count <200 mm3 and a viral load less than 400 copies/mL
   - Chronic lung disease (if asthma, requires daily prescribed therapy)
   - Known diagnosis of hypertension
   - Cardiovascular disease, defined as history of any of the following: myocardial infarction, stroke, TIA, HF, angina with prescribed nitroglycerin, CABG, PCI, carotid endarterectomy, and aortic bypass
   - Type 1 or Type 2 diabetes mellitus
   - Chronic kidney disease (CKD) provided the participant does not meet Exclusion Criterion 5
   - Sickle cell disease
   - Neurodevelopmental disorders (e.g., cerebral palsy, Down's syndrome) or other conditions that confer medical complexity (e.g., genetic or metabolic syndromes and severe congenital anomalies)
   - Active cancer, other than localized skin cancer, including those requiring treatment as long as the treatment is not among the prohibited medications that must be administered/continued during the trial period
   - Medical-related technological dependence (e.g., CPAP [not related to COVID-19])
5. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures
6. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol

Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. History of hospitalization for the medical treatment of COVID-19
2. Current need for hospitalization or anticipated need for hospitalization within 48 hours after randomization in the clinical opinion of the site investigator
3. Prior to current disease episode, any confirmed SARS-CoV-2 infection, as determined by a molecular test (antigen or nucleic acid) from any specimen collection

4. Known medical history of active liver disease (other than nonalcoholic hepatic steatosis), including chronic or active hepatitis B or C infection, primary biliary cirrhosis, Child-Pugh Class B or C or acute liver failure
5. Receiving dialysis or have known renal impairment [i.e., eGFR <45 mL/min/1.73 m^2 within 6 months of the screening visit, using the serum creatinine-based CKD-EPI formula]
6. Known HIV infection with viral load greater than 400 copies/mL or taking prohibited medications for HIV treatment (from known medical history within past 6 months of the screening visit)
7. Suspected or confirmed concurrent active systemic infection other than COVID-19 that may interfere with the evaluation of response to the study intervention
8. Any comorbidity requiring hospitalization and/or surgery within 7 days prior to study entry, or that is considered life threatening within 30 days prior to study entry, as determined by the investigator
9. History of hypersensitivity or other contraindication to any of the components of the study intervention, as determined by the investigator
10. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study
11. Current or expected use of any medications or substances that are highly dependent on CYP3A4 for clearance, and for which elevated plasma concentrations may be associated with serious and/or life-threatening events during treatment and for 4 days after the last dose of PF-07321332/ritonavir
12. Concomitant use of any medications or substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to first dose of PF-07321332/ritonavir and during study treatment
13. Has received or is expected to receive convalescent COVID-19 plasma
14. Has received or is expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit
15. Is unwilling to abstain from participating in another interventional clinical study with an investigational compound or device, including those for COVID-19 therapeutics, through the long-term follow-up visit
16. Previous administration with any investigational drug or vaccine within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer)
17. Known prior participation in this trial or other trial involving PF-07321332
18. Known history of any of the following abnormalities in clinical laboratory tests (within past 6 months of the screening visit):
    - AST or ALT level ≥2.5x ULN
    - Total bilirubin ≥2x ULN (≥3 X ULN for Gilbert's syndrome)

- eGFR <45 mL/min/1.73 m2 within 6 months of the screening visit, using the serum creatinine-based CKD-EPI formula
- Absolute neutrophil count <1000/mm3

Note: If the investigator suspects the participant may have any of the above laboratory values, confirmatory tests should be performed at screening to confirm eligibility before the first dose of study intervention

19. Oxygen saturation of < 92% on room air obtained at rest within 24 hours prior to randomization

Note: For a potential participant who regularly receives chronic supplementary oxygen for an underlying lung condition, oxygen saturation should be measured while on their standard home oxygen supplementation

20. Females who are pregnant or breastfeeding
21. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members

15.2. Applicant's Protocol Synopsis for EPIC-SR

Title

An Interventional Efficacy and Safety, Phase 2/3, Double-Blind, 2-Arm Study to Investigate Orally Administered PF-07321332/Ritonavir Compared With Placebo in Nonhospitalized Symptomatic Adult Participants with COVID-19 who are at Low Risk of Progressing to Severe Illness.

Rationale

The purpose of this trial is to evaluate the efficacy and safety of PF-07321332/ritonavir for the treatment of nonhospitalized, symptomatic, adult participants with COVID-19 who are at low risk of progression to severe illness.

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Objectives, Endpoints, and Estimands

Table 120. Objectives, Endpoints, and Estimands for EPIC-SR

Objectives	Endpoints	Estimands
Primary		
• To compare the efficacy of PF-07321332/ritonavir to placebo for the treatment of symptomatic COVID-19 in nonhospitalized adult participants with COVID-19 who are at low risk of progression to severe disease	• Time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28.	• The difference in median time (days) to sustained alleviation of all targeted COVID-19 signs and symptoms through Day 28 between PF-07321332/ritonavir and placebo in nonhospitalized adult patients with COVID-19 who are at low risk of progression to severe disease at baseline and were treated ≤3 days after COVID-19 symptom onset. This will be estimated irrespective of adherence to randomized treatment.
Secondary		
• To describe the safety and tolerability of PF-07321332/ritonavir relative to placebo in the treatment of nonhospitalized symptomatic adult participants with COVID-19 who are at low risk of progression to severe disease.	• Incidence of TEAEs. • Incidence of SAEs and AEs leading to discontinuations.	• Not applicable.
• To compare the efficacy of PF-07321332/ritonavir to placebo for the treatment of symptomatic COVID-19 in nonhospitalized adult participants with COVID-19 who are at low risk of progression to severe disease.	• Time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28.	• The difference in median time (days) to sustained alleviation of all targeted COVID-19 signs and symptoms through Day 28 between PF-07321332/ritonavir and placebo in nonhospitalized adult patients with COVID-19 who are at low risk of progression to severe disease at baseline and were treated ≤5 days after COVID-19 symptom onset. This will be estimated irrespective of adherence to randomized treatment.

Objectives	Endpoints	Estimands
• To compare PF-07321332/ritonavir versus placebo for COVID-19 related hospitalization and all-cause mortality in nonhospitalized adult participants with COVID-19 who are at low risk of progression to severe disease.	• Proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28 • Proportion of participants with death (all cause) through Week 24.	• The difference in proportions of patients experiencing COVID-19-related hospitalization or death from any cause through Day 28 in nonhospitalized adult patients with COVID-19 who are at low risk of progression to severe disease and were treated ≤5 days after COVID-19 symptom onset. This will be estimated without regard to adherence to randomized treatment. • Not Applicable
• To compare PF-07321332/ritonavir to placebo for the duration and severity of signs and symptoms in nonhospitalized symptomatic adult participants with COVID-19 who are at low risk of progression to severe disease.	• Proportion of participants with severe signs/symptoms attributed to COVID-19 through Day 28. • Time (days) to sustained resolution of all targeted signs/symptoms through Day 28. • Duration of each targeted COVID-19 sign/symptom. • Progression to a worsening status in 1 or more self-reported COVID-19-associated symptoms through Day 28. • Proportion of participants with a resting peripheral oxygen saturation ≥95% at Days 1 and 5.	• Not applicable.
• To compare PF-07321332/ritonavir versus placebo for COVID-19-related medical visits in nonhospitalized adult participants with COVID-19 who are at low risk of progression to severe disease.	• Number of COVID-19 related medical visits through Day 28. • Number of days in hospital and ICU stay in participants with COVID-19 related hospitalization through Day 28.	• Not applicable.
• To determine the PK of PF-07321332 in nonhospitalized adult participants with COVID-19 who are at low risk of progression to severe disease.	• PF-07321332 PK in plasma and whole blood (if feasible).	• Not applicable.
• To describe the viral load in nasal samples over time in nonhospitalized symptomatic adult participants with COVID-19 who are at low risk of progression to severe disease.	• Viral titers measured via RT-PCR in nasal swabs over time.	• Not applicable.

Source: EPIC-SR protocol amendment 4.
Abbreviations: AE, adverse event; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; ICU, intensive care unit; PK, pharmacokinetic; RT-PCR, real-time, reverse transcription-polymerase chain reaction; SAE, serious adverse event; TEAE, treatment-emergent adverse event

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Overall Design

Brief Summary

This Phase 2/3, randomized, double-blind, placebo-controlled study in nonhospitalized symptomatic adult subjects with COVID-19 who are at low risk of progressing to severe illness will determine the efficacy, safety, and tolerability of PF-07321332/ritonavir compared with placebo. Eligible subjects with a confirmed diagnosis of SARS-CoV-2 infection will be randomized (1:1) to receive PF-07321332/ritonavir or placebo orally q12h for 5 days (10 doses total). Randomization will be stratified by geographic region, by vaccination status and by COVID-19 symptom onset (≤3 days versus >3 to 5 days).

Number of Participants

Approximately 1140 subjects will be randomly assigned to study intervention.

"Enrolled" means a subject, or his or her legally authorized representative, agrees to participate in a clinical study following completion of the informed consent process and screening. A subject will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential subjects who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration

Subjects will be screened within 48 hours before randomization. Eligible subjects will receive PF-07321332 plus ritonavir or placebo orally q12h for 5 days. The total study duration is up to 24 weeks, with study intervention through Day 5 or Day 6, efficacy assessments through Day 28, a safety follow-up period through Day 34, and long-term follow-up at Weeks 12 and 24.

Data Monitoring Committee or Other Independent Oversight Committee

An independent E-DMC will review unblinded data to ensure the safety of participants throughout the duration of the study, as specified in the E-DMC Charter. In addition to up to weekly reviews of safety, the E-DMC will review the following:

Sentinel cohort safety review: The E-DMC will review unblinded safety data after approximately the first 100 randomized subjects have completed through Day 10. Whether enrollment is paused for this review will depend on the successful completion of the EPIC-HR sentinel cohort (after approximately the first 60 randomized participants have completed through Day 10). If the EPIC-HR sentinel cohort safety review has successfully completed and no clinically significant safety signals have been identified prior to enrollment of the first 100 participants in EPIC-SR, the study will continue without pause. Otherwise, enrollment of EPIC-SR will be paused pending the E-DMC review of safety data. After review of the sentinel cohort in EPIC-SR, the frequency of safety reviews may be reduced subsequently based on E-DMC recommendations.

- Proof-of-concept assessment: Viral load data when 25% (approximately 200 subjects in the primary analysis set with evaluable data) complete the Day 5 assessments. Enrollment will

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not be paused during review of these data, but may be paused or stopped following E-DMC review.

- Formal interim analysis: A planned formal interim analysis for efficacy and sample size re-estimation will be done after approximately 45% of subjects complete the Day 28 assessments in the mITT analysis set.

Details of the E-DMC are specified in the E-DMC Charter.

Statistical Methods

The primary endpoint of this trial is the time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28. Time to sustained alleviation of all targeted COVID-19 signs/symptoms will be summarized graphically using Kaplan-Meier plots for each of the treatment group. Log-rank test will be used to compare the difference in time (days) to sustained alleviation of all targeted COVID-19 signs and symptoms through Day 28 between treatment groups.

The estimate of required sample size is based on the primary endpoint, the difference in time to sustained alleviation of all targeted COVID-19 associated signs/symptoms between subjects who were treated ≤3 days after COVID-19 symptom onset, treated with PF-07321332/ritonavir compared to placebo. The sample size is calculated based on a 2-sample test-parallel design–log-rank test, assuming a 90% power, 2-sided test at alpha = 0.05, approximate accrual rate of 30 subjects per day, 2 days difference in the median days to sustained alleviation of all targeted COVID-19-associated symptoms (6 days for PF-07321332/ritonavir and 8 days for placebo i.e., a 25% reduction in time to sustained alleviation of all targeted COVID-19 signs/symptoms) based on Lilly-BLAZE-11 and assuming a 18% study discontinuation rate, the sample size of approximately 800 participants (approximately 515 events) will provide 90% power to detect that difference.

Allowing for approximately 30% of subjects with COVID-19 symptom onset >3 days, a sample size of approximately 1140 subjects will be enrolled for this study. Trial enrollment will stop when approximately 800 subjects with COVID-19 symptom onset ≤3 days are randomized.

The primary estimand is the difference between PF-07321332/ritonavir and placebo in median time (days) to sustained alleviation of all targeted signs and symptoms of COVID-19 through Day 28 in non-hospitalized adult patients with COVID-19 who are at low risk of progression to severe disease at baseline and were treated ≤3 days after COVID-19 symptom onset. This will be estimated irrespective of adherence to randomized treatment.

Complete Eligibility Criteria

Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

1. Subjects ≥18 years of age (or the minimum country-specific age of consent if >18) at the time of the Screening Visit
   - WOCBP may be enrolled
   - All fertile participants must agree to use a highly effective method of contraception

2. Confirmed SARS-CoV-2 infection as determined by RT-PCR in any specimen collected within 5 days prior to randomization

Note: RT-PCR is the preferred method; however, with evolving approaches to confirmation of SARS-CoV-2 infection, other molecular or antigen tests that detect viral RNA or protein are allowed. The test result must be available to confirm eligibility. Subjects may be enrolled based on positive results of a rapid SARS-CoV-2 antigen test performed at screening.

3. Initial onset of signs/symptoms attributable to COVID-19 within 5 days prior to the day of randomization and at least 1 of the specified signs/symptoms attributable to COVID-19 present on the day of randomization. The specified signs/symptoms for study entry include:
   - cough
   - shortness of breath or difficulty breathing,
   - fever (documented temperature >38˚C [100.4˚F]) or subjective fever (e.g., feeling feverish)
   - chills or shivering
   - fatigue (low energy or tiredness)
   - muscle or body aches
   - diarrhea (loose or watery stools)
   - nausea (feeling like you wanted to throw up)
   - vomiting (throw up)
   - headache
   - sore throat
   - stuffy or runny nose
4. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures
5. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol

Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Has at least 1 characteristic or underlying medical condition (self-report is acceptable) associated with an increased risk of developing severe illness from COVID-19 including:

Note: Participants with these conditions who are fully vaccinated (as defined by local regulations and practices) against SARS-CoV-2 are considered to be at lower risk of developing severe disease and are therefore considered eligible.

   - ≥60 years of age
   - BMI >25
   - Current smoker (cigarette smoking within the past 30 days) and history of at least 100 lifetime cigarettes
   - Chronic lung disease (if asthma, requires daily prescribed therapy)
   - Known diagnosis of hypertension
   - Cardiovascular disease, defined as history of any of the following: myocardial infarction, stroke, TIA, HF, angina with prescribed nitroglycerin, CABG, PCI, carotid endarterectomy, and aortic bypass

- Type 1 or Type 2 diabetes mellitus
- CKD
- Sickle cell disease
- Neurodevelopmental disorders (e.g., cerebral palsy, Down's syndrome) or other conditions that confer medical complexity (e.g., genetic or metabolic syndromes and severe congenital anomalies)
- Active cancer, other than localized skin cancer, including those requiring treatment (including palliative treatment), as long as the treatment is not among the prohibited medications that must be administered/continued during the trial period
- Medical-related technological dependence (e.g., CPAP [not related to COVID-19])

2. Immunosuppressive disease (e.g., bone marrow or organ transplantation or primary immune deficiencies) OR prolonged use of immune-weakening medications:
   - Has received corticosteroids equivalent to prednisone ≥20 mg daily for at least 14 consecutive days within 30 days prior to study entry
   - Has received treatment with biologics (e.g., infliximab, ustekinumab, etc.), immunomodulators (e.g., methotrexate, 6MP, azathioprine, etc.), or cancer chemotherapy within 90 days prior to study entry'
   - HIV infection with CD4+ cell count <200/mm3
3. History of hospitalization for the medical treatment of COVID-19
4. Current need for hospitalization or anticipated need for hospitalization within 48 hour after randomization in the clinical opinion of the site investigator
5. Prior to current disease episode, any confirmed SARS-CoV-2 infection, as determined by a molecular test (antigen or nucleic acid) from any specimen collection
6. Known medical history of active liver disease (other than nonalcoholic hepatic steatosis), including chronic or active hepatitis B or C infection, primary biliary cirrhosis, Child-Pugh Class B or C or acute liver failure
7. Receiving dialysis or have known renal impairment
8. Known HIV infection with viral load >400 copies/mL or taking prohibited medications for HIV treatment (from known medical history within past 6 months of the screening visit)
9. Suspected or confirmed concurrent active systemic infection other than COVID-19 that may interfere with the evaluation of response to the study intervention
10. Any comorbidity requiring hospitalization and/or surgery within 7 days prior to study entry, or that is considered life threatening within 30 days prior to study entry, as determined by the investigator
11. History of hypersensitivity or other contraindication to any of the components of the study intervention, as determined by the investigator
12. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study
13. Current or expected use of any medications or substances that are highly dependent on CYP3A4 for clearance, and for which elevated plasma concentrations may be associated with

serious and/or life-threatening events during treatment and for 4 days after the last dose of PF-07321332/ritonavir

14. Concomitant use of any medications or substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to first dose of PF-07321332/ritonavir and during study treatment.
15. Has received or is expected to receive monoclonal antibody treatment or convalescent COVID-19 plasma
16. Has received or is expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit, except for participants with any of the underlying medical conditions specified in Exclusion criterion #1 who are fully vaccinated prior to study entry

Note: Fully vaccinated participants with underlying medical conditions associated with an increased risk of developing severe illness from COVID-19 must not receive a SARS-CoV-2 vaccine booster between screening and the Day 34 visit

17. Is unwilling to abstain from participating in another interventional clinical study with an investigational compound or device, including those for COVID-19 therapeutics, through the long-term follow-up visit. Previous administration with any investigational drug or vaccine within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer)
18. Known prior participation in this trial or other trial involving PF-07321332
19. Known history of any of the following abnormalities in clinical laboratory tests (within past 6 months of the screening visit):
    - AST or ALT level ≥2.5x ULN
    - Total bilirubin ≥2 X ULN (≥3x ULN for Gilbert's syndrome)
    - eGFR <45 mL/min/1.73 m2 within 6 months of the screening visit, using the serum creatinine-based CKD-EPI formula
    - Absolute neutrophil count <1000/mm3

Note: If the investigator suspects the participant may have any of the above laboratory values, confirmatory tests should be performed at screening to confirm eligibility before the first dose of study intervention.

20. Oxygen saturation of <92% on room air obtained at rest within 24 hours prior to randomization

Note: For a potential participant who regularly receives chronic supplementary oxygen for an underlying lung condition, oxygen saturation should be measured while on their standard home oxygen supplementation.

21. Females who are pregnant or breastfeeding
22. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members

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15.3. Applicant's Protocol Synopsis for EPIC-PEP

Title

A phase 2/3, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled Study To Evaluate The Safety And Efficacy Of 2 Regimens Of Orally Administered PF-07321332/Ritonavir In Preventing Symptomatic SARS-CoV-2 Infection In Adult Household Contacts Of An Individual With Symptomatic COVID-19.

Rationale

The purpose of this trial is to evaluate the efficacy and safety of PF-07321332/ritonavir as post-exposure prophylaxis for adult household contacts of an individual with symptomatic COVID-19.

Objectives, Endpoints, and Estimands

Table 121. Objectives, Endpoints, and Estimands for EPIC-PEP

Objectives	Endpoints	Estimands
Primary		
• To compare the efficacy of 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in preventing symptomatic RT-PCR or rapid antigen test- confirmed SARS-CoV-2 infection in adult participants who have a negative RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Proportion of participants who develop a symptomatic, RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14.	• The risk reduction between 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in the proportion of individuals who develop symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 in adults who have a negative RT-PCR result at baseline and are household contacts of an individual with symptomatic COVID-19. This will be estimated without regard to adherence to randomized treatment.
Secondary		
• To describe the safety and tolerability of 5-day and 10-day regimens of PF-07321332/ritonavir relative to placebo in adult participants who have a negative or positive RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	• Incidence of TEAEs. • Incidence of SAEs and AEs leading to discontinuations.	• Not applicable.

Objectives	Endpoints	Estimands
• To compare the efficacy of 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in preventing symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection in adult participants who have a negative RT-PCR result at baseline, who are at increased risk of severe COVID-19 illness, and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline and who are at increased risk of severe COVID-19 illness: • Proportion of participants with symptomatic, RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14. • Proportion of participants with COVID-19 related hospitalization or death from any cause by Day 28.	• The risk reduction between 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in the proportion of individuals who develop symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 in adults who have a negative RT-PCR result at baseline, who are at increased risk of severe COVID-19 illness, and who are household contacts of an individual with symptomatic COVID-19. This will be estimated without regard to adherence to randomized treatment.
• To compare the efficacy of 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in preventing SARS-CoV-2 infection in adult participants who have a negative or positive RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Proportion of participants with asymptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14. • Time to RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14. Of the participants who have a positive RT-PCR result at baseline: • Proportion of participants with symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14. Of the participants who have a negative or positive RT-PCR result at baseline: • Proportion of participants with symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14.	• Not applicable.

Objectives	Endpoints	Estimands
• To compare the efficacy of 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in the duration and severity of COVID-19 related signs and symptoms in adult participants who have a negative RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Proportion of participants with no, mild, moderate, or severe signs and symptoms attributed to COVID-19 through Day 28. • Number of days of symptomatic SARS-CoV-2 infection through Day 28.	• Not applicable.
• To determine the PK of PF-07321332 in adult participants who have a negative or positive RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	• PF-07321332 PK in plasma and whole blood (if feasible).	• Not applicable.
• To describe all-cause mortality in adult participants who have a negative RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Proportion of participants with death (all-cause) through Day 38.	• Not applicable.
• To describe the viral load in nasal samples over time in adult participants who have a negative or positive RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Viral titers measured via RT-PCR in nasal swabs over time. Of the participants who have a positive RT-PCR result at baseline: • Viral titers measured via RT-PCR in nasal swabs over time.	• Not applicable.
• To describe hospitalizations in adult participants who have a negative RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Number of days of hospital and ICU stay in participants with COVID-19-related hospitalization through Day 28.	• Not applicable.

Objectives	Endpoints	Estimands
• To describe COVID-19 related medical visits in adult participants who have a negative RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Number of COVID-19 related medical visits through Day 28.	• Not applicable.

Source: EPIC-PEP protocol amendment 2.
Abbreviations: AE, adverse event; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; ICU, intensive care unit; PK, pharmacokinetic; RT-PCR, real-time, reverse transcription-polymerase chain reaction; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TEAE, treatment-emergent adverse event

Overall Design

Brief Summary

This phase 2/3, randomized, double-blind, double-dummy, placebo-controlled study in approximately 2880 subjects who have a negative screening SARS-CoV-2 rapid antigen test result and who are asymptomatic household contacts of individuals who are symptomatic and recently tested positive for SARS-CoV-2 (index case: defined as patient with symptomatic COVID-19) will compare the efficacy of 2 regimens of PF-07321332/ritonavir versus placebo. Index cases may be participants in Phase 2/3 safety and efficacy studies of PF-07321332/ritonavir (EPIC-SR C4671002 EPIC-HR C4671005), but this is not required. Eligible participants for this study will be randomly assigned (1:1:1) within 96 hours after collection of the index case's first positive SARS-CoV-2 test to treatment in 1 of 3 intervention groups.

Randomization will be stratified based on the presence of risk factors associated with severe COVID-19 illness and geographic region at screening.

Number of Participants

Assuming approximately 5% of subjects will have a positive RT-PCR result at baseline, and assuming an approximately 10% dropout rate, the total sample size for this study will be approximately 2880 subjects.

"Enrolled" means a subject, or his or her legally authorized representative, agrees to participate in a clinical study following completion of the informed consent process and screening. A subjects will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential subjects who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration

Eligible subjects for this study (EPIC-PEP C4671006) will be randomly assigned (1:1:1) within 96 hours after collection of the index case's first positive SARS-CoV-2 test to receive:

- PF-07321332/ritonavir q12h for 5 days followed by matching placebo q12h for 5 days
- PF-07321332/ritonavir q12h for 10 days
- Matching placebo for PF-07321332/ritonavir q12h for 10 days

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Subjects will be screened within 24 hours before randomization. The total duration of the study is up to 42 days and includes screening, study intervention through Day 10, efficacy assessments through Day 14, and a safety follow-up period through Day 38 [±3 days].

Data Monitoring Committee or Other Independent Oversight Committee

An independent E-DMC will review unblinded data to ensure the safety of subjects on an ongoing basis throughout the duration of the study. In addition to up to weekly reviews of safety data, the E-DMC will review the following:

- Sentinel cohort safety review: The E-DMC will review unblinded safety data after approximately the first 150 subjects have completed Day 10 of the study, at which point enrollment will be paused pending E-DMC review of the safety data. After review of the sentinel cohort, the frequency of safety reviews may be reduced subsequently based on E-DMC recommendations.
- Interim analysis: An interim analysis will be conducted for efficacy, futility, and sample size re-estimation and reviewed by the E-DMC after a prespecified accrual of subjects (i.e., before or at approximately 70% overall subjects have completed the Day 14 assessments with a minimum number of 24 subjects having symptomatic infection [mITT analysis set]).

Statistical Methods

For the primary efficacy analysis, GEE will be used to analyze the proportion of subjects with a negative RT-PCR result at baseline who develop a symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 for each treatment group. Comparisons between 5-day regimen of PF-07321332/ritonavir versus placebo group and 10-day regimen of PF-07321332/ritonavir versus placebo group will be presented as risk reduction with 95% CIs based on GEE analysis.

Based on the results from Study C4671005, which showed PF-07321332/ritonavir treatment significantly reduced the risk of hospitalization or death from any cause by 89% compared with placebo in nonhospitalized symptomatic adult subjects with COVID-19 who were at increased risk of progression to severe disease when they were treated within 3 days of symptom onset, and the high relative risk reduction (approximately 80%) observed in Regeneron REGEN-COV post-exposure prophylaxis study, the risk reduction between PF-07321332/ritonavir group versus placebo group is assumed to be 70%. The symptomatic infection rate assumption in the placebo group is adjusted to 4% based on the observed seropositivity rate in this study and the impact of seropositivity on the incidence of primary endpoint events in the REGEN-COV post-exposure prophylaxis study where the incidence of symptomatic infection was 2% in subjects who were seropositive and 8% in those who were seronegative.

Among baseline RT-PCR negative subjects, assuming an 4% symptomatic infection rate in the placebo group, a 70% reduction in symptomatic infection (1.2% symptomatic infection rate) in the PF-07321332/ritonavir group (5-day and 10-day regimen), a sample size of 821 subjects per group (2463 subjects total) will provide approximately 90% power for each comparison between 5-day and 10-day regimens of PF-07321332/ritonavir group versus placebo group under a 2-sided type-1 error rate of 5%. Assuming approximately 5% of subjects with negative rapid antigen test at screening will have a positive RT-PCR result at baseline, and assuming an

approximately 10% dropout rate, the total sample size for this study will be approximately 2880 subjects.

An interim analysis will be conducted for efficacy, futility, and sample size re-estimation and reviewed by an independent E-DMC after a prespecified accrual of subjects (i.e., before or at approximately 70% overall subjects have completed the Day 14 assessments with a minimum number of 24 subjects having symptomatic infection [mITT analysis set]).

Complete Eligibility Criteria

Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

1. Subjects ≥18 years of age (or the minimum country-specific age of consent if >18) at the time of the Screening Visit

   WOCBP may be enrolled
   All fertile participants must agree to use a highly effective method of contraception
2. Subjects who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures
3. Subjects who have a negative screening SARS-CoV-2 rapid antigen test result and who are asymptomatic household contacts (i.e., living in the same residence) of an individual who is symptomatic and recently tested positive for SARS-CoV-2 (i.e., index case: patient with symptomatic COVID-19). To be included in the study, subjects must be randomized within 24 hours of their negative SARS-CoV-2 rapid antigen test and within 96 hours of collection of the index case's first positive SARS-CoV-2 test.

Note: The index case will have confirmation of SARS-CoV-2 infection by RT-PCR or other molecular or antigen tests that detect viral RNA or protein.

Note: Subjects with a negative screening SARS-CoV-2 local rapid antigen test result and whose baseline RT-PCR result is returned as positive would be allowed to remain on treatment in the study.

Note: Asymptomatic is defined as having no signs/symptoms consistent with COVID-19 and symptomatic is defined as having at least 1 of the specified signs or symptoms consistent with COVID-19 (cough, shortness of breath or difficulty breathing, fever with documented temperature >38˚C or subjective fever, chills or shivering, fatigue, muscle or body aches, diarrhea, nausea, vomiting, headache, sore throat, stuffy or runny nose, loss of smell, loss of taste).

4. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol

Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. History of SARS-CoV-2 infection as determined by a molecular test (antibody, antigen, or nucleic acid) from any specimen collected within 6 months before or during the screening visit

2. Experiencing measured fever (documented temperature >38˚C or 100.4˚F) or other signs or symptoms consistent with COVID-19
3. Known medical history of active liver disease (other than nonalcoholic hepatic steatosis), including chronic or active hepatitis B or C infection, primary biliary cirrhosis, Child-Pugh Class B or C or acute liver failure
4. CKD or have known moderate to severe renal impairment
5. Known HIV infection with viral load >400 copies/mL within the last 6 months or taking prohibited medications for HIV treatment (from known medical history within past 6 months of the screening visit)
6. Suspected or confirmed concurrent active systemic infection other than COVID-19 that may interfere with the evaluation of response to the study intervention
7. Active cancer requiring treatment, with prohibited medication that must be administered/continued during the trial period
8. Any comorbidity requiring hospitalization and/or surgery within 7 days prior to study entry, or that is considered life threatening within 30 days prior to study entry, as determined by the investigator
9. History of hypersensitivity or other contraindication to any of the components of the study intervention, as determined by the investigator
10. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study
11. Current or expected use of any medications or substances that are highly dependent on CYP3A4 for clearance, and for which elevated plasma concentrations may be associated with serious and/or life-threatening events during treatment and for 4 days after the last dose of PF-07321332/ritonavir
12. Concomitant use of any medications or substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to first dose of PF-07321332/ritonavir and during study treatment.
13. Has received approved, authorized, or investigational anti-SARS-CoV-2 mAb, convalescent plasma, other drugs for treatment of COVID-19, or other anti-SARS-CoV-2 biologic products within 6 months of screening
14. Has received any SARS-CoV-2 vaccine (includes any level of vaccination) within 6 months prior to screening or is expected to receive a SARS-CoV-2 vaccine or other approved, authorized, or investigational post-exposure prophylaxis treatments through Day 38
15. Is unwilling to abstain from participating in another interventional clinical study with an investigational compound or device, including those for COVID-19 therapeutics, through the End of Study visit
16. Previous administration with an investigational drug within 30 days (or as determined by local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer)
17. Known prior participation in this trial or other trial involving PF-07321332.

18. Known history of any of the following abnormalities in clinical laboratory tests (within past 6 months of the screening visit):
    - AST or ALT level ≥2.5x ULN
    - Total bilirubin ≥2x ULN (≥3x ULN for Gilbert's syndrome).
    - eGFR <45 mL/min/1.73 m2 within 6 months of the screening visit, using the serum creatinine-based CKD-EPI formula
    - Absolute neutrophil count <1000/mm3

Note: If the investigator suspects the participant may have any of the above laboratory values, confirmatory tests should be performed at screening to confirm eligibility before the first dose of study intervention.

19. Females who are pregnant or breastfeeding
20. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members

16. Efficacy

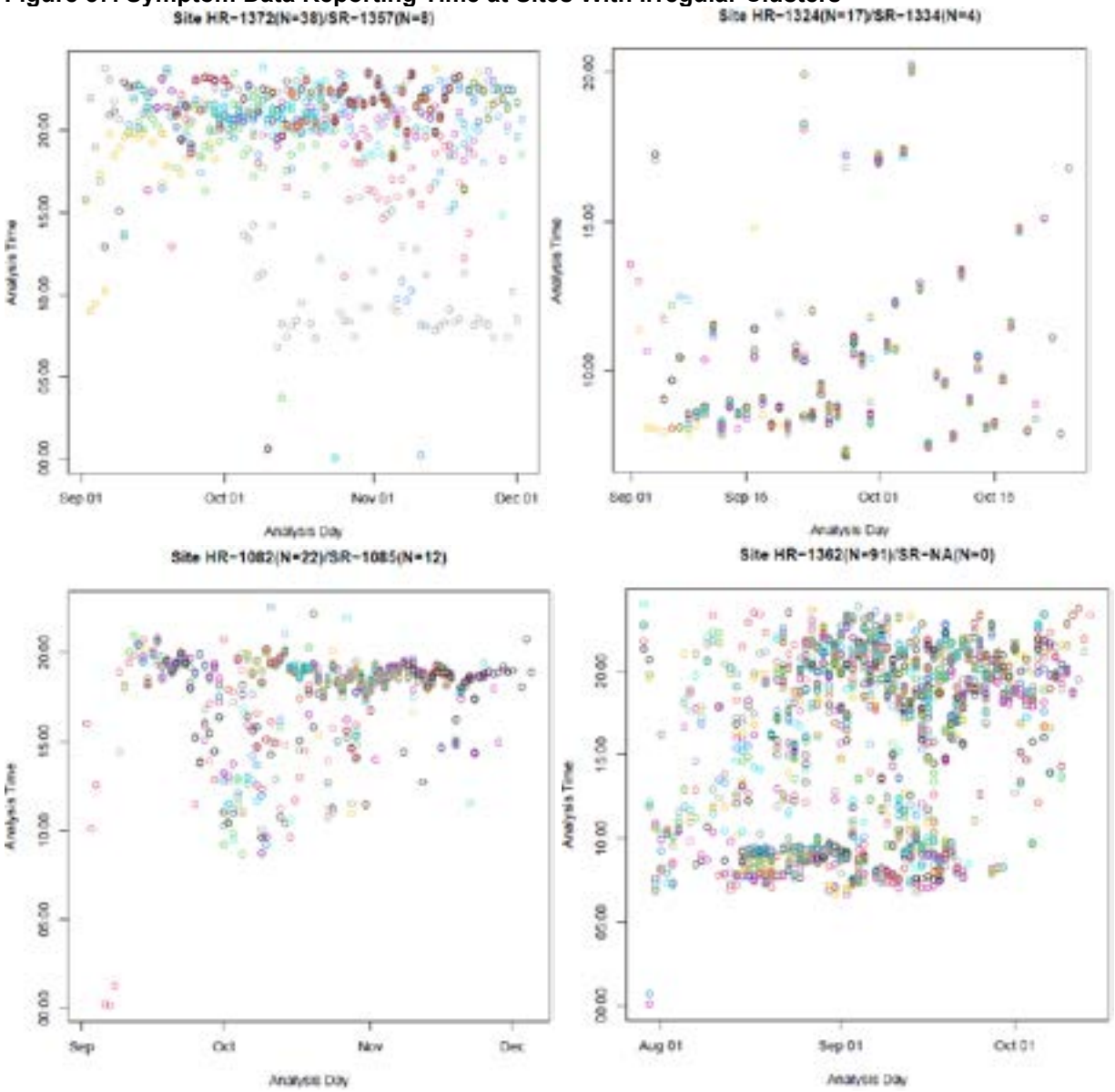
16.1. Sites With Abnormal Symptom Data Reporting Time Patterns

As discussed in Section 6.3.1, irregular symptom data reporting time clusters were observed at site HR1274/SR1281. Similar issues in symptom data with less extremity were observed at other sites, where there were no similar viral RNA data anomalies.

After reviewing symptom reporting time plots for EPIC-HR, EPIC-SR, EPIC-HR and EPIC-SR combined, and EPIC-HR and EPIC-SR (2021) combined, a group of sites, in addition to site HR1274/SR1281, were observed with abnormal symptom data reporting time clusters. These sites include: HR1372/SR1357, HR1324/SR1334, HR1082/SR1085, HR1362, HR1318/SR1388, HR1163, HR1103/SR1107, HR1501/SR1521, HR1014/SR1013(2021), SR1575. Figure 57, Figure 58, and Figure 59 show their symptom data reporting time patterns.

The Applicant conducted CluePoints analyses on two KRIs, SDOOG and SDOSG, for EPIC-HR, EPIC-SR, EPIC-SR (2021), EPIC-SR (2022), EPIC-HR and EPIC-SR combined, and EPIC-HR and EPIC-SR (2021) combined. All sites listed above expect HR1163 were flagged as medium risk or close to medium risk (i.e., HR1103/SR1107) in the Applicant's analyses of EPIC-HR and EPIC-SR (2021) combined and EPIC-SR (2022).

Figure 57. Symptom Data Reporting Time at Sites With Irregular Clusters



Source: Reviewer's analysis on EPIC-HR and EPIC-SR ADSO dataset.
Abbreviations: N, total number of subjects

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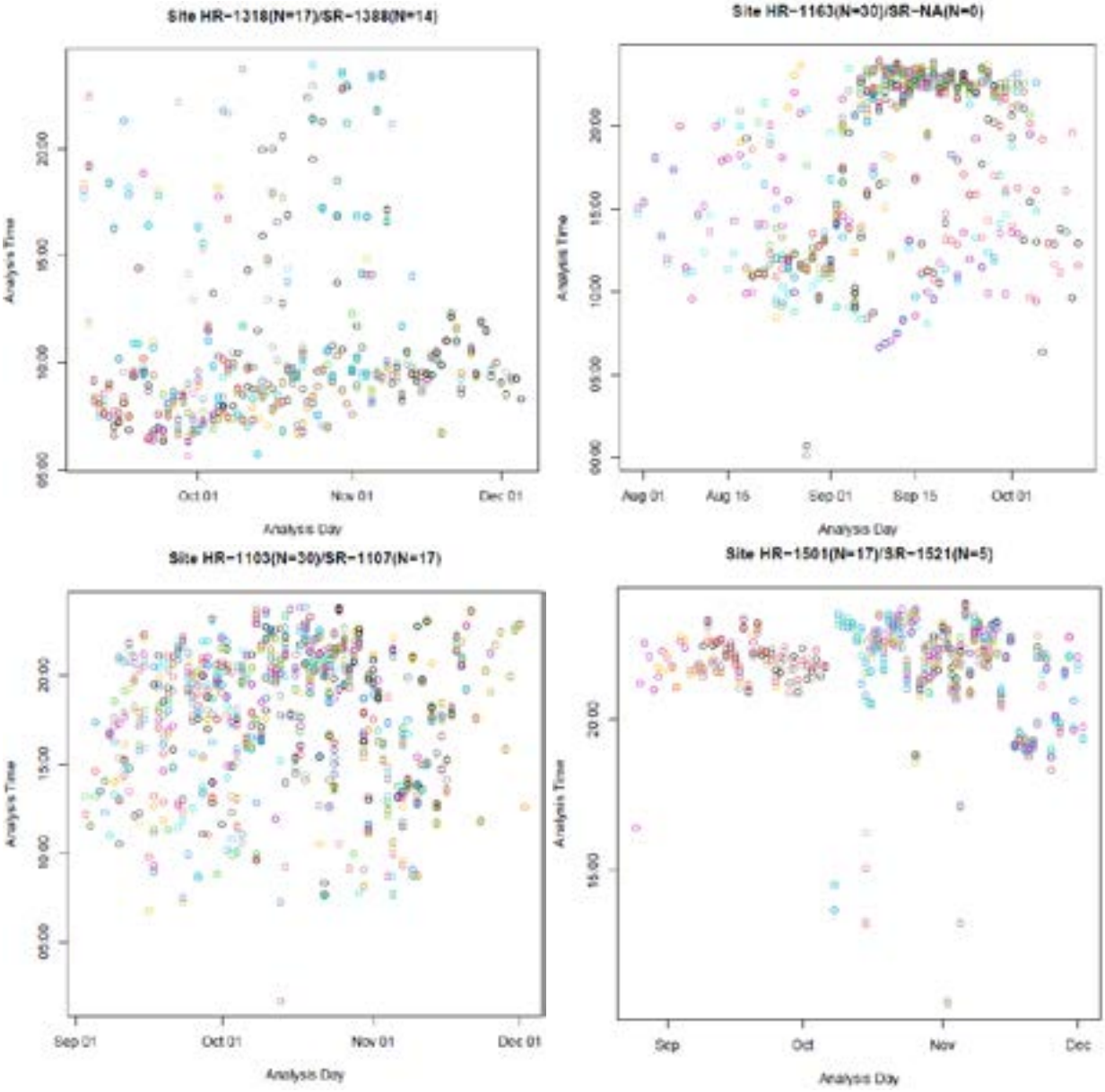
Figure 58. Symptom Data Reporting Time at Sites With Irregular Clusters (Continued)



Source: Reviewer's analysis on EPIC-HR and EPIC-SR ADSO datasets
Abbreviations: N, total number of subjects

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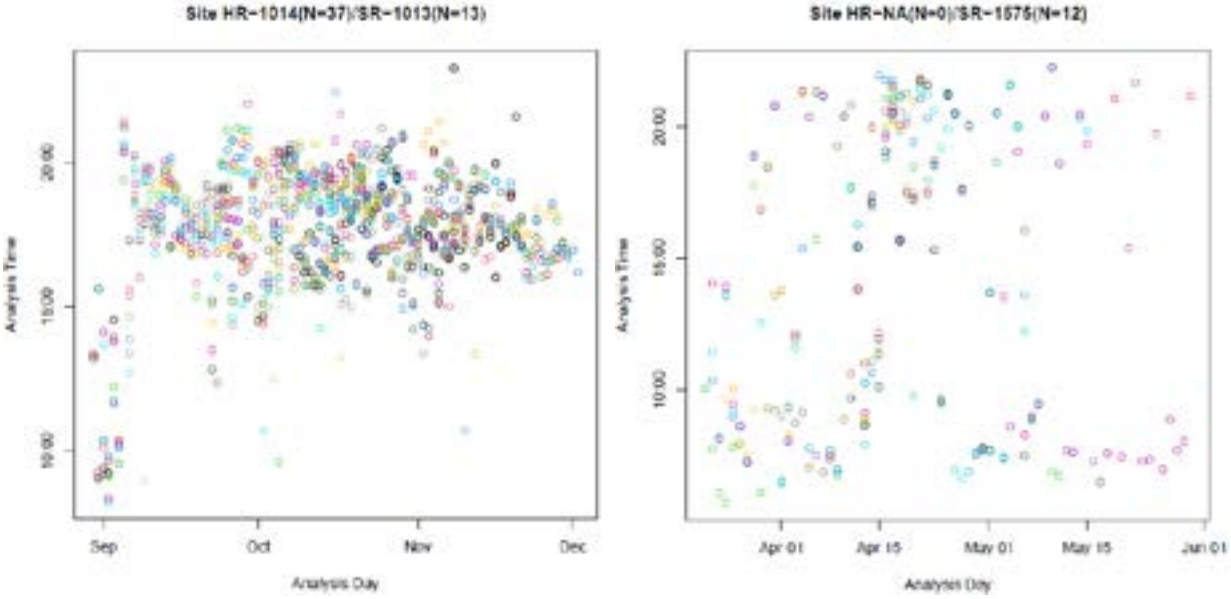
Figure 59. Symptom Data Reporting Time at Sites With Irregular Clusters (Continued)



Source: Reviewer's analysis on EPIC-HR and EPIC-SR ADSO datasets
Abbreviations: N, total number of subjects

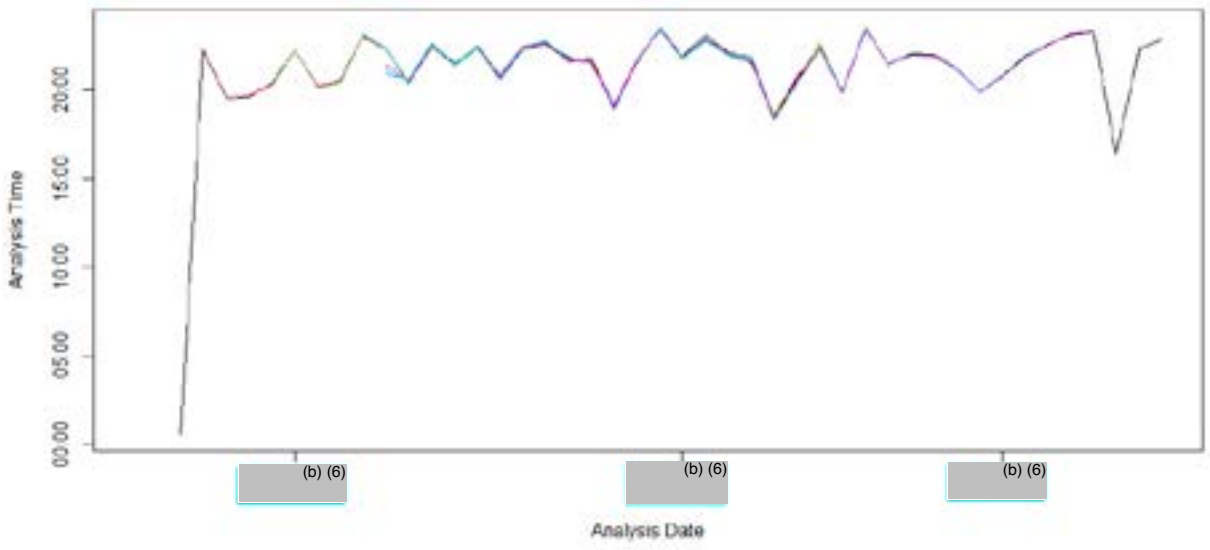
According to the Applicant, clustered data entry times may reflect individual site prescriptive instructions to subjects to ensure compliance. Subjects were provided guidance regarding selection of an easy to remember PIN code and reminder notifications for daily completion of the eDiaries at the same approximate time each day. If the COVID-19 Symptoms Diary was not completed prior to the first reminder being triggered, then 3 alarms sounded at 30-minute intervals. The permitted window for reminders to be sent was between 12:00 am and 10:30 pm. Subjects were able to use the App to change the reminder time on their own. Additionally, after the initial device set-up process, site staff had the ability to adjust the time that reminder notifications were sent to subjects to complete their COVID-19 Symptoms Diary each day. However, there are still patterns of clustered data entry times that cannot be explained by App reminder notifications.

Site HR1372/SR1357 and site HR1324/SR1334 had the highest ranks next to HR1274/SR1281 in the CluePoints analysis of EPIC-HR and EPIC-SR (2021) combined.

Figure 60 below displays symptom data reporting time for 14 subjects from site HR1372/SR1357 with ID in (b) (6) and (b) (6), who were enrolled between (b) (6), and (b) (6). Their symptom data reporting time were within approximately 10 minutes every day. At this site, 45 out of 47 subjects who had a PIN code shared the same PIN code of 3122.

According to the Applicant, subjects from this site were instructed select easy to remember PINs. Site staff provided example PINs but did not recall exact examples provided. Subjects with subject IDs (b) (6) through (b) (6) all have the same daily eDiary reminder time of 22:30. in addition to the reminders in the TrialMax application, study coordinators provided reminders to participants by phone at approximately the same time on a given day.

Figure 60. Symptom Data Reporting Time at Site HR1372/SR1357 for Subjects With IDs Within the Range of (b) (6) or (b) (6)

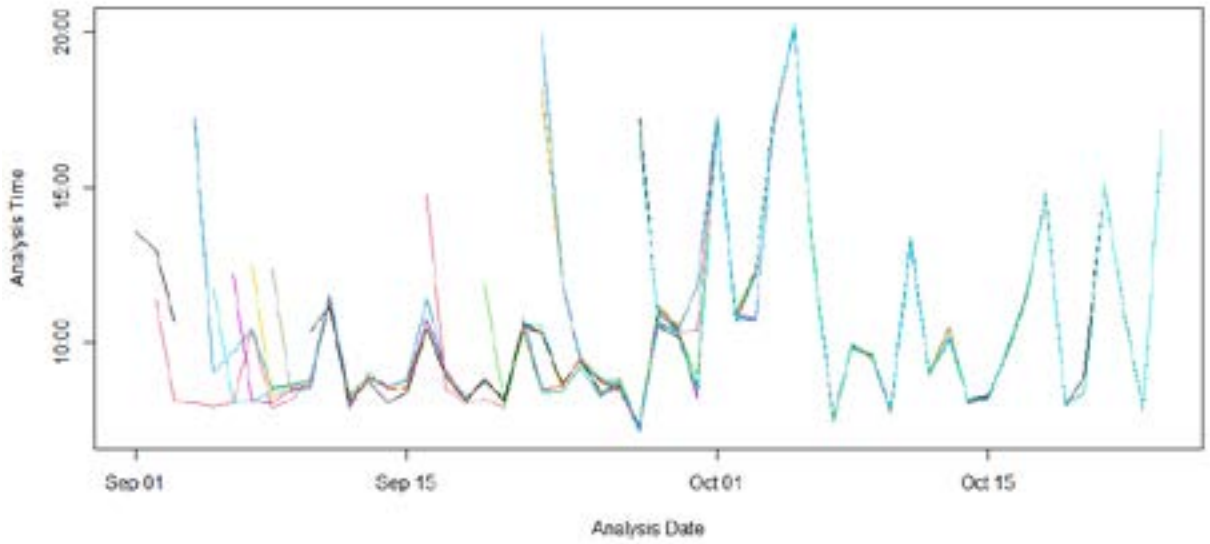


Source: Reviewer's analysis on EPIC-HR and EPIC-SR ADSO datasets.
Abbreviations: ID, identification

Figure 61 below displays symptom data reporting time for all subjects from site HR1324/SR1334. Almost all subjects have very similar symptom reporting time every day. All 21 subjects shared the same PIN code of 2252. A high percentage of subjects reporting resolution of all targeted symptoms after Day 1 was observed at this site, which is rare compared to other sites or sites from the same country.

According to the Applicant, all subjects from this site needed to stay in field hospital for quarantine 10-14 days per government policy. The coordinator reminded subjects in person to complete diary during14 days while subjects were in quarantine. After at home, subjects were reminded to complete eDiary via phone.

Figure 61. Symptom Data Reporting Time at Site HR1324/SR1334



Source: Reviewer's analysis on EPIC-HR and EPIC-SR ADSO datasets.

The following additional sensitivity analyses were conducted to evaluate the impact of certain sites with potential misconduct of symptom diary data collection, for the endpoint of COVID-19 related hospitalization or death from any cause through Day 28, in mITT, mITT1, and mITT2 populations of study EPIC-HR. Similar to the primary efficacy analyses in Section 6, sites 1274 and 1470 were also excluded. Results were consistent with the primary analysis findings as provided in Table 122, Table 123, and Table 124.

- Sites with abnormal symptom data reporting time patterns in EPIC-HR were excluded. These sites include: 1274, 1501, 1324, 1362, 1014, 1372, 1082, 1318, 1103, 1163
- Sites with the shared PIN code issue (after combining EPIC-HR and EPIC-SR 2021 subjects by investigator, >50% subjects used the same PIN code and ≥10 subjects were enrolled) in EPIC-HR were excluded. These sites include: 1309, 1062, 1492, 1153, 1076, 1324, 1034, 1163, 1318, 1082, 1372, 1014, 1097, 1158, 1362, 1325, 1274, 1276, 1030
- Sites with shared PIN code issue (as defined above) or with birth year PIN code issue (after combining EPIC-HR and EPIC-SR 2021 subjects by investigator, >50% subjects used birth year as PIN code and ≥10 subjects were enrolled, with the exception of site 1066, which has = 50%) in EPIC-HR were excluded. These sites include: 1309, 1062, 1492, 1153, 1076, 1324, 1034, 1163, 1318, 1082, 1372, 1014, 1097, 1158, 1362, 1325, 1274, 1276, 1030, 1219, 1155, 1273, 1442, 1382, 1399, 1395, 1058, 1135, 1501, 1331, 1374, 1037, 1149, 1066. Note that subjects' birth years were collected in the trial, while birth months and days were not.

Table 122. Proportion of Participants With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28, Excluding Sites With Abnormal Symptom Data Reporting Time Patterns, EPIC-HR

mITT[a] Analysis	**Paxlovid N=573**	**Placebo N=546**
Participants with event, n (%)	4 (0.7)	42 (7.7)
COVID-19 hospitalization	4 (0.7)	42 (7.7)
Death	0	8 (1.5)
Estimated difference in proportion % (95% CI)[d]	-7.1 (-9.5, -4.7)	
Two-sided nominal p-value	<0.0001	
mITT1[b] Analysis	**Paxlovid N=833**	**Placebo N=843**
Participants with event, n (%)	8 (1.0)	60 (7.1)
COVID-19 hospitalization	8 (1.0)	59 (7.0)
Death	0	11 (1.3)
Estimated difference in proportion % (95% CI)[d]	-6.3 (-8.1, -4.4)	
Two-sided nominal p-value	<0.0001	
mITT2[c] Analysis	**Paxlovid N=892**	**Placebo N=900**
Participants with event, n (%)	9 (1.0)	62 (6.9)
COVID-19 hospitalization	9 (1.0)	61 (6.8)
Death	0	11 (1.2)
Estimated difference in proportion % (95% CI)[d]	-6.0 (-7.8, -4.2)	
Two-sided nominal p-value	<0.0001	

Source: Reviewer's analysis, excluding subjects from sites 1470, 1274, 1501, 1324, 1362, 1014, 1372, 1082, 1318, 1103, 1163
[a.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All participants randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
[d.] The estimated cumulative proportion of participants hospitalized for the treatment of COVID-19 or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent to treat; N, number of patients in treatment group; n, number of patients with given characteristic; PIN, personal identification number

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Table 123. Proportion of Participants With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28, Excluding Sites With Shared PIN Code Issue, EPIC-HR

mITT[a] **Analysis**	**Paxlovid N=467**	**Placebo N=441**
Participants with event, n (%)	3 (0.6)	27 (6.1)
COVID-19 hospitalization	3 (0.6)	27 (6.1)
Death	0	4 (0.9)
Estimated difference in proportion % (95% CI)[d]	-5.6 (-7.9, -3.2)	
Two-sided nominal p-value	<0.0001	
mITT1[b] **Analysis**	**Paxlovid N=682**	**Placebo N=690**
Participants with event, n (%)	6 (0.9)	43 (6.2)
COVID-19 hospitalization	6 (0.9)	42 (6.1)
Death	0	7 (1.0)
Estimated difference in proportion % (95% CI)[d]	-5.5 (-7.4, -3.5)	
Two-sided nominal p-value	<0.0001	
mITT2[c] **Analysis**	**Paxlovid N=740**	**Placebo N=748**
Participants with event, n (%)	7 (0.9)	45 (6.0)
COVID-19 hospitalization	7 (0.9)	44 (5.9)
Death	0	7 (0.9)
Estimated difference in proportion % (95% CI)[d]	-5.2 (-7.0, -3.3)	
Two-sided nominal p-value	<0.0001	

Source: Reviewer's analysis, excluding subjects from sites 1470, 1274, 1309, 1062, 1492, 1153, 1076, 1324, 1034, 1163, 1318, 1082, 1372, 1014, 1097, 1158, 1362, 1325, 1276, 1030.

[a.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.

[b.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.

[c.] All participants randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.

[d.] The estimated cumulative proportion of participants hospitalized for the treatment of COVID-19 or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.

Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent to treat; N, number of patients in treatment group; n, number of patients with given characteristic; PIN, personal identification number

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Table 124. Proportion of Participants With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28, Excluding Sites With Shared PIN Code Issue or Birth Year PIN Code Issue, EPIC-HR

mITT[a] **Analysis**	**Paxlovid N=378**	**Placebo N=353**
Participants with event, n (%)	2 (0.5)	19 (5.4)
COVID-19 hospitalization	2 (0.5)	19 (5.4)
Death	0	3 (0.8)
Estimated difference in proportion % (95% CI)[d]	-4.9 (-7.4, -2.4)	
Two-sided nominal p-value	0.0001	
mITT1[b] **Analysis**	**Paxlovid N=560**	**Placebo N=567**
Participants with event, n (%)	4 (0.7)	33 (5.8)
COVID-19 hospitalization	4 (0.7)	32 (5.6)
Death	0	6 (1.1)
Estimated difference in proportion % (95% CI)[d]	-5.2 (-7.3, -3.1)	
Two-sided nominal p-value	<0.0001	
mITT2[c] **Analysis**	**Paxlovid N=613**	**Placebo N=616**
Participants with event, n (%)	5 (0.8)	35 (5.7)
COVID-19 hospitalization	5 (0.8)	34 (5.5)
Death	0	6 (1.0)
Estimated difference in proportion % (95% CI)[d]	-5.0 (-7.0, -3.0)	
Two-sided nominal p-value	<0.0001	

Source: Reviewer's analysis, excluding subjects from sites 1470, 1274, 1309, 1062, 1492, 1153, 1076, 1324, 1034, 1163, 1318, 1082, 1372, 1014, 1097, 1158, 1362, 1325, 1276, 1030, 1219, 1155, 1273, 1442, 1382, 1399, 1395, 1058, 1135, 1501, 1331, 1374, 1037, 1149, 1066.

[a.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.

[b.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.

[c.] All participants randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.

[d.] The estimated cumulative proportion of participants hospitalized for the treatment of COVID-19 or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.

Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent to treat; N, number of patients in treatment group; n, number of patients with given characteristic; PIN, personal identification number

The following sites in EPIC-SR also had the above-mentioned shared PIN code issue or birth year PIN code issue, when looked at 2021 and 2022 data separately or combined: 1367, 1153, 1306, 1138, 1575, 1197, 1157. However, these sites did not have EPIC-HR enrollment, with the exception of EPIC-SR 1197. No PIN issue was reported in the corresponding EPIC-HR site 1193 (n = 59).

16.2. EPIC-HR

16.2.1. Interim Analysis Results, EPIC-HR

As of the data cutoff (October 26, 2021),1361 subjects were included in the full analysis set in the interim analysis. The primary endpoint was proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28 in the mITT population who received treatment within 3 days of symptom onset. The event rates were 27/387 (7.0%) in the placebo

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group, and 3/393 (0.8%) in the PAXLOVID group (Table 125). After accounting for premature study discontinuation by using the follow-up time in the Kaplan-Meier calculation, treatment with PAXLOVID showed a 6.3% (95% CI: -9.0% to -3.6%; p<0.0001) absolute reduction, or 89.1% relative reduction compared to placebo. The reduction was statistically significant, at α-level of 0.002, which was pre-specified for the interim analysis. This analysis did not exclude those enrolled at site 1274 and site 1470.

Table 125. Proportion of Participants With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28, Interim Analysis, EPIC-HR

mITT[a] **Analysis**	**Paxlovid** **N=393**	**Placebo** **N=387**
Participants with event, n (%)	3 (0.8)	27 (7.0)
COVID-19 hospitalization	3 (0.8)	27 (7.0)
Death	0	7 (1.8)
Estimated difference in proportion % (95% CI)[d]	-6.3 (-9.0, -3.6)	
Two-sided p-value	<0.0001	
mITT1[b] **Analysis**	**Paxlovid** **N=617**	**Placebo** **N=620**
Participants with event, n (%)	6 (1.0)	41 (6.6)
COVID-19 hospitalization	6 (1.0)	41 (6.6)
Death	0	10 (1.6)
Estimated difference in proportion % (95% CI)[d]	-5.8 (-7.9, -3.6)	
Two-sided p-value	<0.0001	
mITT2[c] **Analysis**	**Paxlovid** **N=672**	**Placebo** **N=677**
Participants with event, n (%)	7 (1.0)	43 (6.4)
COVID-19 hospitalization	7 (1.0)	43 (6.4)
Death	0	10 (1.5)
Estimated difference in proportion % (95% CI)[d]	-5.4 (-7.5, -3.4)	
Two-sided nominal p-value	<0.0001	

Source: EUA 105 review. Data from site 1274 and site 1470 were not excluded.
[a.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All participants randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
[d.] The estimated cumulative proportion of participants hospitalized for the treatment of COVID-19 or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent to treat; N, number of patients in treatment group; n, number of patients with given characteristic

Table 126 below displays the results in mITT and mITT1 after excluding site 1274 and site 1470. Treatment with PAXLOVID showed a 6.5% (95% CI: -9.3% to -3.7%; p<0.0001) absolute reduction in mITT.

Table 126. Proportion of Participants With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28, Updated Interim Analysis in mITT and mITT1, EPIC-HR

mITT[a] Analysis	Paxlovid N=380	Placebo N=374
Participants with event, n (%)	3 (0.8)	27 (7.2)
COVID-19 hospitalization	3 (0.8)	27 (7.2)
Death	0	7 (1.9)
Estimated difference in proportion % (95% CI)[c]	-6.5 (-9.3, -3.7)	
Two-sided p-value	<0.0001	
mITT1[b] Analysis	**Paxlovid N=574**	**Placebo N=587**
Participants with event, n (%)	6 (1.0)	39 (6.6)
COVID-19 hospitalization	6 (1.0)	39 (6.6)
Death	0	10 (1.7)
Estimated difference in proportion % (95% CI)[c]	-5.7 (-7.9, -3.5)	
Two-sided p-value	<0.0001	

Source: Reviewer's analysis. Data from site 1274 and site 1470 were excluded.
[a.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] The estimated cumulative proportion of participants hospitalized for the treatment of COVID-19 or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent to treat; N, number of patients in treatment group; n, number of patients with given characteristic

16.2.2. Primary Endpoint Sensitivity Analyses, EPIC-HR

The following sensitivity analyses were conducted for the endpoint of COVID-19 related hospitalization or death from any cause through Day 28, in mITT, mITT1, and mITT2 populations. Results were consistent with the primary analysis findings.

- For subjects who enrolled more than once in EPIC-HR C4671005 or enrolled in EPIC-HR C4671005 and in 1 or 2 other phase 2/3 nirmatrelvir/ritonavir studies, data from a duplicate subject's first enrollment within this study were included and data from a duplicate participant's subsequent enrollments were excluded
- Sites in India were excluded
- Subjects who were lost to follow up before Day 21 were hypothetically assumed to have experienced both COVID-19-related hospitalization and death in a worst-case scenario
- Subjects who did not complete Day 28 follow up and discontinued study treatment due to adverse event were hypothetically assumed to have experienced both COVID-19-related hospitalization and death in a worst case-scenario

Table 127. Proportion of Participants With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28, First Enrollment Sensitivity Analysis, EPIC-HR

mITT[a] **Analysis**	**Paxlovid N=664**	**Placebo N=643**
Participants with event, n (%)	5 (0.8)	44 (6.8)
COVID-19 hospitalization	5 (0.8)	44 (6.8)
Death	0	9 (1.4)
Estimated difference in proportion % (95% CI)[d]	-6.2 (-8.3, -4.1)	
Two-sided nominal p-value	<0.0001	
mITT1[b] **Analysis**	**Paxlovid N=969**	**Placebo N=985**
Participants with event, n (%)	9 (0.9)	64 (6.5)
COVID-19 hospitalization	9 (0.9)	63 (6.4)
Death	0	12 (1.2)
Estimated difference in proportion % (95% CI)[d]	-5.7 (-7.3, -4.0)	
Two-sided nominal p-value	<0.0001	
mITT2[c] **Analysis**	**Paxlovid N=1029**	**Placebo N=1049**
Participants with event, n (%)	10 (1.0)	66 (6.3)
COVID-19 hospitalization	10 (1.0)	65 (6.2)
Death	0	12 (1.1)
Estimated difference in proportion % (95% CI)[d]	-5.4 (-7.0, -3.8)	
Two-sided nominal p-value	<0.0001	

Source: Reviewer's analysis, excluding subjects from site 1274 and site 1470.
[a.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All participants randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
[d.] The estimated cumulative proportion of participants hospitalized for the treatment of COVID-19 or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent to treat; N, number of patients in treatment group; n, number of patients with given characteristic

Table 128. Proportion of Participants With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28, Excluding India Sites, EPIC-HR

mITT[a] Analysis	Paxlovid N=615	Placebo N=593
Participants with event, n (%)	5 (0.8)	44 (7.4)
COVID-19 hospitalization	5 (0.8)	44 (7.4)
Death	0	9 (1.5)
Estimated difference in proportion % (95% CI)[d]	-6.7 (-8.9, -4.4)	
Two-sided nominal p-value	<0.0001	
mITT1[b] Analysis	**Paxlovid N=887**	**Placebo N=897**
Participants with event, n (%)	9 (1.0)	64 (7.1)
COVID-19 hospitalization	9 (1.0)	63 (7.0)
Death	0	12 (1.3)
Estimated difference in proportion % (95% CI)[d]	-6.2 (-8.1, -4.4)	
Two-sided nominal p-value	<0.0001	
mITT2[c] Analysis	**Paxlovid N=944**	**Placebo N=956**
Participants with event, n (%)	10 (1.1)	66 (6.9)
COVID-19 hospitalization	10 (1.1)	65 (6.8)
Death	0	12 (1.3)
Estimated difference in proportion % (95% CI)[d]	-5.9 (-7.7, -4.2)	
Two-sided nominal p-value	<0.0001	

Source: Reviewer's analysis, excluding subjects from site 1274 and site 1470.
[a.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All participants randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
[d.] The estimated cumulative proportion of participants hospitalized for the treatment of COVID-19 or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent to treat; N, number of patients in treatment group; n, number of patients with given characteristic

Table 129. Proportion of Participants With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28, Lost to Follow-Up Before Day 21 as Events, EPIC-HR

mITT[a] Analysis	Paxlovid N=671	Placebo N=647
Participants with event, n (%)	24 (3.6)	58 (9.0)
Estimated difference in proportion % (95% CI)[d]	-5.4 (-8.0, -2.8)	
Two-sided nominal p-value	<0.0001	
mITT1[b] Analysis	**Paxlovid N=977**	**Placebo N=989**
Participants with event, n (%)	44 (4.5)	95 (9.6)
Estimated difference in proportion % (95% CI)[d]	-5.1 (-7.4, -2.9)	
Two-sided nominal p-value	<0.0001	

mITT2[c] Analysis	Paxlovid N=1038	Placebo N=1053
Participants with event, n (%)	46 (4.4)	98 (9.3)
Estimated difference in proportion % (95% CI)[d]	-4.9 (-7.0, -2.7)	
Two-sided nominal p-value	<0.0001	

Source: Reviewer's analysis, excluding subjects from site 1274 and site 1470.
[a.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All participants randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
[d.] The estimated cumulative proportion of participants hospitalized for the treatment of COVID-19 or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent to treat; N, number of patients in treatment group; n, number of patients with given characteristic

Table 130. Proportion of Participants With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28, Treatment Discontinuation Due to Adverse Event and Lost to Follow-Up as Events, EPIC-HR

mITT[a] Analysis	Paxlovid N=671	Placebo N=647
Participants with event, n (%)	7 (1.0)	47 (7.3)
Estimated difference in proportion % (95% CI)[d]	-6.3 (-8.4, -4.1)	
Two-sided nominal p-value	<0.0001	
mITT1[b] Analysis	**Paxlovid N=977**	**Placebo N=989**
Participants with event, n (%)	14 (1.4)	69 (7.0)
Estimated difference in proportion % (95% CI)[d]	-5.6 (-7.4, -3.8)	
Two-sided nominal p-value	<0.0001	
mITT2[c] Analysis	**Paxlovid N=1038**	**Placebo N=1053**
Participants with event, n (%)	15 (1.4)	71 (6.7)
Estimated difference in proportion % (95% CI)[d]	-5.4 (-7.1, -3.7)	
Two-sided nominal p-value	<0.0001	

Source: Reviewer's analysis, excluding subjects from site 1274 and site 1470.
[a.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All participants randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
[d.] The estimated cumulative proportion of participants hospitalized for the treatment of COVID-19 or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent to treat; N, number of patients in treatment group; n, number of patients with given characteristic

16.2.3. Primary Endpoint Subgroup Analyses, EPIC-HR

Subgroup analyses were conducted in mITT, mITT1, and mITT2 populations. Treatment with PAXLOVID showed no inconsistent effect in any subgroup of participants.

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Table 131. Proportion of Participants With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28 by Baseline Demographics, mITT Population, EPIC-HR

Demographic Parameters	Paxlovid n/N (%)	Placebo n/N (%)	Difference in % (95% CI)	Nominal p-value
Overall	5/671 (0.7)	44/647 (6.8)	-6.1 (-8.2, -4.1)	<0.0001
Sex				
Female	2/333 (0.6)	13/310 (4.2)	-3.6 (-6.0, -1.2)	0.0031
Male	3/338 (0.9)	31/337 (9.2)	-8.4 (-11.7, -5.1)	<0.0001
Age Group				
<65	4/580 (0.7)	28/556 (5.0)	-4.4 (-6.4, -2.4)	<0.0001
≥65	1/91 (1.1)	16/91 (17.6)	-16.5 (-24.6, -8.4)	<0.0001
Race				
White	5/484 (1.0)	37/491 (7.5)	-6.6 (-9.1, -4.1)	<0.0001
Black or African American	0/31	0/15	0.0 (0.0, 0.0)	N.A.
Asian	0/89	4/83 (4.8)	-4.9 (-9.5, -0.2)	0.0404
Others	0/67	3/58 (5.2)	-5.2 (-10.9, 0.5)	0.0753
Region				
United States	1/229 (0.4)	6/213 (2.8)	-2.4 (-4.8, 0.0)	0.0506
Europe	4/249 (1.6)	28/252 (11.1)	-9.6 (-13.8, -5.4)	<0.0001
India	0/56	0/54	0.0 (0.0, 0.0)	N.A.
Rest of the World	0/137	10/128 (7.8)	-7.9 (-12.7, -3.2)	0.0010
BMI				
<25	1/143 (0.7)	5/132 (3.8)	-3.1 (-6.6, 0.5)	0.0876
25 to <30	2/291 (0.7)	22/296 (7.4)	-6.8 (-10.0, -3.7)	<0.0001
≥30	2/237 (0.8)	17/219 (7.8)	-7.1 (-10.9, -3.3)	0.0003
Baseline serology status[a]				
Negative	5/339 (1.5)	40/338 (11.8)	-10.6 (-14.3, -6.8)	<0.0001
Positive	0/327	4/301 (1.3)	-1.3 (-2.6, 0.0)	0.0441
Baseline Viral RNA (NP samples, log_{10} copies/mL)[a]				
<4	0/219	1/201 (0.5)	-0.5 (-1.5, 0.5)	0.3161
≥4	5/433 (1.2)	40/428 (9.3)	-8.3 (-11.3, -5.4)	<0.0001
Baseline Viral RNA (NP samples, log_{10} copies/mL)[a]				
<7	3/428 (0.7)	21/425 (4.9)	-4.3 (-6.5, -2.1)	0.0002
≥7	2/224 (0.9)	20/204 (9.8)	-9.0 (-13.4, -4.7)	<0.0001
Number of Comorbidities				
0-1	2/540 (0.4)	26/503 (5.2)	-4.9 (-6.9, -2.8)	<0.0001
2-3	3/128 (2.3)	18/142 (12.7)	-10.3 (-16.4, -4.2)	0.0009
≥4	0/3	0/2	0.0 (0.0, 0.0)	N.A.
Cigarette Smoker[a]				
Yes	3/272 (1.1)	13/277 (4.7)	-3.6 (-6.4, -0.8)	0.0111
No	2/397 (0.5)	31/370 (8.4)	-8.0 (-11.0, -5.0)	<0.0001
Diabetes mellitus[a]				
Yes	0/75	7/77 (9.1)	-9.1 (-15.5, -2.7)	0.0055
No	5/595 (0.8)	37/570 (6.5)	-5.7 (-7.9, -3.6)	<0.0001
Immunosuppression[a]				
Yes	0/3	0/5	0.0 (0.0, 0.0)	N.A.
No	5/667 (0.7)	44/642 (6.9)	-6.2 (-8.3, -4.1)	<0.0001
Chronic lung disease[a]				
Yes	0/37	1/26 (3.8)	-4.0 (-11.7, 3.7)	0.3074
No	5/633 (0.8)	43/621 (6.9)	-6.2 (-8.3, -4.1)	<0.0001

Demographic Parameters	Paxlovid n/N (%)	Placebo n/N (%)	Difference in % (95% CI)	Nominal p-value
Hypertension[a]				
Yes	4/217 (1.8)	29/224 (12.9)	-11.2 (-16.0, -6.4)	<0.0001
No	1/453 (0.2)	15/423 (3.5)	-3.4 (-5.2, -1.5)	0.0003
Cardiovascular disorder[a]				
Yes	0/26	9/33 (27.3)	-27.3 (-42.5, -12.1)	0.0004
No	5/644 (0.8)	35/614 (5.7)	-5.0 (-7.0, -3.0)	<0.0001
Chronic kidney disease[a]				
Yes	0/3	0/1	0.0 (0.0, 0.0)	N.A.
No	5/667 (0.7)	44/646 (6.8)	-6.1 (-8.2, -4.1)	<0.0001
Device dependence[a]				
Yes	0/2	0/1	0.0 (0.0, 0.0)	N.A.
No	5/663 (0.8)	43/643 (6.7)	-6.0 (-8.1, -3.9)	<0.0001
HIV infection[a]				
Yes	0/0	0/0	N.A.	N.A.
No	5/670 (0.7)	44/646 (6.8)	-6.1 (-8.2, -4.1)	<0.0001
Sickle cell disease[a]				
Yes	0/0	0/0	N.A.	N.A.
No	5/670 (0.7)	44/647 (6.8)	-6.1 (-8.2, -4.1)	<0.0001
Neurodevelopmental disorder[a]				
Yes	0/1	0/1	0.00 (0.00, 0.00)	N.A.
No	5/669 (0.7)	44/646 (6.8)	-6.1 (-8.2, -4.1)	<0.0001
Cancer[a]				
Yes	0/3	0/4	0.00 (0.00, 0.00)	N.A.
No	5/667 (0.7)	44/643 (6.8)	-6.2 (-8.3, -4.1)	<0.0001

Source: Reviewer's Analysis, excluding subjects from site 1274 and site 1470.
[a.] Those with missing baseline status were not included.
Abbreviations: BMI, body mass index; CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; log, logarithm; mITT, modified intent to treat; N, total number of subjects; n, number of subjects in sample; N.A., not applicable; NP, nasopharyngeal; RNA, ribonucleic acid

Table 132. Proportion of Participants With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28 by Baseline Demographics, mITT1 Population, EPIC-HR

Demographic Parameters	Paxlovid n/N (%)	Placebo n/N (%)	Difference in % (95% CI)	Nominal p-value
Overall	9/977 (0.9)	64/989 (6.5)	-5.6 (-7.3, -4.0)	<0.0001
Sex				
Female	4/492 (0.8)	25/484 (5.2)	-4.4 (-6.6, -2.3)	<0.0001
Male	5/485 (1.0)	39/505 (7.7)	-6.8 (-9.3, -4.3)	<0.0001
Age Group				
<65	8/853 (0.9)	45/865 (5.2)	-4.3 (-6.0, -2.7)	<0.0001
≥65	1/124 (0.8)	19/124 (15.3)	-14.6 (-21.2, -8.1)	<0.0001
Age Group				
≤60	8/804 (1.0)	36/783 (4.6)	-3.7 (-5.3, -2.0)	<0.0001
>60	1/173 (0.6)	28/206 (13.6)	-13.1 (-18.0, -8.3)	<0.0001
Race				
White	8/682 (1.2)	51/705 (7.2)	-6.1 (-8.3, -4.0)	<0.0001
Black or African American	0/44	1/31 (3.2)	-3.2 (-9.4, 3.0)	0.3094
Asian	1/146 (0.7)	6/149 (4.0)	-3.4 (-6.8, 0.1)	0.0560
Others	0/105	6/104 (5.8)	-5.9 (-10.6, -1.3)	0.0116

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Demographic Parameters	Paxlovid n/N (%)	Placebo n/N (%)	Difference in % (95% CI)	Nominal p-value
Region				
United States	2/341 (0.6)	12/348 (3.4)	-2.9 (-5.0, -0.8)	0.0072
Europe	4/325 (1.2)	37/329 (11.2)	-10.2 (-13.8, -6.5)	<0.0001
India	0/90	0/92	0.0 (0.0, 0.0)	N.A.
Rest of the World	3/341 (0.6)	15/348 (4.3)	-5.6 (-9.3, -1.9)	0.0034
BMI				
<25	1/201 (0.5)	8/200 (4.0)	-3.5 (-6.4, -0.6)	0.0175
25 to <30	3/440 (0.7)	27/444 (6.1)	-5.5 (-7.9, -3.1)	<0.0001
≥30	5/336 (1.5)	29/345 (8.4)	-7.1 (-10.4, -3.8)	<0.0001
BMI				
<30	4/641 (0.6)	35/644 (5.4)	-4.9 (-6.7, -3.0)	<0.0001
≥30	5/336 (1.5)	29/345 (8.4)	-7.1 (-10.4, -3.8)	<0.0001
Duration since first symptom, days				
≤3	5/671 (0.7)	44/647 (6.8)	-6.1 (-8.2, -4.1)	<0.0001
>3	4/306 (1.3)	20/342 (5.8)	-4.6 (-7.4, -1.8)	0.0015
Baseline serology status[a]				
Negative	8/475 (1.7)	56/497 (11.3)	-9.8 (-12.9, -6.7)	<0.0001
Positive	1/490 (0.2)	8/479 (1.7)	-1.5 (-2.7, -0.3)	0.0179
Baseline Viral RNA (NP samples, log_{10} copies/mL)[a]				
<4	1/342 (0.3)	2/352 (0.6)	-0.3 (-1.2, 0.7)	0.5772
≥4	8/607 (1.3)	59/610 (9.7)	-8.5 (-11.1, -6.0)	<0.0001
Baseline Viral RNA (NP samples, log_{10} copies/mL)[a]				
<7	7/676 (1.0)	35/706 (5.0)	-4.0 (-5.8, -2.2)	<0.0001
≥7	2/273 (0.7)	26/256 (10.2)	-9.6 (-13.5, -5.7)	<0.0001
Number of Comorbidities				
0-1	4/789 (0.5)	42/793 (5.3)	-4.9 (-6.5, -3.2)	<0.0001
2-3	5/184 (2.7)	22/194 (11.3)	-8.6 (-13.7, -3.5)	0.0009
≥4	0/4	0/2	0.0 (0.0, 0.0)	N.A.
Cigarette Smoker[a]				
Yes	5/381 (1.3)	16/400 (4.0)	-2.7 (-5.0, -0.5)	0.0184
No	4/594 (0.7)	48/589 (8.2)	-7.6 (-10.0, -5.3)	<0.0001
Diabetes mellitus[a]				
Yes	3/106 (2.8)	9/111 (8.1)	-5.3 (-11.3, 0.7)	0.0839
No	6/870 (0.7)	55/878 (6.3)	-5.7 (-7.4, -3.9)	<0.0001
Immunosuppression[a]				
Yes	0/6	0/6	0.0 (0.0, 0.0)	N.A.
No	9/970 (0.9)	64/983 (6.5)	-5.7 (-7.4, -4.0)	<0.0001
Chronic lung disease[a]				
Yes	0/56	2/33 (6.1)	-6.2 (-14.4, 2.1)	0.1445
No	9/920 (1.0)	62/956 (6.5)	-5.6 (-7.3, -3.9)	<0.0001
Hypertension[a]				
Yes	5/305 (1.6)	41/326 (12.6)	-11.1 (-15.0, -7.2)	<0.0001
No	4/671 (0.6)	23/663 (3.5)	-2.9 (-4.4, -1.4)	0.0002
Cardiovascular disorder[a]				
Yes	0/37	11/45 (24.4)	-24.4 (-37.0, -11.9)	0.0001
No	9/939 (1.0)	53/944 (5.6)	-4.7 (-6.4, -3.1)	<0.0001
Chronic kidney disease[a]				
Yes	0/5	0/7	0.0 (0.0, 0.0)	N.A.
No	9/971 (0.9)	64/982 (6.5)	-5.7 (-7.4, -4.0)	<0.0001

Demographic Parameters	Paxlovid n/N (%)	Placebo n/N (%)	Difference in % (95% CI)	Nominal p-value
Device dependence[a]				
Yes	0/3	0/1	0.0 (0.0, 0.0)	N.A.
No	9/963 (0.9)	63/980 (6.4)	-5.6 (-7.2, -3.9)	<0.0001
HIV infection[a]				
Yes	0/0	0/1	N.A.	N.A.
No	9/976 (0.9)	64/987 (6.5)	-5.7 (-7.3, -4.0)	<0.0001
Sickle cell disease[a]				
Yes	0/0	0/0	N.A.	N.A.
No	9/976 (0.9)	64/989 (6.5)	-5.6 (-7.3, -4.0)	<0.0001
Neurodevelopmental disorder[a]				
Yes	0/1	0/1	0.0 (0.0, 0.0)	N.A.
No	9/975 (0.9)	64/988 (6.5)	-5.6 (-7.3, -4.0)	<0.0001
Cancer[a]				
Yes	0/5	0/6	0.0 (0.0, 0.0)	N.A.
No	9/971 (0.9)	64/983 (6.5)	-5.7 (-7.4, -4.0)	<0.0001

Source: Reviewer's Analysis, excluding subjects from site 1274 and site 1470.
[a.] Those with missing baseline status were not included.
Abbreviations: BMI, body mass index; CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; log, logarithm; mITT, modified intent to treat; N, total number of subjects; n, number of subjects in sample; N.A., not applicable; NP, nasopharyngeal; RNA, ribonucleic acid

Table 133. Proportion of Participants With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28 by Baseline Demographics, mITT2 Population, EPIC-HR

Demographic Parameters	Paxlovid n/N (%)	Placebo n/N (%)	Difference in % (95% CI)	Nominal p-value
Overall	10/1038 (1.0)	66/1053 (6.3)	-5.4 (-7.0, -3.8)	<0.0001
Sex				
Female	4/522 (0.8)	25/515 (4.9)	-4.1 (-6.2, -2.1)	0.0001
Male	6/516 (1.2)	41/538 (7.6)	-6.6 (-9.0, -4.1)	<0.0001
Age Group				
<65	9/909 (1.0)	47/919 (5.1)	-4.2 (-5.8, -2.6)	<0.0001
≥65	1/129 (0.8)	19/134 (14.2)	-13.5 (-19.6, -7.4)	<0.0001
Race				
White	9/728 (1.2)	53/756 (7.0)	-5.6 (-7.9, -3.8)	<0.0001
Black or African American	0/52	1/35 (2.9)	-2.9 (-8.4, 2.7)	0.3103
Asian	1/153 (0.7)	6/156 (3.8)	-3.2 (-6.5, 0.1)	0.0562
Others	0/105	6/106 (5.7)	-5.8 (-10.4, -1.3)	0.0116
Region				
United States	3/387 (0.8)	14/399 (3.5)	-2.8 (-4.8, -0.7)	0.0076
Europe	4/330 (1.2)	37/333 (11.1)	-10.0 (-13.7, -6.4)	<0.0001
India	0/94	0/97	0.0 (0.0, 0.0)	N.A.
Rest of the World	3/227 (1.3)	15/224 (6.7)	-5.5 (-9.2, -1.8)	0.0033
BMI				
<25	1/208 (0.5)	8/206 (3.9)	-3.4 (-6.2, -0.6)	0.0174
25 to <30	3/466 (0.6)	28/464 (6.0)	-5.5 (-7.8, -3.2)	<0.0001
≥30	6/364 (1.6)	30/383 (7.8)	-6.3 (-9.4, -3.3)	<0.0001
Duration since first symptom, days				
≤3	5/715 (0.7)	46/687 (6.7)	-6.1 (-8.1, -4.1)	<0.0001
>3	5/323 (1.5)	20/366 (5.5)	-4.0 (-6.7, -1.2)	0.0044
Baseline COVID-19 mAb treatment,				
Not received/expected	9/977 (0.9)	64/989 (6.5)	-5.6 (-7.3, -4.0)	<0.0001
Received/expected	1/61 (1.6)	2/64 (3.1)	-1.5 (-6.9, 3.8)	0.5756

Demographic Parameters	Paxlovid n/N (%)	Placebo n/N (%)	Difference in % (95% CI)	Nominal p-value
Baseline serology status[a]				
Negative	8/504 (1.6)	58/526 (11.0)	-9.6 (-12.6, -6.7)	<0.0001
Positive	2/521 (0.4)	8/514 (1.6)	-1.2 (-2.4, 0.0)	0.0538
Baseline Viral RNA (NP samples, log_{10} copies/mL)[a]				
<4	2/358 (0.6)	2/374 (0.5)	0.0 (-1.0, 1.1)	0.9661
≥4	8/652 (1.2)	61/650 (9.4)	-8.3 (-10.8, -5.9)	<0.0001
Baseline Viral RNA (NP samples, log_{10} copies/mL)[a]				
<7	8/716 (1.1)	37/750 (4.9)	-3.9 (-5.6, -2.1)	<0.0001
≥7	2/294 (0.7)	26/274 (9.5)	-9.0 (-12.6, -5.3)	<0.0001
Number of Comorbidities				
0-1	5/843 (0.6)	44/844 (5.2)	-4.70 (-6.3, -3.1)	<0.0001
2-3	5/191 (2.6)	22/205 (10.7)	-8.10 (-12.9, -3.3)	0.0010
≥4	0/4	0/4	0.0 (0.0, 0.0)	N.A.
Cigarette smoker[a]				
Yes	5/397 (1.3)	16/418 (3.8)	-2.6 (-4.8, -0.4)	0.0186
No	5/639 (0.8)	50/635 (7.9)	-7.2 (-9.5, -5.0)	<0.0001
Diabetes mellitus[a]				
Yes	3/108 (2.8)	9/118 (7.6)	-4.9 (-10.6, 0.9)	0.0961
No	7/929 (0.8)	57/935 (6.1)	-5.4 (-7.1, -3.8)	<0.0001
Immunosuppression[a]				
Yes	0/6	0/7	0.0 (0.0, 0.0)	N.A.
No	10/1031 (1.0)	66/1046 (6.3)	-5.4 (-7.0, -3.8)	<0.0001
Chronic lung disease[a]				
Yes	0/60	2/38 (5.3)	-5.3 (-12.5, 1.9)	0.1462
No	10/977 (1.0)	64/1015 (6.3)	-5.4 (-7.0, -3.7)	<0.0001
Hypertension[a]				
Yes	5/318 (1.6)	42/346 (12.1)	-10.7 (-14.5, -6.9)	<0.0001
No	5/719 (0.7)	24/707 (3.4)	-2.7 (-4.2, -1.3)	0.0003
Cardiovascular disorder[a]				
Yes	0/39	11/47 (23.4)	-23.4 (-35.5, -11.3)	0.0002
No	10/998 (1.0)	55/1006 (5.5)	-4.5 (-6.1, -3.0)	<0.0001
Chronic kidney disease[a]				
Yes	0/5	0/7	0.0 (0.0, 0.0)	N.A.
No	10/1032 (1.0)	66/1046 (6.3)	-5.4 (-7.0, -3.8)	<0.0001
Device dependence[a]				
Yes	0/4	0/3	0.0 (0.0, 0.0)	N.A.
No	10/1023 (1.0)	65/1042 (6.2)	-5.3 (-6.9, -3.7)	<0.0001
HIV infection[a]				
Yes	0/0	0/1	N.A.	N.A.
No	10/1037 (1.0)	66/1051 (6.3)	-5.4 (-7.0, -3.8)	<0.0001
Sickle cell disease[a]				
Yes	0/0	0/0	N.A.	N.A.
No	10/1037 (1.0)	66/1053 (6.3)	-5.4 (-7.0, -3.8)	<0.0001

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Demographic Parameters	Paxlovid n/N (%)	Placebo n/N (%)	Difference in % (95% CI)	Nominal p-value
Neurodevelopmental disorder[a]				
Yes	0/2	0/1	0.0 (0.0, 0.0)	N.A.
No	10/1035 (1.0)	66/1052 (6.3)	-5.4 (-7.0, -3.8)	<0.0001
Cancer[a]				
Yes	0/5	0/6	0.00 (0.00, 0.00)	N.A.
No	10/1032 (1.0)	66/1047 (6.3)	-5.4 (-7.0, -3.8)	<0.0001

Source: Reviewer's Analysis, excluding subjects from site 1274 and site 1470.
[a.] Those with missing baseline status were not included.
Abbreviations: BMI, body mass index; CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; log, logarithm; mAb, monoclonal ant bodies; mITT, modified intent to treat; N, total number of subjects; n, number of subjects in sample; N.A., not applicable; NP, nasopharyngeal; RNA, ribonucleic acid

16.2.4. Time to Sustained Alleviation and Resolution of Each Targeted Symptom, EPIC-HR

Time to sustained alleviation and time to sustained resolution for each targeted symptom were evaluated in the mITT, mITT1 and mITT2 populations. Numerical reduction in median time to sustained alleviation and median time to sustained resolution was observed in most symptoms. Cough usually lasted longer compared to other symptoms.

Table 134. Time to Sustained Symptom Alleviation of Each Targeted Symptom Through Day 28, EPIC-HR

	Paxlovid N=666			Placebo N=645		
Symptoms in mITT[a]	Achieved Sustained Alleviation (n)	No Sustained Alleviation (n)	Median Time to Sustained Alleviation (Days)	Achieved Sustained Alleviation (n)	No Sustained Alleviation (n)	Median Time to Sustained Alleviation (Days)
Muscle or Body Aches	460	68	6	408	98	7
Shortness of Breath or Difficulty Breathing	230	47	6	227	63	8
Chills or Shivering	370	42	3	309	67	5
Cough	458	81	8	408	117	10
Diarrhea	142	23	4	120	23	4
Feeling Hot or Feverish	384	36	3	327	71	5
Headache	438	56	5	373	80	7
Nausea	191	30	4	178	42	5
Stuffy or Runny Nose	419	47	6	361	79	7
Sore Throat	339	34	5	288	59	6
Vomit	59	10	3	59	11	3

Symptoms in mITT1[b]	Paxlovid N=970 Achieved Sustained Alleviation (n)	Paxlovid N=970 No Sustained Alleviation (n)	Paxlovid N=970 Median Time to Sustained Alleviation (Days)	Placebo N=986 Achieved Sustained Alleviation (n)	Placebo N=986 No Sustained Alleviation (n)	Placebo N=986 Median Time to Sustained Alleviation (Days)
Muscle or Body Aches	650	122	6	603	175	7
Shortness of Breath or Difficulty Breathing	351	72	6	335	116	8
Chills or Shivering	508	76	3	469	109	5
Cough	650	141	9	613	203	10
Diarrhea	224	38	5	200	46	4
Feeling Hot or Feverish	533	70	3	491	122	5
Headache	606	103	5	559	150	7
Nausea	289	59	5	287	76	6
Stuffy or Runny Nose	604	86	6	542	142	7
Sore Throat	481	67	5	447	113	6
Vomit	97	19	3	96	19	3

Symptoms in mITT2[c]	Paxlovid N=1031 Achieved Sustained Alleviation (n)	Paxlovid N=1031 No Sustained Alleviation (n)	Paxlovid N=1031 Median Time to Sustained Alleviation (Days)	Placebo N=1050 Achieved Sustained Alleviation (n)	Placebo N=1050 No Sustained Alleviation (n)	Placebo N=1050 Median Time to Sustained Alleviation (Days)
Muscle or Body Aches	689	132	6	644	186	8
Shortness of Breath or Difficulty Breathing	381	78	6	359	128	9
Chills or Shivering	545	82	3	506	114	5
Cough	690	153	9	653	221	10
Diarrhea	244	43	5	226	50	4
Feeling Hot or Feverish	574	75	3	528	128	5
Headache	646	113	5	604	156	7
Nausea	308	66	5	310	80	6
Stuffy or Runny Nose	644	95	6	586	152	7
Sore Throat	510	72	5	488	119	6
Vomit	110	22	3	112	23	3

Source: Reviewer's analysis, excluding subjects from site 1274 and site 1470
Note: Median time to event calculated from Kaplan-Meier Estimate .
Note: Participants with no symptom diary data were not included in the analyses.
[a.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All participants randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mAb, monoclonal antibodies; mITT, modified intent to treat; N, number of patients in treatment group; n, number of patients with given characteristic

Table 135. Time to Sustained Symptom Resolution of Each Targeted Symptom Through Day 28, Trial EPIC-HR

	Paxlovid N=666			Placebo N=645		
Symptoms in mITT[a]	**Achieved Sustained Resolution (n)**	**No Sustained Resolution (n)**	**Median Time to Sustained Resolution (Days)**	**Achieved Sustained Resolution (n)**	**No Sustained Resolution (n)**	**Median Time to Sustained Resolution (Days)**
Muscle or Body Aches	410	118	9	361	145	12
Shortness of Breath or Difficulty Breathing	215	62	8	198	92	11
Chills or Shivering	360	52	5	290	86	7
Cough	415	124	13	348	177	15
Diarrhea	138	27	6	111	32	6
Feeling Hot or Feverish	374	46	5	308	90	7
Headache	405	89	8	334	119	11
Nausea	184	37	5	163	57	7
Stuffy or Runny Nose	383	83	9	325	115	10
Sore Throat	316	57	7	266	81	9
Vomit	59	10	3	59	11	3

	Paxlovid N=970			Placebo N=986		
Symptoms in mITT1[b]	**Achieved Sustained Resolution (n)**	**No Sustained Resolution (n)**	**Median Time to Sustained Resolution (Days)**	**Achieved Sustained Resolution (n)**	**No Sustained Resolution (n)**	**Median Time to Sustained Resolution (Days)**
Muscle or Body Aches	585	187	9	539	239	12
Shortness of Breath or Difficulty Breathing	325	98	9	288	163	12
Chills or Shivering	494	90	5	441	137	7
Cough	579	212	13	525	291	15
Diarrhea	220	42	6	185	61	6
Feeling Hot or Feverish	519	84	5	464	149	7
Headache	560	149	9	505	204	11
Nausea	276	72	7	269	94	7
Stuffy or Runny Nose	551	139	9	487	197	11
Sore Throat	448	100	7	416	144	9
Vomit	97	19	3	96	19	3

	Paxlovid N=1031			Placebo N=1050		
Symptoms in mITT2[c]	Achieved Sustained Resolution (n)	No Sustained Resolution (n)	Median Time to Sustained Resolution (Days)	Achieved Sustained Resolution (n)	No Sustained Resolution (n)	Median Time to Sustained Resolution (Days)
Muscle or Body Aches	621	200	9	578	252	12
Shortness of Breath or Difficulty Breathing	355	104	9	311	176	13
Chills or Shivering	531	96	5	476	144	7
Cough	615	228	13	563	311	15
Diarrhea	239	48	6	210	66	6
Feeling Hot or Feverish	560	89	5	498	158	7
Headache	598	161	9	547	213	11
Nausea	295	79	7	292	98	7
Stuffy or Runny Nose	589	150	9	527	211	11
Sore Throat	477	105	7	457	150	9
Vomit	110	22	3	112	23	4

Source: Reviewer's analysis, excluding subjects from site 1274 and site 1470.
[a.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All participants randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
Note: Median time to event calculated from Kaplan-Meier Estimate.
Note: Participants with no symptom diary data were not included in the analyses.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mAb, monoclonal antibodies; mITT, modified intent to treat; N, number of patients in treatment group; n, number of patients with given characteristic

16.3. EPIC-SR

16.3.1. Other Efficacy Endpoints, EPIC-SR

Table 136. Time to Sustained Symptom Resolution Through Day 28, EPIC-SR

Sustained Symptom Resolution in mITT1[a]	Paxlovid N=540	Placebo N=528
Participants with sustained symptom resolution, n (%)	347 (64.3)	345 (65.3)
Median time to sustained symptom resolution (95% CI)	15 (14, 16)	16 (15, 18)
Two-sided nominal p-value	0.4248	

Source: Reviewer's analysis, excluding subjects from site 1281 and site 1488.
Note: p-values calculated from log rank test.
[a.] All participants randomly assigned to study intervention who took at least 1 dose of study intervention.
Abbreviations: CI, confidence interval; N, number of patients in treatment group; n, number of patients with given characteristic

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Table 137. Proportion of Participants With Any Severe Targeted Signs and Symptoms Attributed to COVID-19 Through Day 28, EPIC-SR

mITT1[a] Analysis	Paxlovid N=534	Placebo N=527
Participants with event, n (%)	102 (19.1)	119 (22.6)
Two-sided nominal p-value	0.1629	

Source: Reviewer's analysis, excluding subjects from site 1281 and site 1488.
Note: p-values calculated from Pearson's Chi-squared test.
Note: Participants with no symptom diary data were not included in the analyses.
[a.] All participants randomly assigned to study intervention who took at least 1 dose of study intervention.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; N, number of patients in treatment group; n, number of patients with given characteristic

Table 138. Proportion of Participants With Progression to Worsening Status in 1 or More Self-Reported COVID-19-Associated Targeted Symptoms Through Day 28, EPIC-SR

mITT1[a] Analysis	Paxlovid N=534	Placebo N=527
Participants with event, n (%)	410 (76.8)	418 (79.3)
Two-sided nominal p-value	0.3181	

Source: Reviewer's analysis, excluding subjects from site 1281 and site 1488.
Note: p-values calculated from Pearson's Chi-squared test.
Note: Participants with no symptom diary data were not included in the analyses.
[a.] All participants randomly assigned to study intervention who took at least 1 dose of study intervention.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; N, number of patients in treatment group; n, number of patients with given characteristic

Table 139. Proportion of Participants With COVID-19-Related Medical Visits, EPIC-SR

Medical Visits in mITT1[a]	Paxlovid N=540	Placebo N=528
Participants with event, n (%)	12 (2.2)	23 (4.4)
Total number of medical visits across all participants	16	35
Two-sided nominal p-value	0.0740	

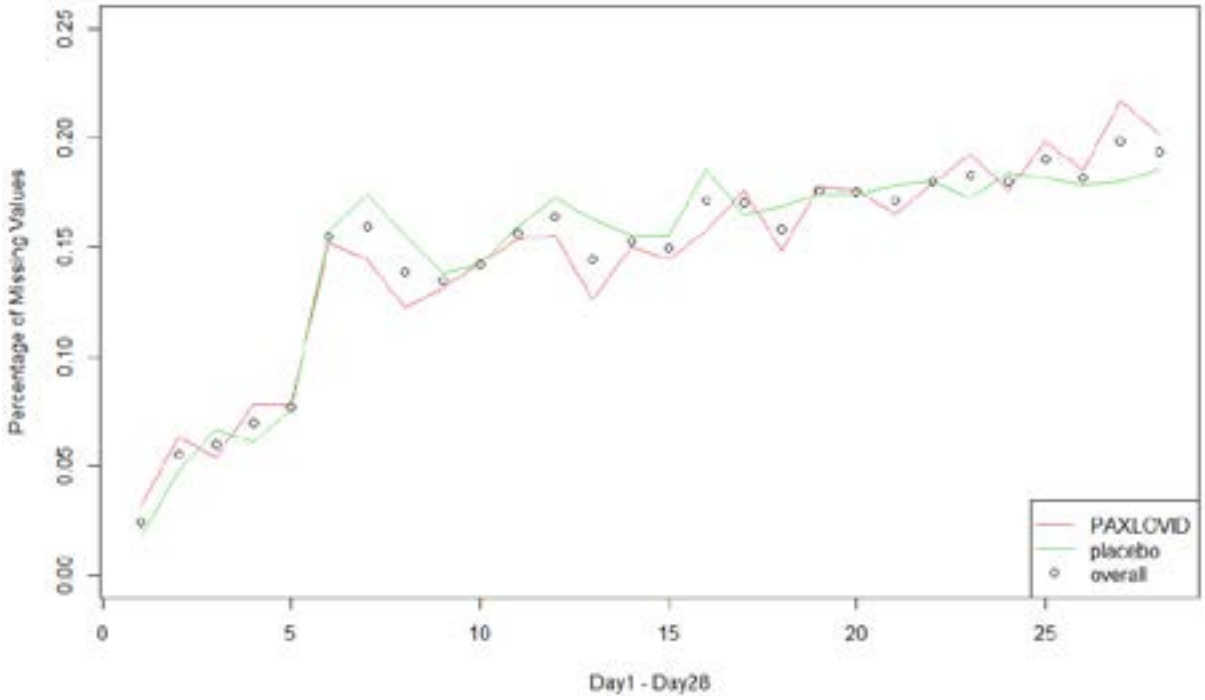
Source: Reviewer's analysis, excluding subjects from site 1281 and site 1488.
Note: Medical Visits include emergency room, practitioner's office, home healthcare services, urgent care, telephone consultation, outpatient infusion center, other, COVID-19-Related-Hospitalization (ICU and non-ICU stays). The medical visits and hospitalization events are limited through Day 34 visit.
Note: p-values calculated from Pearson's Chi-squared test with continuity correction.
[a.] All participants randomly assigned to study intervention who took at least 1 dose of study intervention.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; ICU, intensive care unit; N, number of patients in treatment group; n, number of patients with given characteristic

16.4. Additional Analyses on Symptom Diary Data

16.4.1. Symptom Diary Data Missing Values

In EPIC-HR, there was an average of 18.3% missing symptom diary entries (18.0% in PAXLOVID arm and 18.7% in placebo arm) in mITT2. Figure 62 below shows the missing data percentages on a daily basis. The missing data percentages on Days 1 through 5 were generally lower, as subjects were on treatment. The missing data percentages went up to around 20%-25% after Day 5. The missing data percentages were similar between two arms.

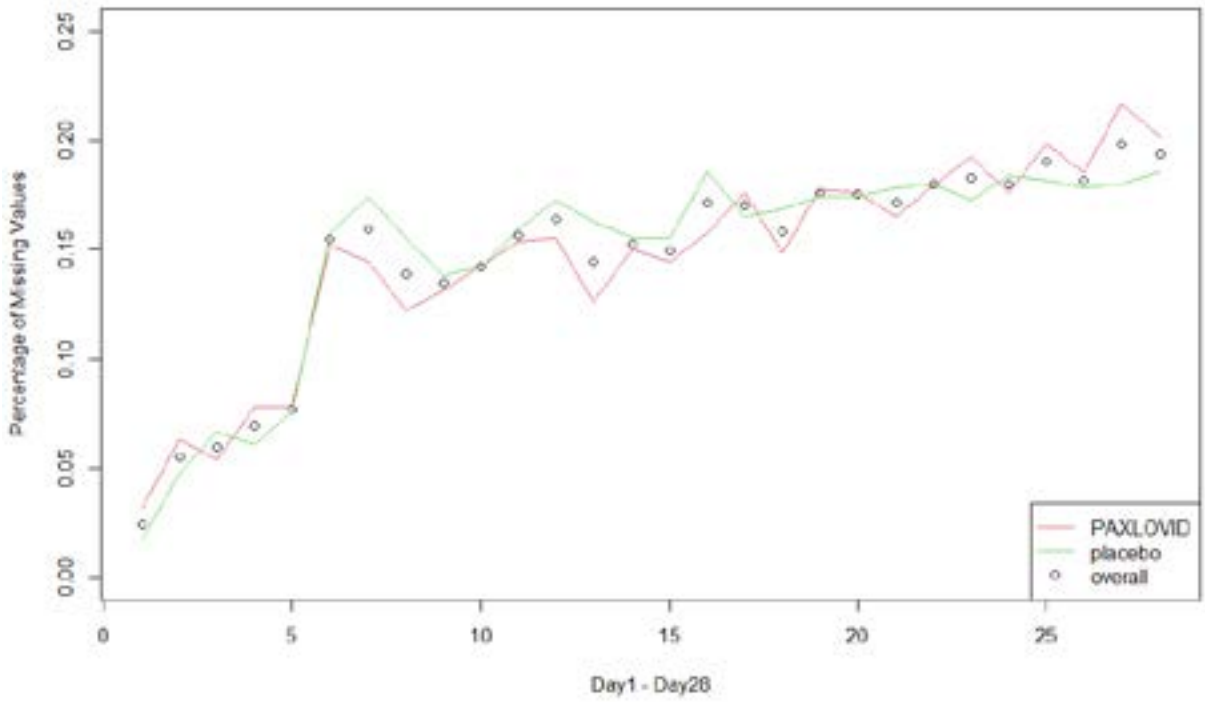
Figure 62. EPIC-HR Missing Symptom Diary Data



Source: Reviewer's analysis on EPIC-HR ADSO dataset.
Note: Data from site 1274 and site 1470 were excluded.

In EPIC-SR 2021, there was an average of 14.7% missing symptom diary entries (14.6% in PAXLOVID arm and 14.8% in placebo arm) in mITT1. Figure 63 below shows the missing data percentages on a daily basis. The missing data percentages on Days 1 through 5 were generally lower, as subjects were on treatment. The missing data percentages went up to around 15%-20% after Day 5. The missing data percentages were similar between two arms.

Figure 63. EPIC-SR 2021 Missing Symptom Diary Data



Source: Reviewer's analysis on EPIC-SR 2021 ADSO dataset.
Data from site 1281 and site 1488 were excluded.

16.4.2. Additional Symptom Rebound Analyses

Table 140 below presents symptom rebound analysis in EPIC-HR seropositive subgroup and EPIC-SR 2021 vaccinated high-risk subgroup. As found in the general analysis in Section 6.3.6, symptom rebound rates were similar in the PAXLOVID group and the placebo group.

Table 140. Symptom Rebound Analysis in Subgroups of Interest

Subgroup	Paxlovid	Placebo
EPIC-HR Seropositive, N	518	512
Short symptom recovery, n (%)[a]	404 (78.0)	381 (74.4)
Symptom rebound, n (%)[b]	41 (10.1)	42 (11.0)
Moderate symptom rebound, n (%)[b]	23 (5.7)	26 (6.8)
EPIC-SR 2021 Vaccinated High-risk, N	316	314
Short symptom recovery, n (%)[a]	246 (77.8)	243 (77.4)
Symptom rebound, n (%)[b]	41 (16.7)	36 (14.8)
Moderate symptom rebound, n (%)[b]	26 (10.6)	27 (11.1)

Source: Reviewer's analysis, excluding subjects from site HR1274/SR1281 and site HR1470/SR1488. Subjects with no symptom data were not included in the analyses.
[a.] Percentage over total N subjects.
[b.] Percentage over those who achieved short symptom recovery.
Abbreviations: N, number of patients in treatment arm; n, number of patients in specified population or group

Table 141 presents symptom rebound analysis, excluding sites with abnormal symptom data reporting time patterns. Table 142 presents symptom rebound analysis, excluding sites with symptom data collection misconduct with respect to PIN codes. As found in the general analysis in Section 6.3.6, symptom rebound rates in PAXLOVID group were similar to or lower than the placebo group in both analyses.

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Table 141. Symptom Rebound Analysis, Excluding Sites With Abnormal Symptom Data Reporting Time Patterns

Rebound Analysis	Paxlovid	Placebo
EPIC-HR, N	885	897
Short symptom recovery, n (%)[a]	630 (71.2)	565 (63.0)
Symptom rebound, n (%)[b]	82 (13.0)	91 (16.1)
Moderate symptom rebound, n (%)[b]	51 (8.1)	58 (10.3)
EPIC-SR 2021 (Pre-Omicron), N	494	494
Short symptom recovery, n (%)[a]	375 (75.9)	377 (76.3)
Symptom rebound, n (%)[b]	63 (16.8)	56 (14.9)
Moderate symptom rebound, n (%)[b]	40 (10.7)	40 (10.6)
EPIC-SR 2022 (Omicron), N	106	102
Short symptom recovery, n (%)[a]	89 (84.0)	84 (82.4)
Symptom rebound, n (%)[b]	7 (7.9)	9 (10.7)
Moderate symptom rebound, n (%)[b]	3 (3.4)	8 (9.5)

Source: Reviewer's analysis, excluding subjects from EPIC-HR sites 1470, 1274, 1501, 1324, 1362, 1014, 1372, 1082, 1318, 1103, 1163, and excluding subjects from EPIC-SR sites 1488, 1281, 1357, 1334, 1085, 1388, 1107, 1521, 1013 (2021), 1575. Subjects with no symptom data were not included in the analyses.
[a.] Percentage over total subjects.
[b.] Percentage over those who achieved short symptom recovery.
Abbreviations: N, number of patients in treatment arm; n, number of patients in specified population or group

Table 142. Symptom Rebound Analysis, Excluding Sites With Symptom Data Collection Issue With Respect to PIN Codes

Rebound Analysis	Paxlovid	Placebo
EPIC-HR, N	607	613
Short symptom recovery, n (%)[a]	432 (71.2)	383 (62.5)
Symptom rebound, n (%)[b]	62 (14.4)	60 (15.7)
Moderate symptom rebound, n (%)[b]	37 (8.6)	34 (8.9)
EPIC-SR 2021 (Pre-Omicron), N	312	328
Short symptom recovery, n (%)[a]	233 (74.7)	251 (76.5)
Symptom rebound, n (%)[b]	36 (15.5)	39 (15.5)
Moderate symptom rebound, n (%)[b]	22 (9.4)	30 (12.0)
EPIC-SR 2022 (Omicron), N	67	60
Short symptom recovery, n (%)[a]	52 (77.6)	44 (73.3)
Symptom rebound, n (%)[b]	5 (9.6)	9 (20.5)
Moderate symptom rebound, n (%)[b]	2 (3.8)	8 (18.2)

Source: Reviewer's analysis, excluding subjects from EPIC-HR sites 1470, 1274, 1309, 1062, 1492, 1153, 1076, 1324, 1034, 1163, 1318, 1082, 1372, 1014, 1097, 1158, 1362, 1325, 1276, 1030, 1219, 1155, 1273, 1442, 1382, 1399, 1395, 1058, 1135, 1501, 1331, 1374, 1037, 1149, 1066, and excluding subjects from EPIC-SR sites 1488, 1281, 1061, 1085, 1150, 1508, 1388, 1282, 1013, 1367, 1100, 1333, 1018, 1317, 1077, 1334, 1022, 1357, 1158, 1222, 1155, 1280, 1393, 1153, 1306, 1459, 1414, 1409, 1137, 1521, 1384, 1029, 1575, 1060, 1138, 1145, 1157, 1197. Subjects with no symptom data were not included in the analyses.
[a.] Percentage over total subjects.
[b.] Percentage over those who achieved short symptom recovery.
Abbreviations: N, number of patients in treatment arm; n, number of patients in specified population or group; PIN, personal identification number

16.5. Real-World Evidence on Effectiveness

16.5.1. Literature Review on PAXLOVID Effectiveness Real-World Evidence

16.5.1.1. Review Methods and Materials

The Division of Epidemiology II searched the WHO COVID-19-research database and PubMed, using the search terms "PAXLOVID" and "epidemiology/RWE study" (Section 16.5.2). We excluded articles that:

- Did not report a study that evaluated PAXLOVID effectiveness.
- Did not report observational studies (e.g., articles reported clinical trials, case reports, case series).
- Did not report findings of analyses on PAXLOVID effectiveness, compared to non-PAXLOVID-treated COVID-19 patients
- Did not evaluate PAXLOVID effectiveness in an outpatient COVID-19 population

We further applied the criteria described below for selecting studies for in-depth review.

Longitudinal Data

Studies that used data source(s) that allow longitudinal capture of the key covariates across different healthcare settings:

- Diagnosis/test of COVID-19 in an ambulatory setting
- Exposure to PAXLOVID as outpatient treatment
- Vaccination status prior to COVID-19 diagnosis/PAXLOVID exposure
- Clinical outcome (hospitalization or death) after COVID-19 diagnosis/PAXLOVID exposure
- Comorbid conditions and concurrent medication use at time of COVID-19 diagnosis/PAXLOVID use

"Nonuser" Reference Group

Included "nonuser" as a reference group, since we do not have trial data to support effectiveness of PAXLOVID against an "active control" (i.e., other potential COVID-19 treatments).

Index Time Selection

Applied design feature that can account for the potential bias introduced by "index time" selection for the treated and untreated patients, given that PAXLOVID users were COVID-19 patients who remained hospitalization-free and survived from diagnosis to treatment, which can lead to bias in favor of finding PAXLOVID effectiveness.

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16.5.1.2. Review Results

Our last literature search was conducted on January 30, 2023. Among the 297 English-language articles identified by our search terms, 22 were observational studies that evaluated PAXLOVID effectiveness in outpatient COVID-19 populations (Section 16.5.2); we excluded:

- Three publications (Najjar-Debbiny et al. 2023; Wai et al. 2023; Yip et al. 2023), of shorter study duration, that used the same data source as another identified publication.[14]
- One publication (Xie et al. 2022),that described a study that only evaluated "post-acute sequelae of COVID-19"[15] occurring from 30 to 90 days after SARS-CoV-2 infection, due to significant design concerns:
  - The validity of code-based algorithms to capture the individual post-acute COVID-19 sequelae were not reported in the article
  - Important confounders (e.g., use of certain medications that could influence the risk of the individual clinical condition that consists of "post-acute COVID-19 sequelae") were neither reported nor accounted for in the analyses

We screened the remaining publications and further excluded 13 studies that did not meet all the key data source and design features criteria for in-depth review (Table 143).

Table 143. Screening of the Identified Observational RWE Studies on Outpatient PAXLOVID Effectiveness

	Fulfilled Key Data Source and Design Features for In-Depth Review		
Study Screened	**Longitudinal Data Source**	**Nonuser Reference Group**	**Design to Handle Bias Due to Index Time Selection**
Excluded			
(Hedvat et al. 2022)	No	Yes	No
(Dryden-Peterson et al. 2023)	No	Yes	Yes
(Ganatra et al. 2022)	No	Yes	No
(Zhou et al. 2022a)	No	Yes	Yes
(Aggarwal et al. 2023)	No	Yes	No
(Bruno et al. 2022a)	Unclear	No	N/A
(Bruno et al. 2022b)	Unclear	No	N/A
(Gentile et al. 2022)	Unclear	No	N/A
(Park et al. 2022a)	Yes	Yes	No
(Park et al. 2022b)	Yes	Yes	No
(Qian et al. 2022)	No	Yes	No
(Shah et al. 2022)	No	Yes	Unclear
(Tiseo et al. 2023)	Unclear	No	N/A

[14] The publication by Najjar-Debbiny et al. was excluded due to an overlapping Israeli data source with Arbel et al. The publications by Yip et al. and Wai et al. were based on the same territory-wide population in Hong Kong as that by Wong et al.

[15] Post-acute death or hospitalization and individual sequela including ischemic heart disease, dysrhythmia, deep vein thrombosis, pulmonary embolism, fatigue, liver disease, acute kidney injury, muscle pain, diabetes, neurocognitive impairment, shortness of breath and cough.

Study Screened	Fulfilled Key Data Source and Design Features for In-Depth Review		
	Longitudinal Data Source	Nonuser Reference Group	Design to Handle Bias Due to Index Time Selection
Included			
(Arbel et al. 2022)	Yes	Yes	Yes
(Wong et al. 2022)	Yes	Yes	Yes
(Bajema et al. 2022)	Yes	Yes	Yes
(Schwartz et al. 2022)	Yes	Yes	Yes
(Lewnard et al. 2023)	Yes	Yes	Yes

Source: FDA reviewer.
Abbreviations: N/A, not applicable; RWE, real-world-evidence

Five studies were included in our in-depth review (Arbel et al. 2022; Bajema et al. 2022; Schwartz et al. 2022; Wong et al. 2022; Lewnard et al. 2023). Of note, the publications by Bajema, Schwartz, and Lewnard are non-peer-reviewed preprints.[16]

Briefly, the five reviewed studies were cohort studies involving non-hospitalized patients with positive SARS-CoV-2 RT-PCR or antigen test results during the period of Omicron-variant dominance. One study in Israel and one study in China (Hong Kong) used nation-wide or territory-wide electronic health records of hospitals and outpatient clinics. One study in Quebec, Canada used a province-wide integrated health-care data. The final two studies used electronic health records and administrative claims data; one was based on the U.S. Veterans Health Administration and the other based on an integrated healthcare system of a single U.S. state. These five studies also included broader study populations than those included in the pivotal trials—with respect to age, underlying high-risk comorbidities, and COVID-19 vaccination status.

All studies evaluated the risk of COVID-19-related hospitalization or all-cause hospitalization in PAXLOVID-treated COVID-19 patients compared to those not treated with PAXLOVID (nonusers). They also evaluated other clinical outcomes, such as mortality or in-hospital COVID-19 progression. The real-world evidence (RWE) studies in general reported PAXLOVID was effective or trended towards effectiveness regardless of COVID-19 vaccination status.

Conclusions on the Quality of the Available PAXLOVID RWE Studies

Seventeen of the twenty-two identified RWE studies reporting effectiveness of outpatient PAXLOVID use were excluded from in-depth review as they included overlapping study populations with the reviewed RWE studies, were based on insufficient longitudinal data in the data sources, and/or were unable to account for potential bias introduced by index time selection. The five remaining studies consistently reported that PAXLOVID use was associated with a reduced risk of worsening COVID-19 outcomes in broader populations than included in the pivotal trials, with respect to age, underlying "high-risk" comorbidities, and COVID-19 vaccination status in the Omicron era.

The information available for the reviewed observational studies was insufficient to determine their quality.

[16] The manuscripts are available as preprints; i.e., they have not been peer-reviewed. Non-peer-reviewed preprints may not be accepted for publication by a peer-reviewed journal. If they are formally published in a peer-reviewed journal, there may be revisions of the methods or analyses to address the editor's or reviewers' comments.

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Details on the Assessment of the Eligible PAXLOVID RWE Studies That Informed the Conclusions

Compared to the studies excluded from in-depth review, the five reviewed RWE studies used more appropriate data sources, study design, or analytical approaches to account for the potential bias introduced by inappropriate handling of index time selection.

However, unlike Applicant-sponsored efficacy trials that provide more information to assess study quality, none of the reviewed RWE studies published their protocol and analytical plan prior to the final study report. In at least one study, Lewnard et al., the analyses and results differed notably between two version of the preprints (Lewnard et al. 2023). So, it was difficult to track whether these studies were conducted according to a prespecified protocol and analytical plan. Additionally, patient-level data on the observational studies were unavailable to verify the correct implementation of study design and statistical methods, which is a standard review process for trial data that are used to support treatment efficacy.

Despite insufficient information on studies due to what is reported in the public domain, we still identified methodological or analytical issues in the reviewed studies. Some of these issues had reasonably predictable impact on the study findings, while there were other review issues for which we would need more information than was provided to determine the potential impact on the study results. These issues are summarized below.

Review Issues With a Reasonably Predictable Impact on Study Findings

Residual Confounding by COVID-19 Severity (All Studies)

Three of the reviewed studies did not capture or adjust for baseline COVID-19 severity (Arbel et al. 2022; Schwartz et al. 2022; Wong et al. 2022). The studies by Bajema and Lewnard accounted for the presence of COVID-19 symptoms at baseline; however, the validity of the operational definitions for COVID-19 symptoms was not reported (Bajema et al. 2022; Lewnard et al. 2023). Residual confounding due to COVID-19 severity would likely to underestimate of PAXLOVID effectiveness, given that PAXLOVID was more likely to be given to symptomatic patients or patients with severe symptoms.

Residual Confounding by High-Risk Comorbidities (Arbel and Wong Studies)

Although the Arbel study captured information on medical conditions that increase a patient's risk for COVID-19 progression (high-risk comorbidities), not all were adjusted for in the analyses (Arbel et al. 2022). The Wong study matched the treated and non-treated patients on a summary comorbidity risk score (i.e., Charlson Comorbidity Index), which did not guarantee the component medical conditions of the risk score would be balanced between treatment groups (Wong et al. 2022). Furthermore, the component medical conditions of the Charlson Comorbidity Index were not an exact match to the high-risk comorbidities for worse COVID-19 progression. For example, the Charlson Comorbidity Index does not account for all immunosuppressive diseases (e.g., bone marrow or organ transplantation), prolonged use of immune-weakening medications, chronic lung diseases (except for chronic obstructive pulmonary disease), neurodevelopmental disorders, sickle cell disease. Lastly, the Wong study

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did not report distribution of high-risk comorbidities for COVID-19 progression to inform if these important confounders were balanced between treatment groups.

Residual confounding due to unbalanced high-risk comorbidities would likely underestimate of PAXLOVID effectiveness, given that PAXLOVID treatment for COVID-19 patients with high-risk comorbidities was likely prioritized.

Outcome Selection (Bajema and Lewnard Studies)

Studies by Bajema and Lewnard used "all-cause hospitalization or death" as the primary outcome, which included events that are unrelated to PAXLOVID effect (i.e., hospitalization or death due to causes other than COVID-19) (Bajema et al. 2022; Lewnard et al. 2023). If the proportion of outcome events unrelated to COVID-19 is nondifferential between treated and nontreated groups, it would bias findings toward null (underestimate of PAXLOVID effectiveness). The proportion of events unrelated to COVID-19 can be higher among PAXLOVID users, given that administration of PAXLOVID is prioritized to patients with comorbidities that may lead to a higher risk of hospitalization or death due to non-COVID-19 causes, which will also lead to underestimate of PAXLOVID effectiveness.

Study Power to Evaluate PAXLOVID Effectiveness in Subgroups (All Studies)

Only one reviewed study reported a priori power analyses (Bajema et al. 2022). All the reviewed studies were not powered to formally test treatment effect modification by patient characteristics, or to evaluate PAXLOVID effectiveness in any patient subgroup. Some studies suggested that PAXLOVID effectiveness may differ by age, for example, Arbel concluded that "no evidence of benefit was found in patients younger than 65 years of age" (Arbel et al. 2022). The study findings did not support a statistically significant reduction in COVID-19 hospitalization risk (hazard ratio = 0.74, 95% CI = 0.35 to 1.58) or death (hazard ratio = 1.32, 95% CI = 0.16 to 10.75) associated with PAXLOVID use among a younger population (40 to 65 years of age). However, it is likely that the study did not have sufficient power to evaluate PAXLOVID effectiveness in the younger population, evidenced by the wide 95% CIs of the effect estimates.

Review Issues That Require More Information to Evaluate the Impact on Study Results

Unvalidated Outcome Measures

COVID-19-Related Hospitalization (Arbel, Wong, and Schwartz Studies)

Three reviewed studies included "hospitalization due to COVID-19" as the endpoint, or part of the endpoints (Arbel et al. 2022; Schwartz et al. 2022; Wong et al. 2022). However, none of the studies provided data to support the validity of the measure for "COVID-related hospitalization." Without a better understanding of how information on COVID-19 related hospitalization was recorded or derived, it is difficult to predict if the outcome misclassification would be differential and how it might influence the study findings.

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Post-COVID-19 Conditions (Bajema Study)

The Bajema study also evaluated PAXLOVID's effectiveness on multiple potential post-COVID-19 conditions (Bajema et al. 2022);[17] however, they did not provide data to support the International Classification of Diseases, 10th Edition diagnosis codes that were used to capture these conditions (WHO 2019). It is difficult to predict if the outcome misclassification would be differential and how it might influence the study findings.

Residual Confounding by Other Potential Confounders

Information on the frequencies and the distribution of the potential confounders (discussed below) by treatment groups is needed to understand the magnitude and direction of potential biases on study findings.

Detailed Information on COVID-19 Vaccination (Arbel, Wong, and Lewnard Studies)

Total dose, timing of last dose, type or manufacturer of the COVID-19 vaccine could impact PAXLOVID effectiveness for COVID-19 outcomes. Not all reviewed studies captured or accounted for detailed information on COVID-19 vaccination in their analyses. The Arbel and Wong studies only reported and accounted for vaccination status as dichotomous variables ("presence of prior immunity or not" in Arbel study, "fully vaccinated or not" in the Wong study) (Arbel et al. 2022; Wong et al. 2022). The Lewnard study only adjusted for the number of total vaccine doses received in their analyses (Lewnard et al. 2023).

Other Outpatient COVID-19 Medication Use at Baseline (Lewnard Study)

Prior or concurrent use of other outpatient medications for COVID-19 at baseline can be a potential confounder as they can influence COVID-19-related clinical outcomes. The Lewnard study did not exclude patients who used other COVID-19 medications at baseline, while several treatment options were available in the United States during the timeframe of the study (Lewnard et al. 2023). The study also did not report the use of the other outpatient COVID-19 treatment at baseline, nor adjusted for baseline use of these medications in their analyses.

Other Medications Use (Bajema Study)

The Bajema study included analyses of PAXLOVID effectiveness on risk of long-term outcomes (i.e., hospital admission, nursing skilled nursing home facility admission, all-cause death, or post-COVID-19 conditions) that occurred 31 to 180 days after diagnosis (Bajema et al. 2022).

[17] Post-COVID-19 conditions in the Bajema study comprise: acute coronary syndrome, cardiac dysrhythmias, cardiovascular disease, chest pain, heart failure and cardiomyopathy, hypertension, myocarditis, respiratory symptoms (shortness of breath/dyspnea, any respiratory distress/failure, any bronchitis, hypoxemia, bronchiectasis, any non-COVID-19 pneumonia including influenza, cough, wheezing, sneezing, nasal congestion/sinusitis, sore throat, pharyngitis, laryngitis, tonsillitis), asthma, COPD and emphysema, obstructive sleep apnea or obesity hypoventilation, renal conditions (acute kidney injury, chronic kidney disease, dialysis), venous thromboembolism, pulmonary embolism, abdominal pain, esophageal disorders, gastrointestinal disorders, cerebrovascular disease, dementia, smell and taste disturbance, headache, sleeping disorders, other neurologic conditions (peripheral nerve disorders [i.e., neuropathy, Guillain-Barre syndrome], epilepsy, multiple sclerosis, complex regional pain syndrome, Parkinson disease), depression, other mood disorders (bipolar, schizophrenia, psychosis), anxiety, PTSD, substance-related disorder, musculoskeletal conditions (any myositis, muscle wasting and atrophy, contracture of muscle, myalgias), diabetes, disorders of lipid metabolism, obesity, malaise and fatigue

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PAXLOVID was prioritized for patients with COVID-19 and certain comorbidities that are also components of the "post-COVID conditions;" for example, cardiovascular disease, hypertension, asthma, chronic obstructive pulmonary disease, chronic kidney disease, cerebrovascular disease, diabetes, obesity. The use of other medications, especially those that are indicated for the components of the post-COVID-19 conditions, are important confounders that were not reported, nor accounted for in the study.

Handling of Post-Index Time COVID-19 Treatment

Information on the frequencies and the distribution of post-index time COVID-19 treatment changes (discussed below) by treatment groups is needed to understand the magnitude and direction of potential biases on study findings.

Other Outpatient COVID-19 Medication Use (All Studies)

In the analyses of PAXLOVID's effectiveness on hospitalization, use of other outpatient COVID-19 medications during follow-up could be on the causal pathway between PAXLOVID use and COVID-19 outcome- the need to use another treatment can be an early indication that PAXLOVID did not work well in preventing disease progression. Use of other COVID-19 treatments also have an impact on COVID-19 outcome, independently from PAXLOVID's effectiveness.

Use of other outpatient COVID-19 medications was a censor criterion in the Wong study, but not in the Lewnard or Bajema studies, while the Arbel and Schwartz studies did not clearly state how they handled patients who initiated another outpatient COVID-19 treatment during follow-up (Arbel et al. 2022; Bajema et al. 2022; Schwartz et al. 2022; Wong et al. 2022; Lewnard et al. 2023). If the use of other outpatient COVID-19 medication is uncommon, these different approaches would likely all be acceptable; however, none of the three reviewed studies reported the extent of other COVID-19 medications used during follow-up.

Inpatient Medical Management (Arbel, Wong, Bajema, and Lewnard Studies)

Four of the reviewed studies (Arbel, Wong, Bajema, and Lewnard) also evaluated outpatient PAXLOVID's impact on in-patient outcomes, such as in-hospital disease progression, invasive mechanical ventilation use, intensive care unit admission and death, or post-acute COVID-19 symptoms (Arbel et al. 2022; Bajema et al. 2022; Wong et al. 2022; Lewnard et al. 2023). In these analyses, the medical treatment that patients received during hospitalization, such as inpatient COVID-19 treatment, could be on the causal pathway. None of these studies reported information on inpatient medical management during follow-up, nor accounted for its impact in the analyses.

Concern on Statistical Methods

Ambiguous Statistical Methods and Results (Lewnard Study)

The details of the analyses and the results are not clear. Without knowledge of the details, some of the results are difficult to review and interpret. The definition of the discordant pairs in the results tables (Table 2 and Table 3) is not clear and the summaries of the discordant pairs do not seem to align with the effectiveness estimates (Lewnard et al. 2023). It is also unclear whether immortal time in treated subjects is handled properly when determining discordant pairs. In

addition, about 42% of eligible PAXLOVID-treated patients were not included in the analyses, calling into question the generalizability of the results.

Handling of Immortal Time Bias (Schwartz and Wong Studies)

The Schwartz study assigned random index dates to the unexposed group based on the time-to-dispense distribution from the exposed group (Schwartz et al. 2022). This approach did not consider factors that may impact the dispensing time for each subject (e.g., the presence of symptoms) and may not fully fix the immortal time bias problem.

The primary analyses of the Wong study set the index time at COVID-19 symptom onset or diagnosis, which introduced immortal time in the PAXLOVID-treated group and could overestimate PAXLOVID effectiveness (Wong et al. 2022). The investigators conducted post hoc sensitivity analyses that treated exposure status as a "time-varying" variable to account for immortal time bias. The findings of this sensitivity analysis that accounted for immortal time bias consistently support PAXLOVID effectiveness as the primary analyses in the overall study population. It is unclear if the conclusion would be the same for the subgroup analyses stratified by vaccination status, as the author did not report the findings of the sensitivity analyses by patient subgroup.

Handling of Missing Data (All Studies)

All the studies except for the Lewnard study did not report the degree of missing data for important baseline covariates (Lewnard et al. 2023). Most of the studies did not specify a method of handling missing data other than excluding subjects with missing covariates.

16.5.2. RWE Literature Search Process (Steps and Numbers of Articles Remaining)

English language articles with "Paxlovid OR nirmatrelvir" AND keywords of "epidemiology or RWE study," *excluding* animal, cellular, pharmacokinetic/pharmacodynamics, identified 297 articles (*search terms are required in Title, Abstract, or Subject*).

- Restrict to studies evaluating PAXLOVID effectiveness 44
- Exclude duplicate publications 26
- Exclude studies involving hospitalized subjects with COVID-19 22

16.5.2.1. RWE Literature Search Terms

Key Words for Epidemiology or RWE Studies

epidemiology OR observational OR non-randomized OR cohort OR sample OR adjustment OR "propensity score" OR "inverse probability weighting" OR "integrated health care system" OR multivariate OR multivariable OR population-based OR case-control OR database OR bayesian OR abstracted OR "convenience sample" OR "electronic health record" OR "systematic review" OR cohort OR case-control OR database OR datalink OR "claims data" OR "drug utilization" OR "electronic health records" OR "electronic medical records" OR biobank OR "pooled analysis" OR crossover OR registry OR registries OR meta-analysis OR retrospective OR

prospective OR "cross sectional" OR cross-sectional OR "prevalence study" OR "longitudinal study" OR "before-after study" OR "administrative database" OR "insurance claim" OR matched-cohort OR population-based OR "insurance database" OR "claims database" OR "pharmaceutical claims" OR "case control" OR "meta analysis" OR self-controlled OR "self controlled" OR comparative OR emr OR prevalence OR incidence OR rate OR "administrative claim" OR “Real-World” OR “Real World” OR “RWE”.

Key Words for Animal, Cellular, and Pharmacokinetic/Pharmacodynamics Studies (for Exclusion)

animals OR animal OR mice OR mus OR mouse OR murine OR woodmouse OR rats OR rat OR murinae OR muridae OR cottonrat OR cottonrats OR hamster OR hamsters OR cricetinae OR rodentia OR rodent OR rodents OR pigs OR pig OR swine OR swines OR piglets OR piglet OR boar OR boars OR "sus scrofa" OR ferrets OR ferret OR polecat OR polecats OR "mustela putorius" OR "guinea pigs" OR "guinea pig" OR cavia OR callithrix OR marmoset OR marmosets OR cebuella OR hapale OR octodon OR chinchilla OR chinchillas OR gerbillinae OR gerbil OR gerbils OR jird OR jirds OR merione OR meriones OR rabbits OR rabbit OR hares OR hare OR diptera OR flies OR fly OR dipteral OR drosophila OR drosophilidae OR cats OR cat OR carus OR felis OR nematoda OR nematode OR nematoda OR nematode OR nematodes OR sipunculida OR dogs OR dog OR canine OR canines OR canis OR sheep OR sheeps OR mouflon OR mouflons OR ovis OR goats OR goat OR capra OR capras OR rupicapra OR chamois OR haplorhini OR monkey OR monkeys OR anthropoidea OR anthropoids OR saguinus OR tamarin OR tamarins OR leontopithecus OR hominidae OR ape OR apes OR pan OR paniscus OR "pan paniscus" OR bonobo OR bonobos OR troglodytes OR "pan troglodytes" OR gibbon OR gibbons OR siamang OR siamangs OR nomascus OR symphalangus OR chimpanzee OR chimpanzees OR prosimians OR "bush baby" OR prosimian OR bush babies OR galagos OR galago OR pongidae OR gorilla OR gorillas OR pongo OR pygmaeus OR "pongo pygmaeus" OR orangutans OR pygmaeus OR lemur OR lemurs OR lemuridae OR horse OR horses OR pongo OR equus OR cow OR calf OR bull OR chicken OR chickens OR gallus OR quail OR bird OR birds OR quails OR poultry OR poultries OR fowl OR fowls OR reptile OR reptilia OR reptiles OR snakes OR snake OR lizard OR lizards OR alligator OR alligators OR crocodile OR crocodiles OR turtle OR turtles OR amphibian OR amphibians OR amphibia OR frog OR frogs OR bombina OR salientia OR toad OR toads OR "epidalea calamita" OR salamander OR salamanders OR eel OR eels OR fish OR fishes OR pisces OR catfish OR catfishes OR siluriformes OR arius OR heteropneustes OR sheatfish OR perch OR perches OR percidae OR perca OR trout OR trouts OR char OR chars OR salvelinus OR "fathead minnow" OR minnow OR cyprinidae OR carps OR carp OR zebrafish OR zebrafishes OR goldfish OR goldfishes OR guppy OR guppies OR chub OR chubs OR tinca OR barbels OR barbus OR pimephales OR promelas OR "poecilia reticulata" OR mullet OR mullets OR seahorse OR seahorses OR mugil curema OR atlantic cod OR shark OR sharks OR catshark OR anguilla OR salmonid OR salmonids OR whitefish OR whitefishes OR salmon OR salmons OR sole OR solea OR "sea lamprey" OR lamprey OR lampreys OR pumpkinseed OR sunfish OR sunfishes OR tilapia OR tilapias OR turbot OR turbots OR flatfish OR flatfishes OR sciuridae OR squirrel OR squirrels OR chipmunk OR chipmunks OR suslik OR susliks OR vole OR voles OR lemming OR lemmings OR muskrat OR muskrats OR lemmus OR otter OR otters OR marten OR martens OR martes OR weasel OR badger OR badgers OR ermine OR mink OR minks OR sable OR sables OR gulo OR gulos OR wolverine OR wolverines OR minks OR mustela OR

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llama OR llamas OR alpaca OR alpacas OR camelid OR camelids OR guanaco OR guanacos OR chiroptera OR chiropteras OR bat OR bats OR fox OR foxes OR iguana OR iguanas OR xenopus laevis OR parakeet OR parakeets OR parrot OR parrots OR donkey OR donkeys OR mule OR mules OR zebra OR zebras OR shrew OR shrews OR bison OR bisons OR buffalo OR buffaloes OR deer OR deers OR bear OR bears OR panda OR pandas OR "wild hog" OR "wild boar" OR fitchew OR fitch OR beaver OR beavers OR jerboa OR jerboas OR capybara OR capybaras OR cell OR "cell line" OR cellular OR tissue OR "in vitro" OR spectroscopic OR spectrometer OR spectrophotometry OR "transformation products" OR synthesized OR "gene variants" OR polymorphism OR plant OR pharmacokinetics OR pharmacokinetic OR pharmacodynamic OR pharmacodynamics.

17. Clinical Safety

17.1. Adverse Event Definitions

AEs were defined in the protocol as: “An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.”

Treatment-emergent adverse events (TEAEs) were defined in the Applicant’s analysis plan, and for the purpose of this review, as: “Any AE that occurred on or after the medication start date and time.”

Adverse drug reactions were defined for the purpose of this review as: “Any TEAE that was considered by the investigator to be related to the study drug with reasonable possibility.”

“Reasonable possibility” of a relationship was defined in the protocol to convey that there are facts, evidence, or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Serious adverse events (SAEs) were protocol-defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:

- Results in death.
- Is life threatening. The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- If suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition.

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17.2. Deaths, EPIC-HR and EPIC-SR

Table 144 and Table 145 describe deaths in EPIC-HR and EPIC-SR.

Table 144. Deaths[1], Safety Population, EPIC-HR and EPIC-SR[2]

	EPIC-HR			EPIC-SR			Pooled		
Preferred Term	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)	Risk Difference (%) (95% CI)[3]
Any AE leading to death	0	13 (1.2)	-1.2 (-1.9, -0.6)*	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	14 (0.9)	-0.9 (-1.3, -0.4)*
Acute respiratory failure	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Pneumonitis	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
COVID-19	0	3 (0.3)	-0.3 (-0.6, 0.0)	0	0	0 (0, 0)	0	3 (0.2)	-0.2 (-0.4, 0.0)
COVID-19 pneumonia	0	8 (0.8)	-0.8 (-1.3, -0.2)*	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	9 (0.6)	-0.6 (-0.9, -0.2)*

Source: adae.xpt; Software: R.
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (incl. those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (incl. those switched to 1282) are excluded.
1. Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
2. Duration of treatment is 5 days.
3. Difference is shown between PAXLOVID vs placebo
Abbreviations: AE, adverse event; CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; N, number of patients in treatment arm; n, number of patients with adverse event

Table 145. Listing of All Individual Patient Deaths[1], Safety Population, EPIC-HR and EPIC-SR[2]

					Dosing Duration	Study Day	Cause of Death	
Study Arm	Patient ID	Age	Sex	Dosage	(Days)	of Death	Preferred Term	Verbatim Term
EPIC-HR Placebo	(b) (6)	75	M	NA	3	9	COVID-19	COVID-19 worsening
EPIC-HR Placebo		73	M	NA	5	9	COVID-19 pneumonia	Respiratory failure caused by COVID-19 pneumonia
EPIC-HR Placebo		72	M	NA	3	32	Pneumonitis	Progression of the lung inflammation
EPIC-HR Placebo		52	M	NA	2	11	COVID-19 pneumonia	COVID-19 pneumonia
EPIC-HR Placebo		68	F	NA	5	9	COVID-19 pneumonia	COVID-19 pneumonia
EPIC-HR Placebo		72	F	NA	4	13	COVID-19 pneumonia	COVID-19 bilateral pneumonia
EPIC-HR Placebo		67	F	NA	2	4	COVID-19 pneumonia	COVID 19 bilateral pneumonia
EPIC-HR Placebo		70	M	NA	5	11	COVID-19 pneumonia	Death due to COVID-19 pneumonia
EPIC-HR Placebo		75	M	NA	5	25	COVID-19 pneumonia	Bilateral COVID-19 pneumonia
EPIC-HR Placebo		84	F	NA	2	9	COVID-19 pneumonia	COVID-19 pneumonia
EPIC-HR Placebo		54	M	NA	5	27	COVID-19	COVID-19 complications
EPIC-HR Placebo		61	M	NA	5	12	COVID-19	COVID-19
EPIC-HR Placebo		64	M	NA	4	12	Acute respiratory failure	Acute respiratory failure
EPIC-SR Placebo		67	M	NA	5	6	COVID-19 pneumonia	COVID-19 pneumonia

Source: adae.xpt; Software: R.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (incl. those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (incl. those switched to 1282) are excluded.
1. Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
2. Duration of treatment is 5 days.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; F, female; ID, identifier; M, male; NA, not applicable

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17.3. Safety Results, Vaccinated Participants With at Least One Risk Factor for Progression to Severe Disease, EPIC-SR

Table 146 provides a summary of TEAEs reported through Day 34 in subjects who were vaccinated with at least one risk factor for progression to severe disease in EPIC-SR. The frequencies of severe (Grade 3) or higher TEAEs were similar in the PAXLOVID group when compared to the placebo group in these subjects. There were no SAEs or deaths in the PAXLOVID group, and five (1.6%) subjects had an AE leading to permanent discontinuation of study drug. The frequency of any AE was similar between the PAXLOVID and placebo groups.

Table 146. Overview of Adverse Events[1], Vaccinated Participants With Risk Factors Assessed by the Applicant, Safety Population, EPIC-SR[2]

Event Category	PAXLOVID N=317 n (%)	Placebo N=314 n (%)	Risk Difference (%) (95% CI)[3]
SAE	5 (1.6)	8 (2.5)	-1.0 (-3.2, 1.2)
SAEs with fatal outcome	0	1 (0.3)	-0.3 (-0.9, 0.3)
Life-threatening SAEs	1 (0.3)	2 (0.6)	-0.3 (-1.4, 0.8)
AE leading to permanent discontinuation of study drug	5 (1.6)	4 (1.3)	0.3 (-1.5, 2.2)
AE leading to dose modification of study drug	0	1 (0.3)	-0.3 (-0.9, 0.3)
AE leading to interruption of study drug	0	1 (0.3)	-0.3 (-0.9, 0.3)
AE leading to reduction of study drug	0	0	0 (0, 0)
AE leading to dose delay of study drug	0	0	0 (0, 0)
Other	0	0	0 (0, 0)
Any AE[4]	80 (25.2)	84 (26.8)	-1.5 (-8.4, 5.3)
Severe and worse	12 (3.8)	16 (5.1)	-1.3 (-4.5, 1.9)
Moderate	22 (6.9)	20 (6.4)	0.6 (-3.3, 4.5)
Mild	46 (14.5)	48 (15.3)	-0.8 (-6.3, 4.8)

Source: adae.xpt; Software: R.
Note: Participants enrolled at sites 1281 and 1488 (including those switched to 1282) are excluded.
1. Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
2. Duration of treatment is 5 days.
3. Difference is shown between PAXLOVID and placebo.
4. Severity as assessed by the investigator.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event

When comparing the vaccinated subjects with at least one risk factor for progression to severe disease in EPIC-SR, the incidence of overall TEAEs were similar between the PAXLOVID group when compared to the placebo group. Table 147 summarizes the AEs occurring in at least 0.5% of subjects in any group.

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Table 147. Patients With Common Adverse Events[1] Occurring at ≥0.5% Frequency, Vaccinated Participants With Risk Factors Assessed by the Applicant, Safety Population, EPIC-SR[2]

Preferred Term	PAXLOVID N=317 n (%)	Placebo N=314 n (%)	Risk Difference (%) (95% CI)[3]
Any AE	80 (25.2)	84 (26.8)	-1.5 (-8.4, 5.3)
Dysgeusia	16 (5.0)	1 (0.3)	4.7 (2.2, 7.2)*
Headache	6 (1.9)	2 (0.6)	1.3 (-0.5, 3.0)
Aspartate aminotransferase increased	4 (1.3)	1 (0.3)	0.9 (-0.4, 2.3)
Blood lactate dehydrogenase increased	2 (0.6)	0	0.6 (-0.2, 1.5)
Hypothyroidism	2 (0.6)	0	0.6 (-0.2, 1.5)
Prothrombin time prolonged	2 (0.6)	0	0.6 (-0.2, 1.5)
Pruritus	2 (0.6)	0	0.6 (-0.2, 1.5)
Renal failure	2 (0.6)	0	0.6 (-0.2, 1.5)
C-reactive protein increased	3 (0.9)	1 (0.3)	0.6 (-0.6, 1.9)
Dyspepsia	4 (1.3)	2 (0.6)	0.6 (-0.9, 2.1)
Creatinine renal clearance decreased	5 (1.6)	3 (1.0)	0.6 (-1.1, 2.4)
Alanine aminotransferase increased	6 (1.9)	4 (1.3)	0.6 (-1.3, 2.6)
Dehydration	2 (0.6)	1 (0.3)	0.3 (-0.8, 1.4)
Hepatic enzyme increased	2 (0.6)	1 (0.3)	0.3 (-0.8, 1.4)
Type 2 diabetes mellitus	2 (0.6)	1 (0.3)	0.3 (-0.8, 1.4)
Hyperkalemia	2 (0.6)	2 (0.6)	-0.0 (-1.2, 1.2)
Hypertension	2 (0.6)	2 (0.6)	-0.0 (-1.2, 1.2)
Nausea	12 (3.8)	12 (3.8)	-0.0 (-3.0, 2.9)
Diarrhea	14 (4.4)	14 (4.5)	-0.0 (-3.3, 3.2)
Asthenia	1 (0.3)	2 (0.6)	-0.3 (-1.4, 0.8)
Back pain	1 (0.3)	2 (0.6)	-0.3 (-1.4, 0.8)
Blood thyroid stimulating hormone increased	1 (0.3)	2 (0.6)	-0.3 (-1.4, 0.8)
Dyspnea	2 (0.6)	3 (1.0)	-0.3 (-1.7, 1.1)
Alopecia	0	2 (0.6)	-0.6 (-1.5, 0.2)
Bronchospasm	0	2 (0.6)	-0.6 (-1.5, 0.2)
Flatulence	0	2 (0.6)	-0.6 (-1.5, 0.2)
Migraine	0	2 (0.6)	-0.6 (-1.5, 0.2)
Musculoskeletal pain	0	2 (0.6)	-0.6 (-1.5, 0.2)
Productive cough	0	2 (0.6)	-0.6 (-1.5, 0.2)
Rhinitis allergic	0	2 (0.6)	-0.6 (-1.5, 0.2)
Blood creatine phosphokinase increased	1 (0.3)	3 (1.0)	-0.6 (-1.9, 0.6)
Fibrin D dimer increased	1 (0.3)	3 (1.0)	-0.6 (-1.9, 0.6)
Tachycardia	1 (0.3)	3 (1.0)	-0.6 (-1.9, 0.6)
Activated partial thromboplastin time prolonged	2 (0.6)	4 (1.3)	-0.6 (-2.2, 0.9)
Vomiting	5 (1.6)	7 (2.2)	-0.7 (-2.8, 1.5)
Abdominal pain upper	0	3 (1.0)	-1.0 (-2.0, 0.1)
Pneumonia	0	4 (1.3)	-1.3 (-2.5, -0.0)*
Dizziness	1 (0.3)	5 (1.6)	-1.3 (-2.8, 0.2)
COVID-19 pneumonia	2 (0.6)	8 (2.5)	-1.9 (-3.9, 0.0)

Source: adae.xpt; Software: R.
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Note: Coded as MedDRA preferred terms.
Note: Participants enrolled at sites 1281 and 1488 (including those switched to 1282) are excluded.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
[2.] Duration of treatment is 5 days.
[3.] Difference is shown between PAXLOVID vs. placebo
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment arm; n, number of patients with adverse event

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The incidence of TEAEs among PAXLOVID recipients was similar in the seropositive (21.5%, 197/918) and seronegative subgroups (23.9%, 152/637). The most common adverse events in PAXLOVID recipients were dysgeusia (4.7% in the seronegative subgroup and 5.1% in the seropositive subgroup) and diarrhea (3.3% in the seronegative subgroup and 3.5% in the seropositive subgroup)[18].

Additionally, the incidence of TEAE in subjects in EPIC-SR who were unvaccinated was similar between the PAXLOVID group (21.8%, 272/1248) and the placebo group (23.5%, 296/1259). The most common adverse events in recipients of PAXLOVID in the unvaccinated subgroup were dysgeusia (5.0%) and diarrhea (3.0%)[19].

17.4. Adverse Event Assessment, EPIC-HR and EPIC-SR

Overviews of adverse events in EPIC-HR and EPIC-SR were provided in Sections 7.6.1.3, 7.6.1.4, and 7.6.1.5 Assessment of SAEs using FDA medical queries (FMQs) (Table 148), AEs leading to treatment discontinuation (Table 149), and subjects with adverse events (Table 150 and Table 151) were similar to the respective assessments using preferred terms.

[18] Source: Applicant's Table 84d.3.1.2.2.13i, Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (All Causalities), by Baseline Serology Status

[19] Source: Applicant's Table 84d.3.1.2.2.10i, Treatment-Emergent Adverse Events by System Organ Class and Preferred Term [All Causalities], by Vaccination Status

Table 148. Patients With Serious Adverse Events[1] by System Organ Class and FDA Medical Query (Narrow), Safety Population, EPIC-HR and EPIC-SR[2]

	EPIC-HR			EPIC-SR			Pooled		
System Organ Class FMQ[4] (Narrow)	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)	Risk Difference (%) (95% CI)[3]
Blood and lymphatic system disorders (SOC)									
Anemia	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	0	0 (0, 0)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Thrombosis	1 (0.1)	2 (0.2)	-0.1 (-0.4, 0.2)	0	0	0 (0, 0)	1 (0.06)	2 (0.1)	-0.1 (-0.3, 0.2)
Thrombosis venous	0	2 (0.2)	-0.2 (-0.5, 0.1)	0	0	0 (0, 0)	0	2 (0.1)	-0.1 (-0.3, 0.0)
Cardiac disorders (SOC)									
Palpitations	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Systemic hypertension	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Hepatobiliary disorders (SOC)									
Hepatic injury	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Infections and infestations (SOC)									
Purulent material	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Bacterial infection	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	1 (0.2)	-0.2 (-0.6, 0.2)	1 (0.06)	2 (0.1)	-0.1 (-0.3, 0.2)
Pneumonia	1 (0.1)	12 (1.1)	-1.0 (-1.7, -0.4)*	2 (0.4)	2 (0.4)	-0.0 (-0.7, 0.7)	3 (0.2)	14 (0.9)	-0.7 (-1.2, -0.2)*
Viral infection	9 (0.9)	43 (4.1)	-3.2 (-4.5, -1.9)*	3 (0.6)	9 (1.7)	-1.1 (-2.4, 0.1)	12 (0.8)	52 (3.3)	-2.5 (-3.5, -1.6)*
Musculoskeletal and connective tissue disorders (SOC)									
Fracture	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Nervous system disorders (SOC)									
Stroke TIA	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Respiratory, thoracic, and mediastinal disorders (SOC)									
Dyspnea	1 (0.1)	3 (0.3)	-0.2 (-0.6, 0.2)	1 (0.2)	0	0.2 (-0.2, 0.5)	2 (0.1)	3 (0.2)	-0.1 (-0.3, 0.2)
Respiratory failure	1 (0.1)	6 (0.6)	-0.5 (-1.0, 0.0)	0	0	0 (0, 0)	1 (0.06)	6 (0.4)	-0.3 (-0.6, 0.0)
Pneumonitis	0	7 (0.7)	-0.7 (-1.2, -0.2)*	0	0	0 (0, 0)	0	7 (0.4)	-0.4 (-0.8, -0.1)*

System Organ Class FMQ[4] (Narrow)	EPIC-HR PAXLOVID N=1038 n (%)	EPIC-HR Placebo N=1053 n (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n (%)	EPIC-SR Placebo N=528 n (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n (%)	Pooled Placebo N=1581 n (%)	Pooled Risk Difference (%) (95% CI)[3]
Vascular disorders (SOC)									
Hemorrhage	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)

Source: adae.xpt; Software: R
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit. Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
[2.] Duration of treatment is 5 days.
[3.] Difference is shown between PAXLOVID and placebo
[4.] Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC. Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class; TIA, transient ischemic attack

Table 149. Patients With Adverse Events[1] Leading to Treatment Discontinuation by System Organ Class and FDA Medical Query (Narrow), Safety Population, EPIC-HR and EPIC-SR[2]

System Organ Class[4] FMQ (Narrow)	EPIC-HR PAXLOVID N=1038 n (%)	EPIC-HR Placebo N=1053 n (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n (%)	EPIC-SR Placebo N=528 n (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n (%)	Pooled Placebo N=1581 n (%)	Pooled Risk Difference (%) (95% CI)[3]
Blood and lymphatic system disorders (SOC)									
Leukopenia	2 (0.2)	0	0.2 (-0.1, 0.5)	0	0	0 (0, 0)	2 (0.1)	0	0.1 (-0.0, 0.3)
Anemia	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Cardiac disorders (SOC)									
Palpitations	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Systemic hypertension	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Endocrine disorders (SOC)									
Hyperglycemia	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Gastrointestinal disorders (SOC)									
Diarrhea	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	2 (0.4)	0	0.4 (-0.1, 0.9)	3 (0.2)	1 (0.06)	0.1 (-0.1, 0.4)
Abdominal pain	1 (0.1)	0	0.1 (-0.1, 0.3)	1 (0.2)	0	0.2 (-0.2, 0.5)	2 (0.1)	0	0.1 (-0.0, 0.3)
Nausea	5 (0.5)	5 (0.5)	0.0 (-0.6, 0.6)	1 (0.2)	0	0.2 (-0.2, 0.5)	6 (0.4)	5 (0.3)	0.1 (-0.3, 0.5)
Vomiting	4 (0.4)	2 (0.2)	0.2 (-0.3, 0.7)	1 (0.2)	2 (0.4)	-0.2 (-0.8, 0.4)	5 (0.3)	4 (0.3)	0.1 (-0.3, 0.4)

	EPIC-HR			EPIC-SR			Pooled		
System Organ Class[4] FMQ (Narrow)	**PAXLOVID N=1038 n (%)**	**Placebo N=1053 n (%)**	**Risk Difference (%) (95% CI)**	**PAXLOVID N=540 n (%)**	**Placebo N=528 n (%)**	**Risk Difference (%) (95% CI)**	**PAXLOVID N=1578 n (%)**	**Placebo N=1581 n (%)**	**Risk Difference (%) (95% CI)[3]**
General disorders and administration site conditions (SOC)									
Dizziness	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	1 (0.2)	0	0.2 (-0.2, 0.5)	2 (0.1)	1 (0.06)	0.1 (-0.2, 0.3)
Fatigue	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Peripheral edema	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Hepatobiliary disorders (SOC)									
Hepatic injury	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	0	0 (0, 0)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Infections and infestations (SOC)									
Pneumonia	0	3 (0.3)	-0.3 (-0.6, 0.0)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	1 (0.06)	4 (0.3)	-0.2 (-0.5, 0.1)
Viral infection	2 (0.2)	15 (1.4)	-1.2 (-2.0, -0.5)*	0	2 (0.4)	-0.4 (-0.9, 0.1)	2 (0.1)	17 (1.1)	-0.9 (-1.5, -0.4)*
Musculoskeletal and connective tissue disorders (SOC)									
Myalgia	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Nervous system disorders (SOC)									
Dysgeusia	2 (0.2)	0	0.2 (-0.1, 0.5)	2 (0.4)	0	0.4 (-0.1, 0.9)	4 (0.3)	0	0.3 (0.0, 0.5)*
Psychiatric disorders (SOC)									
Insomnia	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Reproductive system and breast disorders (SOC)									
Abnormal uterine bleeding	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Respiratory, thoracic, and mediastinal disorders (SOC)									
Dyspnea	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	1 (0.2)	0	0.2 (-0.2, 0.5)	2 (0.1)	1 (0.06)	0.1 (-0.2, 0.3)
Cough	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Respiratory failure	1 (0.1)	3 (0.3)	-0.2 (-0.6, 0.2)	0	0	0 (0, 0)	1 (0.06)	3 (0.2)	-0.1 (-0.4, 0.1)
Pneumonitis	0	4 (0.4)	-0.4 (-0.8, -0.0)*	0	0	0 (0, 0)	0	4 (0.3)	-0.3 (-0.5, -0.0)*

System Organ Class[4] FMQ (Narrow)	EPIC-HR PAXLOVID N=1038 n (%)	EPIC-HR Placebo N=1053 n (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n (%)	EPIC-SR Placebo N=528 n (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n (%)	Pooled Placebo N=1581 n (%)	Pooled Risk Difference (%) (95% CI)[3]
Skin and subcutaneous tissue disorders (SOC)									
Rash	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	0	0 (0, 0)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Vascular disorders (SOC)									
Hemorrhage	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)

Source: adae.xpt; Software: R.
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Note: Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
[1]Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
[2]Duration of treatment is 5 days.
[3] Difference is shown between PAXLOVID vs placebo.
[4] Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Table 150. Patients With Adverse Events[1] by System Organ Class and FDA Medical Query (Narrow), Safety Population, EPIC-HR and EPIC-SR[2]

System Organ Class[3] FMQ (Narrow)	EPIC-HR PAXLOVID N=1038 n (%)	EPIC-HR Placebo N=1053 n (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n (%)	EPIC-SR Placebo N=528 n (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n (%)	Pooled Placebo N=1581 n (%)	Pooled Risk Difference (%) (95% CI)[4]
Blood and lymphatic system disorders (SOC)									
Leukopenia	4 (0.4)	5 (0.5)	-0.1 (-0.7, 0.5)	0	0	0 (0, 0)	4 (0.3)	5 (0.3)	-0.1 (-0.4, 0.3)
Anemia	2 (0.2)	2 (0.2)	0.0 (-0.4, 0.4)	0	2 (0.4)	-0.4 (-0.9, 0.1)	2 (0.1)	4 (0.3)	-0.1 (-0.4, 0.2)
Thrombosis	1 (0.1)	3 (0.3)	-0.2 (-0.6, 0.2)	0	0	0 (0, 0)	1 (0.06)	3 (0.2)	-0.1 (-0.4, 0.1)
Thrombocytopenia	1 (0.1)	4 (0.4)	-0.3 (-0.7, 0.1)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	2 (0.1)	5 (0.3)	-0.2 (-0.5, 0.1)
Thrombosis venous	0	3 (0.3)	-0.3 (-0.6, 0.0)	0	0	0 (0, 0)	0	3 (0.2)	-0.2 (-0.4, 0.0)
Cardiac disorders (SOC)									
Systemic hypertension	8 (0.8)	3 (0.3)	0.5 (-0.1, 1.1)	2 (0.4)	4 (0.8)	-0.4 (-1.3, 0.5)	10 (0.6)	7 (0.4)	0.2 (-0.3, 0.7)
Heart failure	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Palpitations	2 (0.2)	2 (0.2)	0.0 (-0.4, 0.4)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	3 (0.2)	3 (0.2)	0.0 (-0.3, 0.3)
Cardiac conduction disturbance	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Tachycardia	0	1 (0.09)	-0.1 (-0.3, 0.1)	1 (0.2)	3 (0.6)	-0.4 (-1.1, 0.4)	1 (0.06)	4 (0.3)	-0.2 (-0.5, 0.1)
Arrhythmia	0	3 (0.3)	-0.3 (-0.6, 0.0)	2 (0.4)	5 (0.9)	-0.6 (-1.5, 0.4)	2 (0.1)	8 (0.5)	-0.4 (-0.8, 0.0)

	EPIC-HR			EPIC-SR			Pooled		
System Organ Class[3] FMQ (Narrow)	**PAXLOVID N=1038 n (%)**	**Placebo N=1053 n (%)**	**Risk Difference (%) (95% CI)**	**PAXLOVID N=540 n (%)**	**Placebo N=528 n (%)**	**Risk Difference (%) (95% CI)**	**PAXLOVID N=1578 n (%)**	**Placebo N=1581 n (%)**	**Risk Difference (%) (95% CI)[4]**
Ear and labyrinth disorders (SOC)									
Vertigo	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	2 (0.1)	2 (0.1)	0.0 (-0.2, 0.2)
Endocrine disorders (SOC)									
Hypoglycemia	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Hyperglycemia	8 (0.8)	16 (1.5)	-0.7 (-1.7, 0.2)	5 (0.9)	3 (0.6)	0.4 (-0.7, 1.4)	13 (0.8)	19 (1.2)	-0.4 (-1.1, 0.3)
Gastrointestinal disorders (SOC)									
Diarrhea	31 (3.0)	16 (1.5)	1.5 (0.2, 2.7)*	22 (4.1)	16 (3.0)	1.0 (-1.2, 3.3)	53 (3.4)	32 (2.0)	1.3 (0.2, 2.5)*
Vomiting	12 (1.2)	9 (0.9)	0.3 (-0.6, 1.2)	10 (1.9)	11 (2.1)	-0.2 (-1.9, 1.4)	22 (1.4)	20 (1.3)	0.1 (-0.7, 0.9)
Dyspepsia	7 (0.7)	6 (0.6)	0.1 (-0.6, 0.8)	5 (0.9)	5 (0.9)	-0.0 (-1.2, 1.1)	12 (0.8)	11 (0.7)	0.1 (-0.5, 0.7)
Dry mouth	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Abdominal pain	6 (0.6)	5 (0.5)	0.1 (-0.5, 0.7)	2 (0.4)	4 (0.8)	-0.4 (-1.3, 0.5)	8 (0.5)	9 (0.6)	-0.1 (-0.6, 0.4)
Constipation	1 (0.1)	3 (0.3)	-0.2 (-0.6, 0.2)	1 (0.2)	0	0.2 (-0.2, 0.5)	2 (0.1)	3 (0.2)	-0.1 (-0.3, 0.2)
Nausea	15 (1.4)	19 (1.8)	-0.4 (-1.4, 0.7)	17 (3.1)	16 (3.0)	0.1 (-2.0, 2.2)	32 (2.0)	35 (2.2)	-0.2 (-1.2, 0.8)
General disorders and administration site conditions (SOC)									
Pyrexia	8 (0.8)	7 (0.7)	0.1 (-0.6, 0.8)	3 (0.6)	1 (0.2)	0.4 (-0.4, 1.1)	11 (0.7)	8 (0.5)	0.2 (-0.3, 0.7)
Volume depletion	2 (0.2)	1 (0.09)	0.1 (-0.2, 0.4)	2 (0.4)	1 (0.2)	0.2 (-0.5, 0.8)	4 (0.3)	2 (0.1)	0.1 (-0.2, 0.4)
Local administration reaction	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Decreased appetite	1 (0.1)	0	0.1 (-0.1, 0.3)	0	1 (0.2)	-0.2 (-0.6, 0.2)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Fall	0	2 (0.2)	-0.2 (-0.5, 0.1)	0	0	0 (0, 0)	0	2 (0.1)	-0.1 (-0.3, 0.0)
Peripheral edema	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	2 (0.1)	-0.1 (-0.3, 0.0)
Dizziness	4 (0.4)	6 (0.6)	-0.2 (-0.8, 0.4)	5 (0.9)	7 (1.3)	-0.4 (-1.7, 0.9)	9 (0.6)	13 (0.8)	-0.3 (-0.8, 0.3)
Fatigue	5 (0.5)	8 (0.8)	-0.3 (-1.0, 0.4)	2 (0.4)	3 (0.6)	-0.2 (-1.0, 0.6)	7 (0.4)	11 (0.7)	-0.3 (-0.8, 0.3)
Hepatobiliary disorders (SOC)									
Hepatic injury	20 (1.9)	31 (2.9)	-1.0 (-2.3, 0.3)	13 (2.4)	10 (1.9)	0.5 (-1.2, 2.3)	33 (2.1)	41 (2.6)	-0.5 (-1.6, 0.6)
Immune system disorders (SOC)									
Hypersensitivity	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Infections and infestations (SOC)									
Opportunistic infection	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Purulent material	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Fungal infection	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	0	0 (0, 0)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Bacterial infection	4 (0.4)	3 (0.3)	0.1 (-0.4, 0.6)	2 (0.4)	4 (0.8)	-0.4 (-1.3, 0.5)	6 (0.4)	7 (0.4)	-0.1 (-0.5, 0.4)
Nasopharyngitis	2 (0.2)	1 (0.09)	0.1 (-0.2, 0.4)	1 (0.2)	6 (1.1)	-1.0 (-1.9, 0.0)	3 (0.2)	7 (0.4)	-0.3 (-0.6, 0.1)
Pneumonia	2 (0.2)	17 (1.6)	-1.4 (-2.2, -0.6)*	3 (0.6)	5 (0.9)	-0.4 (-1.4, 0.6)	5 (0.3)	22 (1.4)	-1.1 (-1.7, -0.4)*
Viral infection	15 (1.4)	59 (5.6)	-4.2 (-5.7, -2.6)*	4 (0.7)	12 (2.3)	-1.5 (-3.0, -0.1)*	19 (1.2)	71 (4.5)	-3.3 (-4.4, -2.1)*

	EPIC-HR			EPIC-SR			Pooled		
System Organ Class[3] FMQ (Narrow)	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)	Risk Difference (%) (95% CI)[4]
Metabolism and nutrition disorders (SOC)									
Lipid disorder	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Musculoskeletal and connective tissue disorders (SOC)									
Myalgia	7 (0.7)	1 (0.09)	0.6 (0.0, 1.1)*	0	0	0 (0, 0)	7 (0.4)	1 (0.06)	0.4 (0.0, 0.7)*
Arthralgia	3 (0.3)	1 (0.09)	0.2 (-0.2, 0.6)	0	0	0 (0, 0)	3 (0.2)	1 (0.06)	0.1 (-0.1, 0.4)
Gout	1 (0.1)	0	0.1 (-0.1, 0.3)	1 (0.2)	0	0.2 (-0.2, 0.5)	2 (0.1)	0	0.1 (-0.0, 0.3)
Back pain	1 (0.1)	2 (0.2)	-0.1 (-0.4, 0.2)	2 (0.4)	2 (0.4)	-0.0 (-0.7, 0.7)	3 (0.2)	4 (0.3)	-0.1 (-0.4, 0.3)
Rhabdomyolysis	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Fracture	0	2 (0.2)	-0.2 (-0.5, 0.1)	0	0	0 (0, 0)	0	2 (0.1)	-0.1 (-0.3, 0.0)
Nervous system disorders (SOC)									
Dysgeusia	48 (4.6)	1 (0.09)	4.5 (3.2, 5.8)*	30 (5.6)	2 (0.4)	5.2 (3.2, 7.2)*	78 (4.9)	3 (0.2)	4.8 (3.7, 5.8)*
Stroke TIA	2 (0.2)	0	0.2 (-0.1, 0.5)	0	0	0 (0, 0)	2 (0.1)	0	0.1 (-0.0, 0.3)
Syncope	0	1 (0.09)	-0.1 (-0.3, 0.1)	2 (0.4)	0	0.4 (-0.1, 0.9)	2 (0.1)	1 (0.06)	0.1 (-0.2, 0.3)
Confusional state	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	0	0 (0, 0)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Paresthesia	0	0	0 (0, 0)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Somnolence	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Tremor	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Headache	12 (1.2)	13 (1.2)	-0.1 (-1.0, 0.9)	6 (1.1)	8 (1.5)	-0.4 (-1.8, 1.0)	18 (1.1)	21 (1.3)	-0.2 (-1.0, 0.6)
Psychiatric disorders (SOC)									
Insomnia	2 (0.2)	2 (0.2)	0.0 (-0.4, 0.4)	1 (0.2)	0	0.2 (-0.2, 0.5)	3 (0.2)	2 (0.1)	0.1 (-0.2, 0.3)
Irritability	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Anxiety	3 (0.3)	2 (0.2)	0.1 (-0.3, 0.5)	0	1 (0.2)	-0.2 (-0.6, 0.2)	3 (0.2)	3 (0.2)	0.0 (-0.3, 0.3)
Arthritis	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	2 (0.1)	2 (0.1)	0.0 (-0.2, 0.2)
Depression	1 (0.1)	0	0.1 (-0.1, 0.3)	0	1 (0.2)	-0.2 (-0.6, 0.2)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Renal and urinary disorders (SOC)									
Renal and urinary tract infection	2 (0.2)	1 (0.09)	0.1 (-0.2, 0.4)	1 (0.2)	2 (0.4)	-0.2 (-0.8, 0.4)	3 (0.2)	3 (0.2)	0.0 (-0.3, 0.3)
Reproductive system and breast disorders (SOC)									
Excessive menstrual bleeding	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Abnormal uterine bleeding	1 (0.1)	3 (0.3)	-0.2 (-0.6, 0.2)	0	0	0 (0, 0)	1 (0.06)	3 (0.2)	-0.1 (-0.4, 0.1)

System Organ Class[3] FMQ (Narrow)	EPIC-HR PAXLOVID N=1038 n (%)	EPIC-HR Placebo N=1053 n (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n (%)	EPIC-SR Placebo N=528 n (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n (%)	Pooled Placebo N=1581 n (%)	Pooled Risk Difference (%) (95% CI)[4]
Respiratory, thoracic, and mediastinal disorders (SOC)									
Cough	8 (0.8)	6 (0.6)	0.2 (-0.5, 0.9)	0	3 (0.6)	-0.6 (-1.2, 0.1)	8 (0.5)	9 (0.6)	-0.1 (-0.6, 0.4)
Dyspnea	7 (0.7)	9 (0.9)	-0.2 (-0.9, 0.6)	3 (0.6)	3 (0.6)	-0.0 (-0.9, 0.9)	10 (0.6)	12 (0.8)	-0.1 (-0.7, 0.5)
Bronchospasm	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	2 (0.4)	-0.4 (-0.9, 0.1)	1 (0.06)	3 (0.2)	-0.1 (-0.4, 0.1)
Respiratory failure	2 (0.2)	8 (0.8)	-0.6 (-1.2, 0.0)	1 (0.2)	0	0.2 (-0.2, 0.5)	3 (0.2)	8 (0.5)	-0.3 (-0.7, 0.1)
Pneumonitis	1 (0.1)	8 (0.8)	-0.7 (-1.2, -0.1)*	0	0	0 (0, 0)	1 (0.06)	8 (0.5)	-0.4 (-0.8, -0.1)*
Skin and subcutaneous tissue disorders (SOC)									
Pruritus	1 (0.1)	0	0.1 (-0.1, 0.3)	2 (0.4)	0	0.4 (-0.1, 0.9)	3 (0.2)	0	0.2 (-0.0, 0.4)
Rash	5 (0.5)	5 (0.5)	0.0 (-0.6, 0.6)	0	0	0 (0, 0)	5 (0.3)	5 (0.3)	0.0 (-0.4, 0.4)
Alopecia	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	2 (0.4)	-0.4 (-0.9, 0.1)	1 (0.06)	3 (0.2)	-0.1 (-0.4, 0.1)
Urticaria	0	2 (0.2)	-0.2 (-0.5, 0.1)	0	0	0 (0, 0)	0	2 (0.1)	-0.1 (-0.3, 0.0)
Erythema	0	4 (0.4)	-0.4 (-0.8, -0.0)*	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	1 (0.06)	5 (0.3)	-0.3 (-0.6, 0.1)
Vascular disorders (SOC)									
Hemorrhage	3 (0.3)	3 (0.3)	0.0 (-0.5, 0.5)	2 (0.4)	1 (0.2)	0.2 (-0.5, 0.8)	5 (0.3)	4 (0.3)	0.1 (-0.3, 0.4)
Hypotension	1 (0.1)	5 (0.5)	-0.4 (-0.8, 0.1)	3 (0.6)	0	0.6 (-0.1, 1.2)	4 (0.3)	5 (0.3)	-0.1 (-0.4, 0.3)

Source: adae.xpt; Software: R.
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
[2.] Duration of treatment is 5 days.
[3.] Difference is shown between PAXLOVID vs placebo.
[4.] Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class; TIA, transient ischemic attack

Table 151. Patients With Adverse Events[1] by System Organ Class and FDA Medical Query (Broad), Safety Population, EPIC-HR and EPIC-SR[2]

	EPIC-HR			EPIC-SR			Pooled		
System Organ Class FMQ (Broad)	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)	Risk Difference (%) (95% CI)
Blood and lymphatic system disorders (SOC)									
Thrombosis arterial	1 (0.1)	2 (0.2)	-0.1 (-0.4, 0.2)	0	0	0 (0, 0)	1 (0.06)	2 (0.1)	-0.1 (-0.3, 0.2)
Anemia	2 (0.2)	2 (0.2)	0.0 (-0.4, 0.4)	0	2 (0.4)	-0.4 (-0.9, 0.1)	2 (0.1)	4 (0.3)	-0.1 (-0.4, 0.2)
Thrombocytopenia	1 (0.1)	4 (0.4)	-0.3 (-0.7, 0.1)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	2 (0.1)	5 (0.3)	-0.2 (-0.5, 0.1)
Thrombosis	1 (0.1)	5 (0.5)	-0.4 (-0.8, 0.1)	0	0	0 (0, 0)	1 (0.06)	5 (0.3)	-0.3 (-0.6, 0.1)
Thrombosis venous	0	5 (0.5)	-0.5 (-0.9, -0.1)*	0	0	0 (0, 0)	0	5 (0.3)	-0.3 (-0.6, -0.0)*
Leukopenia	4 (0.4)	10 (0.9)	-0.6 (-1.3, 0.1)	0	0	0 (0, 0)	4 (0.3)	10 (0.6)	-0.4 (-0.8, 0.1)
Cardiac disorders (SOC)									
Systemic hypertension	8 (0.8)	3 (0.3)	0.5 (-0.1, 1.1)	2 (0.4)	4 (0.8)	-0.4 (-1.3, 0.5)	10 (0.6)	7 (0.4)	0.2 (-0.3, 0.7)
Palpitations	2 (0.2)	2 (0.2)	0.0 (-0.4, 0.4)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	3 (0.2)	3 (0.2)	0.0 (-0.3, 0.3)
Cardiac conduction disturbance	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Myocardial infarction	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Myocardial ischemia	0	0	0 (0, 0)	0	2 (0.4)	-0.4 (-0.9, 0.1)	0	2 (0.1)	-0.1 (-0.3, 0.0)
Tachycardia	0	1 (0.09)	-0.1 (-0.3, 0.1)	1 (0.2)	3 (0.6)	-0.4 (-1.1, 0.4)	1 (0.06)	4 (0.3)	-0.2 (-0.5, 0.1)
Heart failure	7 (0.7)	10 (0.9)	-0.3 (-1.0, 0.5)	2 (0.4)	4 (0.8)	-0.4 (-1.3, 0.5)	9 (0.6)	14 (0.9)	-0.3 (-0.9, 0.3)
Acute coronary syndrome	1 (0.1)	5 (0.5)	-0.4 (-0.8, 0.1)	4 (0.7)	5 (0.9)	-0.2 (-1.3, 0.9)	5 (0.3)	10 (0.6)	-0.3 (-0.8, 0.2)
Arrhythmia	5 (0.5)	11 (1.0)	-0.6 (-1.3, 0.2)	9 (1.7)	12 (2.3)	-0.6 (-2.3, 1.1)	14 (0.9)	23 (1.5)	-0.6 (-1.3, 0.2)
Ear and labyrinth disorders (SOC)									
Vertigo	4 (0.4)	6 (0.6)	-0.2 (-0.8, 0.4)	5 (0.9)	7 (1.3)	-0.4 (-1.7, 0.9)	9 (0.6)	13 (0.8)	-0.3 (-0.8, 0.3)
Endocrine disorders (SOC)									
Hypoglycemia	3 (0.3)	1 (0.09)	0.2 (-0.2, 0.6)	0	1 (0.2)	-0.2 (-0.6, 0.2)	3 (0.2)	2 (0.1)	0.1 (-0.2, 0.3)
Diabetic ketoacidosis	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	1 (0.2)	-0.2 (-0.6, 0.2)	1 (0.06)	2 (0.1)	-0.1 (-0.3, 0.2)
Hyperglycemia	9 (0.9)	17 (1.6)	-0.7 (-1.7, 0.2)	5 (0.9)	3 (0.6)	0.4 (-0.7, 1.4)	14 (0.9)	20 (1.3)	-0.4 (-1.1, 0.3)
Eye disorders (SOC)									
Glaucoma	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Gastrointestinal disorders (SOC)									
Diarrhea	32 (3.1)	17 (1.6)	1.5 (0.2, 2.8)*	22 (4.1)	16 (3.0)	1.0 (-1.2, 3.3)	54 (3.4)	33 (2.1)	1.3 (0.2, 2.5)*
Dyspepsia	14 (1.3)	9 (0.9)	0.5 (-0.4, 1.4)	9 (1.7)	7 (1.3)	0.3 (-1.1, 1.8)	23 (1.5)	16 (1.0)	0.4 (-0.3, 1.2)
Dry mouth	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Abdominal pain	6 (0.6)	5 (0.5)	0.1 (-0.5, 0.7)	2 (0.4)	4 (0.8)	-0.4 (-1.3, 0.5)	8 (0.5)	9 (0.6)	-0.1 (-0.6, 0.4)
Constipation	1 (0.1)	3 (0.3)	-0.2 (-0.6, 0.2)	1 (0.2)	0	0.2 (-0.2, 0.5)	2 (0.1)	3 (0.2)	-0.1 (-0.3, 0.2)
Nausea	21 (2.0)	25 (2.4)	-0.4 (-1.6, 0.9)	23 (4.3)	23 (4.4)	-0.1 (-2.5, 2.3)	44 (2.8)	48 (3.0)	-0.2 (-1.4, 0.9)
Vomiting	21 (2.0)	26 (2.5)	-0.4 (-1.7, 0.8)	23 (4.3)	23 (4.4)	-0.1 (-2.5, 2.3)	44 (2.8)	49 (3.1)	-0.3 (-1.5, 0.9)

	EPIC-HR			EPIC-SR			Pooled		
System Organ Class FMQ (Broad)	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)	Risk Difference (%) (95% CI)
General disorders and administration site conditions (SOC)									
Pyrexia	9 (0.9)	7 (0.7)	0.2 (-0.5, 0.9)	4 (0.7)	1 (0.2)	0.6 (-0.3, 1.4)	13 (0.8)	8 (0.5)	0.3 (-0.2, 0.9)
Volume depletion	3 (0.3)	2 (0.2)	0.1 (-0.3, 0.5)	2 (0.4)	2 (0.4)	-0.0 (-0.7, 0.7)	5 (0.3)	4 (0.3)	0.1 (-0.3, 0.4)
Local administration reaction	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Decreased appetite	1 (0.1)	0	0.1 (-0.1, 0.3)	0	1 (0.2)	-0.2 (-0.6, 0.2)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Peripheral edema	2 (0.2)	2 (0.2)	0.0 (-0.4, 0.4)	0	1 (0.2)	-0.2 (-0.6, 0.2)	2 (0.1)	3 (0.2)	-0.1 (-0.3, 0.2)
Dizziness	4 (0.4)	6 (0.6)	-0.2 (-0.8, 0.4)	5 (0.9)	7 (1.3)	-0.4 (-1.7, 0.9)	9 (0.6)	13 (0.8)	-0.3 (-0.8, 0.3)
Fatigue	5 (0.5)	9 (0.9)	-0.4 (-1.1, 0.3)	2 (0.4)	3 (0.6)	-0.2 (-1.0, 0.6)	7 (0.4)	12 (0.8)	-0.3 (-0.9, 0.2)
Fall	5 (0.5)	11 (1.0)	-0.6 (-1.3, 0.2)	6 (1.1)	7 (1.3)	-0.2 (-1.5, 1.1)	11 (0.7)	18 (1.1)	-0.4 (-1.1, 0.2)
Hepatobiliary disorders (SOC)									
Hepatic failure	2 (0.2)	1 (0.09)	0.1 (-0.2, 0.4)	1 (0.2)	2 (0.4)	-0.2 (-0.8, 0.4)	3 (0.2)	3 (0.2)	0.0 (-0.3, 0.3)
Hepatic injury	23 (2.2)	36 (3.4)	-1.2 (-2.6, 0.2)	16 (3.0)	12 (2.3)	0.7 (-1.2, 2.6)	39 (2.5)	48 (3.0)	-0.6 (-1.7, 0.6)
Immune system disorders (SOC)									
Angioedema	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Hypersensitivity	7 (0.7)	10 (0.9)	-0.3 (-1.0, 0.5)	3 (0.6)	6 (1.1)	-0.6 (-1.7, 0.5)	10 (0.6)	16 (1.0)	-0.4 (-1.0, 0.3)
Infections and infestations (SOC)									
Purulent material	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Fungal infection	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	0	0 (0, 0)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Opportunistic infection	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	0	0 (0, 0)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Nasopharyngitis	2 (0.2)	1 (0.09)	0.1 (-0.2, 0.4)	2 (0.4)	6 (1.1)	-0.8 (-1.8, 0.3)	4 (0.3)	7 (0.4)	-0.2 (-0.6, 0.2)
Bacterial infection	8 (0.8)	19 (1.8)	-1.0 (-2.0, -0.1)*	5 (0.9)	10 (1.9)	-1.0 (-2.4, 0.4)	13 (0.8)	29 (1.8)	-1.0 (-1.8, -0.2)*
Pneumonia	6 (0.6)	21 (2.0)	-1.4 (-2.4, -0.5)*	4 (0.7)	7 (1.3)	-0.6 (-1.8, 0.6)	10 (0.6)	28 (1.8)	-1.1 (-1.9, -0.4)*
Viral infection	18 (1.7)	71 (6.7)	-5.0 (-6.7, -3.3)*	6 (1.1)	18 (3.4)	-2.3 (-4.1, -0.5)*	24 (1.5)	89 (5.6)	-4.1 (-5.4, -2.8)*
Metabolism and nutrition disorders (SOC)									
Lipid disorder	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Musculoskeletal and connective tissue disorders (SOC)									
Arthralgia	3 (0.3)	2 (0.2)	0.1 (-0.3, 0.5)	2 (0.4)	1 (0.2)	0.2 (-0.5, 0.8)	5 (0.3)	3 (0.2)	0.1 (-0.2, 0.5)
Gout	1 (0.1)	0	0.1 (-0.1, 0.3)	1 (0.2)	0	0.2 (-0.2, 0.5)	2 (0.1)	0	0.1 (-0.0, 0.3)
Myalgia	7 (0.7)	4 (0.4)	0.3 (-0.3, 0.9)	1 (0.2)	3 (0.6)	-0.4 (-1.1, 0.4)	8 (0.5)	7 (0.4)	0.1 (-0.4, 0.5)
Back pain	1 (0.1)	2 (0.2)	-0.1 (-0.4, 0.2)	3 (0.6)	2 (0.4)	0.2 (-0.6, 1.0)	4 (0.3)	4 (0.3)	0.0 (-0.4, 0.4)
Fracture	0	2 (0.2)	-0.2 (-0.5, 0.1)	0	0	0 (0, 0)	0	2 (0.1)	-0.1 (-0.3, 0.0)
Rhabdomyolysis	1 (0.1)	5 (0.5)	-0.4 (-0.8, 0.1)	4 (0.7)	5 (0.9)	-0.2 (-1.3, 0.9)	5 (0.3)	10 (0.6)	-0.3 (-0.8, 0.2)

System Organ Class FMQ (Broad)	EPIC-HR PAXLOVID N=1038 n (%)	EPIC-HR Placebo N=1053 n (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n (%)	EPIC-SR Placebo N=528 n (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n (%)	Pooled Placebo N=1581 n (%)	Pooled Risk Difference (%) (95% CI)
Nervous system disorders (SOC)									
Dysgeusia	48 (4.6)	1 (0.09)	4.5 (3.2, 5.8)*	32 (5.9)	2 (0.4)	5.5 (3.5, 7.6)*	80 (5.1)	3 (0.2)	4.9 (3.8, 6.0)*
Stroke TIA	2 (0.2)	0	0.2 (-0.1, 0.5)	1 (0.2)	0	0.2 (-0.2, 0.5)	3 (0.2)	0	0.2 (-0.0, 0.4)
Confusional state	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	0	0 (0, 0)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Paresthesia	0	0	0 (0, 0)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Tremor	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Headache	12 (1.2)	13 (1.2)	-0.1 (-1.0, 0.9)	6 (1.1)	8 (1.5)	-0.4 (-1.8, 1.0)	18 (1.1)	21 (1.3)	-0.2 (-1.0, 0.6)
Syncope	4 (0.4)	9 (0.9)	-0.5 (-1.1, 0.2)	6 (1.1)	6 (1.1)	-0.0 (-1.3, 1.2)	10 (0.6)	15 (0.9)	-0.3 (-0.9, 0.3)
Somnolence	2 (0.2)	6 (0.6)	-0.4 (-0.9, 0.1)	0	1 (0.2)	-0.2 (-0.6, 0.2)	2 (0.1)	7 (0.4)	-0.3 (-0.7, 0.1)
Psychiatric disorders (SOC)									
Arthritis	4 (0.4)	3 (0.3)	0.1 (-0.4, 0.6)	2 (0.4)	2 (0.4)	-0.0 (-0.7, 0.7)	6 (0.4)	5 (0.3)	0.1 (-0.3, 0.5)
Anxiety	4 (0.4)	3 (0.3)	0.1 (-0.4, 0.6)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	5 (0.3)	4 (0.3)	0.1 (-0.3, 0.4)
Insomnia	2 (0.2)	2 (0.2)	0.0 (-0.4, 0.4)	1 (0.2)	0	0.2 (-0.2, 0.5)	3 (0.2)	2 (0.1)	0.1 (-0.2, 0.3)
Depression	1 (0.1)	0	0.1 (-0.1, 0.3)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	2 (0.1)	1 (0.06)	0.1 (-0.2, 0.3)
Irritability	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Psychosis	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Parasomnia	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Study agent abuse potential	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Renal and urinary disorders (SOC)									
Acute kidney injury	17 (1.6)	20 (1.9)	-0.3 (-1.4, 0.9)	7 (1.3)	4 (0.8)	0.5 (-0.7, 1.7)	24 (1.5)	24 (1.5)	0.0 (-0.9, 0.9)
Renal and urinary tract infection	2 (0.2)	1 (0.09)	0.1 (-0.2, 0.4)	1 (0.2)	3 (0.6)	-0.4 (-1.1, 0.4)	3 (0.2)	4 (0.3)	-0.1 (-0.4, 0.3)
Urinary retention	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Reproductive system and breast disorders (SOC)									
Excessive menstrual bleeding	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Abnormal uterine bleeding	1 (0.1)	3 (0.3)	-0.2 (-0.6, 0.2)	0	1 (0.2)	-0.2 (-0.6, 0.2)	1 (0.06)	4 (0.3)	-0.2 (-0.5, 0.1)
Respiratory, thoracic, and mediastinal disorders (SOC)									
Cough	8 (0.8)	6 (0.6)	0.2 (-0.5, 0.9)	0	3 (0.6)	-0.6 (-1.2, 0.1)	8 (0.5)	9 (0.6)	-0.1 (-0.6, 0.4)
Dyspnea	7 (0.7)	9 (0.9)	-0.2 (-0.9, 0.6)	3 (0.6)	3 (0.6)	-0.0 (-0.9, 0.9)	10 (0.6)	12 (0.8)	-0.1 (-0.7, 0.5)
Respiratory depression	2 (0.2)	8 (0.8)	-0.6 (-1.2, 0.0)	1 (0.2)	0	0.2 (-0.2, 0.5)	3 (0.2)	8 (0.5)	-0.3 (-0.7, 0.1)
Bronchospasm	8 (0.8)	10 (0.9)	-0.2 (-1.0, 0.6)	2 (0.4)	6 (1.1)	-0.8 (-1.8, 0.3)	10 (0.6)	16 (1.0)	-0.4 (-1.0, 0.3)
Respiratory failure	9 (0.9)	17 (1.6)	-0.7 (-1.7, 0.2)	4 (0.7)	3 (0.6)	0.2 (-0.8, 1.1)	13 (0.8)	20 (1.3)	-0.4 (-1.1, 0.3)
Pneumonitis	2 (0.2)	12 (1.1)	-0.9 (-1.6, -0.3)*	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	3 (0.2)	13 (0.8)	-0.6 (-1.1, -0.1)*

System Organ Class FMQ (Broad)	EPIC-HR PAXLOVID N=1038 n (%)	EPIC-HR Placebo N=1053 n (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n (%)	EPIC-SR Placebo N=528 n (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n (%)	Pooled Placebo N=1581 n (%)	Pooled Risk Difference (%) (95% CI)
Skin and subcutaneous tissue disorders (SOC)									
Pruritus	1 (0.1)	0	0.1 (-0.1, 0.3)	2 (0.4)	0	0.4 (-0.1, 0.9)	3 (0.2)	0	0.2 (-0.0, 0.4)
Urticaria	3 (0.3)	5 (0.5)	-0.2 (-0.7, 0.3)	0	0	0 (0, 0)	3 (0.2)	5 (0.3)	-0.1 (-0.5, 0.2)
Alopecia	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	2 (0.4)	-0.4 (-0.9, 0.1)	1 (0.06)	3 (0.2)	-0.1 (-0.4, 0.1)
Rash	5 (0.5)	9 (0.9)	-0.4 (-1.1, 0.3)	0	0	0 (0, 0)	5 (0.3)	9 (0.6)	-0.3 (-0.7, 0.2)
Erythema	0	4 (0.4)	-0.4 (-0.8, -0.0)*	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	1 (0.06)	5 (0.3)	-0.3 (-0.6, 0.1)
Vascular disorders (SOC)									
Hypotension	3 (0.3)	5 (0.5)	-0.2 (-0.7, 0.3)	5 (0.9)	1 (0.2)	0.7 (-0.2, 1.6)	8 (0.5)	6 (0.4)	0.1 (-0.3, 0.6)
Hemorrhage	3 (0.3)	3 (0.3)	0.0 (-0.5, 0.5)	2 (0.4)	1 (0.2)	0.2 (-0.5, 0.8)	5 (0.3)	4 (0.3)	0.1 (-0.3, 0.4)

Source: adae.xpt; Software: R.
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
[2.] Duration of treatment is 5 days.
[3.] Difference is shown between PAXLOVID vs. placebo.
[4.] Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class; TIA, transient ischemic attack

Table 152 includes the AEs considered by the investigator to be related to study drug in EPIC-HR and EPIC-SR. These AEs were previously discussed in Section 7.6.1.5.

Table 152. Patients With Adverse Events[1] Assessed by Investigator as Treatment-Related, Safety Population, EPIC-HR and EPIC-SR[2]

Preferred Term	EPIC-HR PAXLOVID N=1038 n (%)	EPIC-HR Placebo N=1053 n (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n (%)	EPIC-SR Placebo N=528 n (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n (%)	Pooled Placebo N=1581 n (%)	Pooled Risk Difference (%) (95% CI)[3]
Any treatment-related AE	67 (6.5)	39 (3.7)	2.8 (0.9, 4.6)*	61 (11.3)	28 (5.3)	6.0 (2.7, 9.3)*	128 (8.1)	67 (4.2)	3.9 (2.2, 5.5)*
Dysgeusia	36 (3.5)	0	3.5 (2.4, 4.6)*	24 (4.4)	1 (0.2)	4.3 (2.5, 6.0)*	60 (3.8)	1 (0.06)	3.7 (2.8, 4.7)*
Diarrhea	11 (1.1)	2 (0.2)	0.9 (0.2, 1.5)*	12 (2.2)	8 (1.5)	0.7 (-0.9, 2.3)	23 (1.5)	10 (0.6)	0.8 (0.1, 1.5)*
AST increased	4 (0.4)	0	0.4 (0.0, 0.8)*	3 (0.6)	0	0.6 (-0.1, 1.2)	7 (0.4)	0	0.4 (0.1, 0.8)*
ALT increased	5 (0.5)	2 (0.2)	0.3 (-0.2, 0.8)	4 (0.7)	1 (0.2)	0.6 (-0.3, 1.4)	9 (0.6)	3 (0.2)	0.4 (-0.0, 0.8)
Product after taste	3 (0.3)	0	0.3 (-0.0, 0.6)	2 (0.4)	0	0.4 (-0.1, 0.9)	5 (0.3)	0	0.3 (0.0, 0.6)*
Dyspepsia	3 (0.3)	2 (0.2)	0.1 (-0.3, 0.5)	2 (0.4)	0	0.4 (-0.1, 0.9)	5 (0.3)	2 (0.1)	0.2 (-0.1, 0.5)

	EPIC-HR			EPIC-SR			Pooled		
Preferred Term	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)	Risk Difference (%) (95% CI)[3]
Vomiting	6 (0.6)	4 (0.4)	0.2 (-0.4, 0.8)	4 (0.7)	4 (0.8)	-0.0 (-1.1, 1.0)	10 (0.6)	8 (0.5)	0.1 (-0.4, 0.7)
Blood TSH decreased	1 (0.1)	0	0.1 (-0.1, 0.3)	1 (0.2)	0	0.2 (-0.2, 0.5)	2 (0.1)	0	0.1 (-0.0, 0.3)
Chest discomfort	1 (0.1)	0	0.1 (-0.1, 0.3)	1 (0.2)	0	0.2 (-0.2, 0.5)	2 (0.1)	0	0.1 (-0.0, 0.3)
Myalgia	2 (0.2)	0	0.2 (-0.1, 0.5)	0	0	0 (0, 0)	2 (0.1)	0	0.1 (-0.0, 0.3)
Nausea	8 (0.8)	9 (0.9)	-0.1 (-0.9, 0.7)	11 (2.0)	9 (1.7)	0.3 (-1.3, 2.0)	19 (1.2)	18 (1.1)	0.1 (-0.7, 0.8)
Dizziness	2 (0.2)	1 (0.09)	0.1 (-0.2, 0.4)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	3 (0.2)	2 (0.1)	0.1 (-0.2, 0.3)
Abdominal discomfort	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Anxiety	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Aphthous ulcer	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Blood bilirubin increased	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Blood fibrinogen increased	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Blood LDH increased	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
CRP increased	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Chromaturia	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Colitis	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Decreased appetite	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Feces soft	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
GERD	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Hiccups	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Hypertension	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Hypothyroidism	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Oral discomfort	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Oropharyngeal pain	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Paresthesia	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Parosmia	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Pollakiuria	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Rash maculo-papular	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Skin exfoliation	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Taste disorder	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
APTT prolonged	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	0	0 (0, 0)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Alopecia	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	0	0 (0, 0)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Blood CPK increased	0	0	0 (0, 0)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Dyspnea	1 (0.1)	0	0.1 (-0.1, 0.3)	0	1 (0.2)	-0.2 (-0.6, 0.2)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Gastritis	0	1 (0.09)	-0.1 (-0.3, 0.1)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)

	EPIC-HR			EPIC-SR			Pooled		
Preferred Term	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)	Risk Difference (%) (95% CI)[3]
Palpitations	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	0	0 (0, 0)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Thyroxine free increased	0	1 (0.09)	-0.1 (-0.3, 0.1)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Vertigo	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	0	0 (0, 0)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Rash	1 (0.1)	2 (0.2)	-0.1 (-0.4, 0.2)	0	0	0 (0, 0)	1 (0.06)	2 (0.1)	-0.1 (-0.3, 0.2)
Abdominal distension	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Abdominal pain	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Acne	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Anterograde amnesia	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Asthenia	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Blood glucose increased	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Confusional state	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Dehydration	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Eosinophil count increased	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Erythema	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Fibrin D dimer increased	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Flatulence	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Haptoglobin increased	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Hypersomnia	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Hypoesthesia	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Migraine	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Orthostatic hypotension	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Pain in extremity	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Peripheral swelling	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Platelet count decreased	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Pyrexia	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Thyroxine increased	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Hepatic enzyme increased	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	2 (0.1)	-0.1 (-0.3, 0.0)

	EPIC-HR			EPIC-SR			Pooled		
Preferred Term	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)	Risk Difference (%) (95% CI)[3]
Blood TSH increased	1 (0.1)	2 (0.2)	-0.1 (-0.4, 0.2)	1 (0.2)	3 (0.6)	-0.4 (-1.1, 0.4)	2 (0.1)	5 (0.3)	-0.2 (-0.5, 0.1)
Abdominal pain upper	1 (0.1)	2 (0.2)	-0.1 (-0.4, 0.2)	0	2 (0.4)	-0.4 (-0.9, 0.1)	1 (0.06)	4 (0.3)	-0.2 (-0.5, 0.1)
Headache	1 (0.1)	3 (0.3)	-0.2 (-0.6, 0.2)	0	3 (0.6)	-0.6 (-1.2, 0.1)	1 (0.06)	6 (0.4)	-0.3 (-0.6, 0.0)

Source: adae.xpt; Software: R.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
[2.] Duration of treatment is 5 days.
[3.] Difference is shown between PAXLOVID vs placebo.
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CI, confidence interval; CPK, creatine phosphokinase; CRP, C-reactive protein; GERD, gastroesophageal reflux disease; LDH, lactate dehydrogenase; N, number of patients in treatment arm; n, number of patients with adverse event; TSH, thyroid stimulating hormone

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17.5. Laboratory Findings, EPIC-HR and EPIC-SR

Table 153, Table 154, and Table 155 describe laboratory outliers assessed by the Safety Standard & Figures Integrated Guide (August 2022). An overview was previously provided in Section 7.6.1.6.

Table 153. Patients With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels[1], Safety Population, EPIC-HR and EPIC-SR[2]

	EPIC-HR			EPIC-SR			Pooled		
Laboratory Parameter	PAXLOVID N=1038 n/Nw (%)	Placebo N=1053 n/Nw (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n/Nw (%)	Placebo N=528 n/Nw (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n/Nw (%)	Placebo N=1581 n/Nw (%)	Risk Difference (%) (95% CI)[3]
Sodium, low (mEq/L)									
Level 1 (<132)	28/991 (2.8)	30/999 (3.0)	-0.2 (-1.7, 1.3)	14/524 (2.7)	8/510 (1.6)	1.1 (-0.6, 2.9)	42/1515 (2.8)	38/1509 (2.5)	0.3 (-0.9, 1.4)
Level 2 (<130)	4/991 (0.4)	11/999 (1.1)	-0.7 (-1.5, 0.1)	4/524 (0.8)	2/510 (0.4)	0.4 (-0.6, 1.3)	8/1515 (0.5)	13/1509 (0.9)	-0.3 (-0.9, 0.3)
Level 3 (<125)	0/991 (0)	0/999 (0)	0 (0, 0)	1/524 (0.2)	0/510 (0)	0.2 (-0.2, 0.6)	1/1515 (0.07)	0/1509 (0)	0.1 (-0.1, 0.2)
Sodium, high (mEq/L)									
Level 1 (>150)	2/991 (0.2)	1/999 (0.1)	0.1 (-0.2, 0.4)	2/524 (0.4)	0/510 (0)	0.4 (-0.1, 0.9)	4/1515 (0.3)	1/1509 (0.07)	0.2 (-0.1, 0.5)
Level 2 (>155)	1/991 (0.1)	0/999 (0)	0.1 (-0.1, 0.3)	1/524 (0.2)	0/510 (0)	0.2 (-0.2, 0.6)	2/1515 (0.1)	0/1509 (0)	0.1 (-0.1, 0.3)
Level 3 (>160)	0/991 (0)	0/999 (0)	0 (0, 0)	0/524 (0)	0/510 (0)	0 (0, 0)	0/1515 (0)	0/1509 (0)	0 (0, 0)
Potassium, low (mEq/L)									
Level 1 (<3.6)	76/985 (7.7)	65/1000 (6.5)	1.2 (-1.0, 3.5)	24/519 (4.6)	17/509 (3.3)	1.3 (-1.1, 3.7)	100/1504 (6.6)	82/1509 (5.4)	1.2 (-0.5, 2.9)
Level 2 (<3.4)	29/985 (2.9)	19/1000 (1.9)	1.0 (-0.3, 2.4)	7/519 (1.3)	3/509 (0.6)	0.8 (-0.4, 2.0)	36/1504 (2.4)	22/1509 (1.5)	0.9 (-0.0, 1.9)
Level 3 (<3)	3/985 (0.3)	5/1000 (0.5)	-0.2 (-0.8, 0.4)	1/519 (0.2)	0/509 (0)	0.2 (-0.2, 0.6)	4/1504 (0.3)	5/1509 (0.3)	-0.1 (-0.5, 0.3)
Potassium, high (mEq/L)									
Level 1 (>5.5)	24/985 (2.4)	24/1000 (2.4)	0.0 (-1.3, 1.4)	8/519 (1.5)	16/509 (3.1)	-1.6 (-3.5, 0.2)	32/1504 (2.1)	40/1509 (2.7)	-0.5 (-1.6, 0.6)
Level 2 (>6)	1/985 (0.1)	5/1000 (0.5)	-0.4 (-0.9, 0.1)	1/519 (0.2)	3/509 (0.6)	-0.4 (-1.2, 0.4)	2/1504 (0.1)	8/1509 (0.5)	-0.4 (-0.8, 0.0)
Level 3 (>6.5)	0/985 (0)	1/1000 (0.1)	-0.1 (-0.3, 0.1)	0/519 (0)	2/509 (0.4)	-0.4 (-0.9, 0.2)	0/1504 (0)	3/1509 (0.2)	-0.2 (-0.4, 0.0)
Chloride, low (mEq/L)									
Level 1 (<95)	84/991 (8.5)	82/998 (8.2)	0.3 (-2.2, 2.7)	31/524 (5.9)	16/509 (3.1)	2.8 (0.2, 5.3)	115/1515 (7.6)	98/1507 (6.5)	1.1 (-0.7, 2.9)
Level 2 (<88)	2/991 (0.2)	4/998 (0.4)	-0.2 (-0.7, 0.3)	4/524 (0.8)	0/509 (0)	0.8 (0.0, 1.5)	6/1515 (0.4)	4/1507 (0.3)	0.1 (-0.3, 0.5)
Level 3 (<80)	0/991 (0)	0/998 (0)	0 (0, 0)	1/524 (0.2)	0/509 (0)	0.2 (-0.2, 0.6)	1/1515 (0.07)	0/1507 (0)	0.1 (-0.1, 0.2)
Chloride, high (mEq/L)									
Level 1 (>108)	8/991 (0.8)	12/998 (1.2)	-0.4 (-1.3, 0.5)	6/524 (1.1)	1/509 (0.2)	0.9 (-0.0, 1.9)	14/1515 (0.9)	13/1507 (0.9)	0.1 (-0.6, 0.7)
Level 2 (>112)	0/991 (0)	0/998 (0)	0 (0, 0)	0/524 (0)	0/509 (0)	0 (0, 0)	0/1515 (0)	0/1507 (0)	0 (0, 0)
Level 3 (>115)	0/991 (0)	0/998 (0)	0 (0, 0)	0/524 (0)	0/509 (0)	0 (0, 0)	0/1515 (0)	0/1507 (0)	0 (0, 0)
Bicarbonate, low (mEq/L)									
Level 1 (<20)	169/989 (17.1)	157/997 (15.7)	1.3 (-1.9, 4.6)	70/519 (13.5)	79/506 (15.6)	-2.1 (-6.4, 2.2)	239/1508 (15.8)	236/1503 (15.7)	0.1 (-2.5, 2.8)
Level 2 (<18)	45/989 (4.6)	56/997 (5.6)	-1.1 (-3.0, 0.9)	17/519 (3.3)	21/506 (4.2)	-0.9 (-3.2, 1.4)	62/1508 (4.1)	77/1503 (5.1)	-1.0 (-2.5, 0.5)
Level 3 (<15)	2/989 (0.2)	9/997 (0.9)	-0.7 (-1.4, -0.1)	2/519 (0.4)	1/506 (0.2)	0.2 (-0.5, 0.8)	4/1508 (0.3)	10/1503 (0.7)	-0.4 (-0.9, 0.1)
Bicarbonate, high (mEq/L)									
Level 3 (>30)	11/989 (1.1)	16/997 (1.6)	-0.5 (-1.5, 0.5)	5/519 (1.0)	4/506 (0.8)	0.2 (-1.0, 1.3)	16/1508 (1.1)	20/1503 (1.3)	-0.3 (-1.0, 0.5)
Glucose, low (mg/dL)									
Level 1 (<70)	52/987 (5.3)	54/997 (5.4)	-0.1 (-2.1, 1.8)	38/517 (7.4)	27/506 (5.3)	2.0 (-1.0, 5.0)	90/1504 (6.0)	81/1503 (5.4)	0.6 (-1.1, 2.3)
Level 2 (<54)	6/987 (0.6)	4/997 (0.4)	0.2 (-0.4, 0.8)	2/517 (0.4)	4/506 (0.8)	-0.4 (-1.3, 0.5)	8/1504 (0.5)	8/1503 (0.5)	-0.0 (-0.5, 0.5)
Level 3 (<40)	2/987 (0.2)	0/997 (0)	0.2 (-0.1, 0.5)	0/517 (0)	0/506 (0)	0 (0, 0)	2/1504 (0.1)	0/1503 (0)	0.1 (-0.1, 0.3)
Glucose, fasting, high (mg/dL)									
Missing	NA	NA	NA	NA	NA	NA	NA	NA	NA

	EPIC-HR			EPIC-SR			Pooled		
Laboratory Parameter	PAXLOVID N=1038 n/Nw (%)	Placebo N=1053 n/Nw (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n/Nw (%)	Placebo N=528 n/Nw (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n/Nw (%)	Placebo N=1581 n/Nw (%)	Risk Difference (%) (95% CI)[3]
Glucose, random, high (mg/dL)									
Level 2 (≥200)	75/987 (7.6)	75/997 (7.5)	0.1 (-2.3, 2.4)	19/517 (3.7)	22/506 (4.3)	-0.7 (-3.1, 1.7)	94/1504 (6.2)	97/1503 (6.5)	-0.2 (-1.9, 1.5)
Level 3 (>250)	43/987 (4.4)	44/997 (4.4)	-0.1 (-1.9, 1.7)	9/517 (1.7)	17/506 (3.4)	-1.6 (-3.6, 0.3)	52/1504 (3.5)	61/1503 (4.1)	-0.6 (-2.0, 0.8)
Calcium, low (mg/dL)									
Level 1 (<8.4)	40/985 (4.1)	61/999 (6.1)	-2.0 (-4.0, -0.1)	17/520 (3.3)	23/509 (4.5)	-1.2 (-3.6, 1.1)	57/1505 (3.8)	84/1508 (5.6)	-1.8 (-3.3, -0.3)
Level 2 (<8)	16/985 (1.6)	19/999 (1.9)	-0.3 (-1.4, 0.9)	5/520 (1.0)	12/509 (2.4)	-1.4 (-3.0, 0.2)	21/1505 (1.4)	31/1508 (2.1)	-0.7 (-1.6, 0.3)
Level 3 (<7.5)	5/985 (0.5)	7/999 (0.7)	-0.2 (-0.9, 0.5)	4/520 (0.8)	7/509 (1.4)	-0.6 (-1.9, 0.7)	9/1505 (0.6)	14/1508 (0.9)	-0.3 (-1.0, 0.3)
Calcium, high (mg/dL)									
Level 1 (>10.5)	23/985 (2.3)	14/999 (1.4)	0.9 (-0.3, 2.1)	5/520 (1.0)	3/509 (0.6)	0.4 (-0.7, 1.4)	28/1505 (1.9)	17/1508 (1.1)	0.7 (-0.1, 1.6)
Level 2 (>11)	1/985 (0.1)	3/999 (0.3)	-0.2 (-0.6, 0.2)	0/520 (0)	1/509 (0.2)	-0.2 (-0.6, 0.2)	1/1505 (0.07)	4/1508 (0.3)	-0.2 (-0.5, 0.1)
Level 3 (>12)	0/985 (0)	0/999 (0)	0 (0, 0)	0/520 (0)	0/509 (0)	0 (0, 0)	0/1505 (0)	0/1508 (0)	0 (0, 0)
Magnesium, low (mg/dL)									
Missing	NA	NA	NA	NA	NA	NA	NA	NA	NA
Magnesium, high (mg/dL)									
Missing	NA	NA	NA	NA	NA	NA	NA	NA	NA
Phosphate, low (mg/dL)									
Missing	NA	NA	NA	NA	NA	NA	NA	NA	NA
Protein, total, low (g/dL)									
Level 1 (<6)	35/989 (3.5)	34/997 (3.4)	0.1 (-1.5, 1.7)	5/519 (1.0)	7/506 (1.4)	-0.4 (-1.7, 0.9)	40/1508 (2.7)	41/1503 (2.7)	-0.1 (-1.2, 1.1)
Level 2 (<5.4)	2/989 (0.2)	4/997 (0.4)	-0.2 (-0.7, 0.3)	0/519 (0)	0/506 (0)	0 (0, 0)	2/1508 (0.1)	4/1503 (0.3)	-0.1 (-0.5, 0.2)
Level 3 (<5)	1/989 (0.1)	0/997 (0)	0.1 (-0.1, 0.3)	0/519 (0)	0/506 (0)	0 (0, 0)	1/1508 (0.07)	0/1503 (0)	0.1 (-0.1, 0.2)
Albumin, low (g/dL)									
Level 1 (<3.1)	2/992 (0.2)	4/1001 (0.4)	-0.2 (-0.7, 0.3)	0/524 (0)	0/510 (0)	0 (0, 0)	2/1516 (0.1)	4/1511 (0.3)	-0.1 (-0.4, 0.2)
Level 2 (<2.5)	0/992 (0)	0/1001 (0)	0 (0, 0)	0/524 (0)	0/510 (0)	0 (0, 0)	0/1516 (0)	0/1511 (0)	0 (0, 0)
Level 3 (<2)	0/992 (0)	0/1001 (0)	0 (0, 0)	0/524 (0)	0/510 (0)	0 (0, 0)	0/1516 (0)	0/1511 (0)	0 (0, 0)
CPK, high (U/L)									
Level 1 (>3X ULN)	31/990 (3.1)	27/997 (2.7)	0.4 (-1.1, 1.9)	17/519 (3.3)	17/506 (3.4)	-0.1 (-2.3, 2.1)	48/1509 (3.2)	44/1503 (2.9)	0.3 (-1.0, 1.5)
Level 2 (>5X ULN)	11/990 (1.1)	12/997 (1.2)	-0.1 (-1.0, 0.8)	5/519 (1.0)	6/506 (1.2)	-0.2 (-1.5, 1.0)	16/1509 (1.1)	18/1503 (1.2)	-0.1 (-0.9, 0.6)
Level 3 (>10X ULN)	5/990 (0.5)	4/997 (0.4)	0.1 (-0.5, 0.7)	3/519 (0.6)	3/506 (0.6)	-0.0 (-0.9, 0.9)	8/1509 (0.5)	7/1503 (0.5)	0.1 (-0.4, 0.6)
Amylase, high (U/L)									
Missing	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lipase, high (U/L)									
Missing	NA	NA	NA	NA	NA	NA	NA	NA	NA
Blood urea nitrogen, high (mg/dL)									
Level 1 (>23)	64/991 (6.5)	77/1000 (7.7)	-1.2 (-3.5, 1.0)	16/524 (3.1)	20/509 (3.9)	-0.9 (-3.1, 1.4)	80/1515 (5.3)	97/1509 (6.4)	-1.1 (-2.8, 0.5)
Level 2 (>27)	37/991 (3.7)	34/1000 (3.4)	0.3 (-1.3, 2.0)	6/524 (1.1)	6/509 (1.2)	-0.0 (-1.3, 1.3)	43/1515 (2.8)	40/1509 (2.7)	0.2 (-1.0, 1.4)
Level 3 (>31)	16/991 (1.6)	21/1000 (2.1)	-0.5 (-1.7, 0.7)	2/524 (0.4)	3/509 (0.6)	-0.2 (-1.1, 0.6)	18/1515 (1.2)	24/1509 (1.6)	-0.4 (-1.2, 0.4)

Laboratory Parameter	EPIC-HR PAXLOVID N=1038 n/Nw (%)	EPIC-HR Placebo N=1053 n/Nw (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n/Nw (%)	EPIC-SR Placebo N=528 n/Nw (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n/Nw (%)	Pooled Placebo N=1581 n/Nw (%)	Pooled Risk Difference (%) (95% CI)[3]
Creatinine, high (mg/dL)									
Level 1 (≥1.5X baseline)	37/969 (3.8)	28/985 (2.8)	1.0 (-0.6, 2.6)	22/508 (4.3)	15/497 (3.0)	1.3 (-1.0, 3.6)	59/1477 (4.0)	43/1482 (2.9)	1.1 (-0.2, 2.4)
Level 2 (≥2X baseline)	4/969 (0.4)	3/985 (0.3)	0.1 (-0.4, 0.6)	4/508 (0.8)	3/497 (0.6)	0.2 (-0.8, 1.2)	8/1477 (0.5)	6/1482 (0.4)	0.1 (-0.4, 0.6)
Level 3 (≥3X baseline)	0/969 (0)	0/985 (0)	0 (0, 0)	0/508 (0)	0/497 (0)	0 (0, 0)	0/1477 (0)	0/1482 (0)	0 (0, 0)
eGFR, low (ml/min/1.73 m2)									
Level 1 (≥25% decrease)	46/969 (4.7)	39/985 (4.0)	0.8 (-1.0, 2.6)	22/508 (4.3)	22/497 (4.4)	-0.1 (-2.6, 2.4)	68/1477 (4.6)	61/1482 (4.1)	0.5 (-1.0, 2.0)
Level 2 (≥50% decrease)	2/969 (0.2)	2/985 (0.2)	0.0 (-0.4, 0.4)	1/508 (0.2)	1/497 (0.2)	-0.0 (-0.6, 0.5)	3/1477 (0.2)	3/1482 (0.2)	0.0 (-0.3, 0.3)
Level 3 (≥75% decrease)	0/969 (0)	0/985 (0)	0 (0, 0)	0/508 (0)	0/497 (0)	0 (0, 0)	0/1477 (0)	0/1482 (0)	0 (0, 0)

Source: adlb.xpt; Software: R.
Note: Glucose values for hyperglycemia do not follow a nested format l ke the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.
Note: Participants enrolled in Trial EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in Trial EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
[1.] Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (August 2022).
[2.] Duration of treatment is 5 days.
[3.] Difference is shown between PAXLOVID vs placebo
Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; ULN, upper limit of normal

Table 154. Patients With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels[1], Safety Population, EPIC-HR and EPIC-SR[2]

Laboratory Parameter	EPIC-HR PAXLOVID N=1038 n/N_w (%)	EPIC-HR Placebo N=1053 n/N_w (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n/N_w (%)	EPIC-SR Placebo N=528 n/N_w (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n/N_w (%)	Pooled Placebo N=1581 n/N_w (%)	Pooled Risk Difference (%) (95% CI)[3]
ALP, high (U/L)									
Level 1 (>1.5X ULN)	5/986 (0.5)	11/999 (1.1)	-0.6 (-1.4, 0.2)	3/520 (0.6)	4/509 (0.8)	-0.2 (-1.2, 0.8)	8/1506 (0.5)	15/1508 (1.0)	-0.5 (-1.1, 0.2)
Level 2 (>2X ULN)	1/986 (0.1)	4/999 (0.4)	-0.3 (-0.7, 0.1)	1/520 (0.2)	0/509 (0)	0.2 (-0.2, 0.6)	2/1506 (0.1)	4/1508 (0.3)	-0.1 (-0.5, 0.2)
Level 3 (>3X ULN)	0/986 (0)	2/999 (0.2)	-0.2 (-0.5, 0.1)	1/520 (0.2)	0/509 (0)	0.2 (-0.2, 0.6)	1/1506 (0.07)	2/1508 (0.1)	-0.1 (-0.3, 0.2)
ALT, high (U/L)									
Level 1 (>3X ULN)	35/990 (3.5)	45/997 (4.5)	-1.0 (-2.7, 0.7)	11/519 (2.1)	12/506 (2.4)	-0.3 (-2.1, 1.6)	46/1509 (3.0)	57/1503 (3.8)	-0.7 (-2.0, 0.6)
Level 2 (>5X ULN)	6/990 (0.6)	14/997 (1.4)	-0.8 (-1.7, 0.1)	3/519 (0.6)	3/506 (0.6)	-0.0 (-0.9, 0.9)	9/1509 (0.6)	17/1503 (1.1)	-0.5 (-1.2, 0.1)
Level 3 (>10X ULN)	0/990 (0)	1/997 (0.1)	-0.1 (-0.3, 0.1)	1/519 (0.2)	0/506 (0)	0.2 (-0.2, 0.6)	1/1509 (0.07)	1/1503 (0.07)	-0.0 (-0.2, 0.2)

Laboratory Parameter	EPIC-HR PAXLOVID N=1038 n/N_w (%)	EPIC-HR Placebo N=1053 n/N_w (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n/N_w (%)	EPIC-SR Placebo N=528 n/N_w (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n/N_w (%)	Pooled Placebo N=1581 n/N_w (%)	Pooled Risk Difference (%) (95% CI)[3]
AST, high (U/L)									
Level 1 (>3X ULN)	14/990 (1.4)	14/996 (1.4)	0.0 (-1.0, 1.0)	4/519 (0.8)	2/506 (0.4)	0.4 (-0.6, 1.3)	18/1509 (1.2)	16/1502 (1.1)	0.1 (-0.6, 0.9)
Level 2 (>5X ULN)	5/990 (0.5)	5/996 (0.5)	0.0 (-0.6, 0.6)	2/519 (0.4)	0/506 (0)	0.4 (-0.1, 0.9)	7/1509 (0.5)	5/1502 (0.3)	0.1 (-0.3, 0.6)
Level 3 (>10X ULN)	1/990 (0.1)	1/996 (0.1)	0.0 (-0.3, 0.3)	0/519 (0)	0/506 (0)	0 (0, 0)	1/1509 (0.07)	1/1502 (0.07)	-0.0 (-0.2, 0.2)
Bilirubin, total, high (mg/dL)									
Level 1 (>1.5X ULN)	5/990 (0.5)	2/997 (0.2)	0.3 (-0.2, 0.8)	2/519 (0.4)	5/506 (1.0)	-0.6 (-1.6, 0.4)	7/1509 (0.5)	7/1503 (0.5)	-0.0 (-0.5, 0.5)
Level 2 (>2X ULN)	2/990 (0.2)	0/997 (0)	0.2 (-0.1, 0.5)	1/519 (0.2)	3/506 (0.6)	-0.4 (-1.2, 0.4)	3/1509 (0.2)	3/1503 (0.2)	-0.0 (-0.3, 0.3)
Level 3 (>3X ULN)	1/990 (0.1)	0/997 (0)	0.1 (-0.1, 0.3)	0/519 (0)	0/506 (0)	0 (0, 0)	1/1509 (0.07)	0/1503 (0)	0.1 (-0.1, 0.2)

Source: adlb.xpt; Software: R.
Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
[1.] Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (August 2022).
[2.] Duration of treatment is 5 days.
[3.] Difference is shown between PAXLOVID vs placebo.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; ULN, upper limit of normal

Table 155. Patients With One or More Hematology Analyte Values Exceeding Specified Levels[1], Safety Population, EPIC-HR and EPIC-SR[2]

Laboratory Parameter	EPIC-HR PAXLOVID N=1038 n/N_w (%)	EPIC-HR Placebo N=1053 n/N_w (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n/N_w (%)	EPIC-SR Placebo N=528 n/N_w (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n/N_w (%)	Pooled Placebo N=1581 n/N_w (%)	Pooled Risk Difference (%) (95% CI)[3]
Complete Blood Count									
WBC, low (cells/uL)									
Level 1 (<3500)	40/873 (4.6)	81/890 (9.1)	-4.5 (-6.9, -2.2)	18/461 (3.9)	33/446 (7.4)	-3.5 (-6.5, -0.5)	58/1334 (4.3)	114/1336 (8.5)	-4.2 (-6.0, -2.3)
Level 2 (<3000)	14/873 (1.6)	39/890 (4.4)	-2.8 (-4.4, -1.2)	8/461 (1.7)	13/446 (2.9)	-1.2 (-3.1, 0.8)	22/1334 (1.6)	52/1336 (3.9)	-2.2 (-3.5, -1.0)
Level 3 (<1000)	0/873 (0)	1/890 (0.1)	-0.1 (-0.3, 0.1)	0/461 (0)	0/446 (0)	0 (0, 0)	0/1334 (0)	1/1336 (0.07)	-0.1 (-0.2, 0.1)
WBC, high (cells/uL)									
Level 1 (>10800)	122/873 (14.0)	98/890 (11.0)	3.0 (-0.1, 6.0)	35/461 (7.6)	29/446 (6.5)	1.1 (-2.2, 4.4)	157/1334 (11.8)	127/1336 (9.5)	2.3 (-0.1, 4.6)
Level 2 (>13000)	48/873 (5.5)	33/890 (3.7)	1.8 (-0.2, 3.7)	12/461 (2.6)	8/446 (1.8)	0.8 (-1.1, 2.7)	60/1334 (4.5)	41/1336 (3.1)	1.4 (-0.0, 2.9)
Level 3 (>15000)	18/873 (2.1)	15/890 (1.7)	0.4 (-0.9, 1.6)	3/461 (0.7)	5/446 (1.1)	-0.5 (-1.7, 0.8)	21/1334 (1.6)	20/1336 (1.5)	0.1 (-0.9, 1.0)
Hemoglobin, low (g/dL)									
Level 2 (>1.5 dec. from BL)	85/586 (14.5)	109/630 (17.3)	-2.8 (-6.9, 1.3)	41/314 (13.1)	40/316 (12.7)	0.4 (-4.8, 5.6)	126/900 (14.0)	149/946 (15.8)	-1.8 (-5.0, 1.5)
Level 3 (>2 dec. from BL)	43/586 (7.3)	49/630 (7.8)	-0.4 (-3.4, 2.5)	15/314 (4.8)	14/316 (4.4)	0.3 (-2.9, 3.6)	58/900 (6.4)	63/946 (6.7)	-0.2 (-2.5, 2.0)
Hemoglobin, high (g/dL)									
Level 2 (>2 inc. from BL)	6/586 (1.0)	13/630 (2.1)	-1.0 (-2.4, 0.3)	1/314 (0.3)	4/316 (1.3)	-0.9 (-2.3, 0.4)	7/900 (0.8)	17/946 (1.8)	-1.0 (-2.0, 0.0)
Level 3 (>3 inc. from BL)	2/586 (0.3)	3/630 (0.5)	-0.1 (-0.9, 0.6)	0/314 (0)	0/316 (0)	0 (0, 0)	2/900 (0.2)	3/946 (0.3)	-0.1 (-0.6, 0.4)

	EPIC-HR			EPIC-SR			Pooled		
Laboratory Parameter	**PAXLOVID N=1038 n/N_w (%)**	**Placebo N=1053 n/N_w (%)**	**Risk Difference (%) (95% CI)**	**PAXLOVID N=540 n/N_w (%)**	**Placebo N=528 n/N_w (%)**	**Risk Difference (%) (95% CI)**	**PAXLOVID N=1578 n/N_w (%)**	**Placebo N=1581 n/N_w (%)**	**Risk Difference (%) (95% CI)[3]**
Platelets, low (cells/uL)									
Level 1 (<140000)	28/864 (3.2)	40/884 (4.5)	-1.3 (-3.1, 0.5)	11/456 (2.4)	13/439 (3.0)	-0.5 (-2.7, 1.6)	39/1320 (3.0)	53/1323 (4.0)	-1.1 (-2.4, 0.3)
Level 2 (<125000)	12/864 (1.4)	23/884 (2.6)	-1.2 (-2.5, 0.1)	6/456 (1.3)	6/439 (1.4)	-0.1 (-1.6, 1.5)	18/1320 (1.4)	29/1323 (2.2)	-0.8 (-1.8, 0.2)
Level 3 (<100000)	1/864 (0.1)	6/884 (0.7)	-0.6 (-1.1, 0.0)	1/456 (0.2)	2/439 (0.5)	-0.2 (-1.0, 0.5)	2/1320 (0.2)	8/1323 (0.6)	-0.5 (-0.9, 0.0)
WBC Differential									
Lymphocytes, low (cells/uL)									
Level 1 (<1000)	68/870 (7.8)	101/882 (11.5)	-3.6 (-6.4, -0.9)	16/457 (3.5)	21/441 (4.8)	-1.3 (-3.9, 1.3)	84/1327 (6.3)	122/1323 (9.2)	-2.9 (-4.9, -0.9)
Level 2 (<750)	22/870 (2.5)	46/882 (5.2)	-2.7 (-4.5, -0.9)	5/457 (1.1)	7/441 (1.6)	-0.5 (-2.0, 1.0)	27/1327 (2.0)	53/1323 (4.0)	-2.0 (-3.3, -0.7)
Level 3 (<500)	7/870 (0.8)	10/882 (1.1)	-0.3 (-1.2, 0.6)	1/457 (0.2)	3/441 (0.7)	-0.5 (-1.3, 0.4)	8/1327 (0.6)	13/1323 (1.0)	-0.4 (-1.1, 0.3)
Lymphocytes, high (cells/uL)									
Level 1 (>4000)	21/870 (2.4)	19/882 (2.2)	0.3 (-1.1, 1.7)	7/457 (1.5)	3/441 (0.7)	0.9 (-0.5, 2.2)	28/1327 (2.1)	22/1323 (1.7)	0.4 (-0.6, 1.5)
Level 2 (>10000)	0/870 (0)	0/882 (0)	0 (0, 0)	0/457 (0)	0/441 (0)	0 (0, 0)	0/1327 (0)	0/1323 (0)	0 (0, 0)
Level 3 (>20000)	0/870 (0)	0/882 (0)	0 (0, 0)	0/457 (0)	0/441 (0)	0 (0, 0)	0/1327 (0)	0/1323 (0)	0 (0, 0)
Neutrophils, low (cells/uL)									
Level 1 (<2000)	110/866 (12.7)	138/881 (15.7)	-3.0 (-6.2, 0.3)	58/455 (12.7)	73/439 (16.6)	-3.9 (-8.5, 0.8)	168/1321 (12.7)	211/1320 (16.0)	-3.3 (-5.9, -0.6)
Level 2 (<1000)	8/866 (0.9)	15/881 (1.7)	-0.8 (-1.8, 0.3)	5/455 (1.1)	8/439 (1.8)	-0.7 (-2.3, 0.9)	13/1321 (1.0)	23/1320 (1.7)	-0.8 (-1.6, 0.1)
Level 3 (<500)	1/866 (0.1)	2/881 (0.2)	-0.1 (-0.5, 0.3)	0/455 (0)	1/439 (0.2)	-0.2 (-0.7, 0.2)	1/1321 (0.08)	3/1320 (0.2)	-0.2 (-0.4, 0.1)
Eosinophils, high (cells/uL)									
Level 1 (>650)	24/870 (2.8)	16/882 (1.8)	0.9 (-0.5, 2.3)	2/457 (0.4)	7/441 (1.6)	-1.1 (-2.5, 0.2)	26/1327 (2.0)	23/1323 (1.7)	0.2 (-0.8, 1.2)
Level 2 (>1500)	2/870 (0.2)	2/882 (0.2)	0.0 (-0.4, 0.5)	0/457 (0)	1/441 (0.2)	-0.2 (-0.7, 0.2)	2/1327 (0.2)	3/1323 (0.2)	-0.1 (-0.4, 0.3)
Level 3 (>5000)	0/870 (0)	0/882 (0)	0 (0, 0)	0/457 (0)	0/441 (0)	0 (0, 0)	0/1327 (0)	0/1323 (0)	0 (0, 0)
Coagulation Studies									
PT, high (sec)									
Level 1 (>1.1X ULN)	92/931 (9.9)	106/942 (11.3)	-1.4 (-4.2, 1.4)	14/513 (2.7)	12/498 (2.4)	0.3 (-1.6, 2.3)	106/1444 (7.3)	118/1440 (8.2)	-0.9 (-2.8, 1.1)
Level 2 (>1.3X ULN)	24/931 (2.6)	22/942 (2.3)	0.2 (-1.2, 1.6)	4/513 (0.8)	3/498 (0.6)	0.2 (-0.8, 1.2)	28/1444 (1.9)	25/1440 (1.7)	0.2 (-0.8, 1.2)
Level 3 (>1.5X ULN)	19/931 (2.0)	7/942 (0.7)	1.3 (0.2, 2.4)	3/513 (0.6)	2/498 (0.4)	0.2 (-0.7, 1.0)	22/1444 (1.5)	9/1440 (0.6)	0.9 (0.1, 1.7)
PTT, high (sec)									
Level 1 (>1X ULN)	327/928 (35.2)	336/942 (35.7)	-0.4 (-4.8, 3.9)	191/513 (37.2)	180/498 (36.1)	1.1 (-4.9, 7.0)	518/1441 (35.9)	516/1440 (35.8)	0.1 (-3.4, 3.6)
Level 2 (>1.21X ULN)	75/928 (8.1)	90/942 (9.6)	-1.5 (-4.0, 1.1)	28/513 (5.5)	50/498 (10.0)	-4.6 (-7.9, -1.3)	103/1441 (7.1)	140/1440 (9.7)	-2.6 (-4.6, -0.5)
Level 3 (>1.41X ULN)	32/928 (3.4)	32/942 (3.4)	0.1 (-1.6, 1.7)	9/513 (1.8)	9/498 (1.8)	-0.1 (-1.7, 1.6)	41/1441 (2.8)	41/1440 (2.8)	-0.0 (-1.2, 1.2)

Source: adlb.xpt; Software: R.
Note: Participants enrolled in Trial EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in Trial EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
[1.] Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (August 2022).
[2.] Duration of treatment is 5 days.
[3.] Difference is shown between PAXLOVID vs placebo
Abbreviations: BL, baseline; CI, confidence interval; dec, decrease; inc, increase; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; PT, prothrombin time; PTT, partial thromboplastin time; ULN, upper limit of normal; WBC, White blood cells

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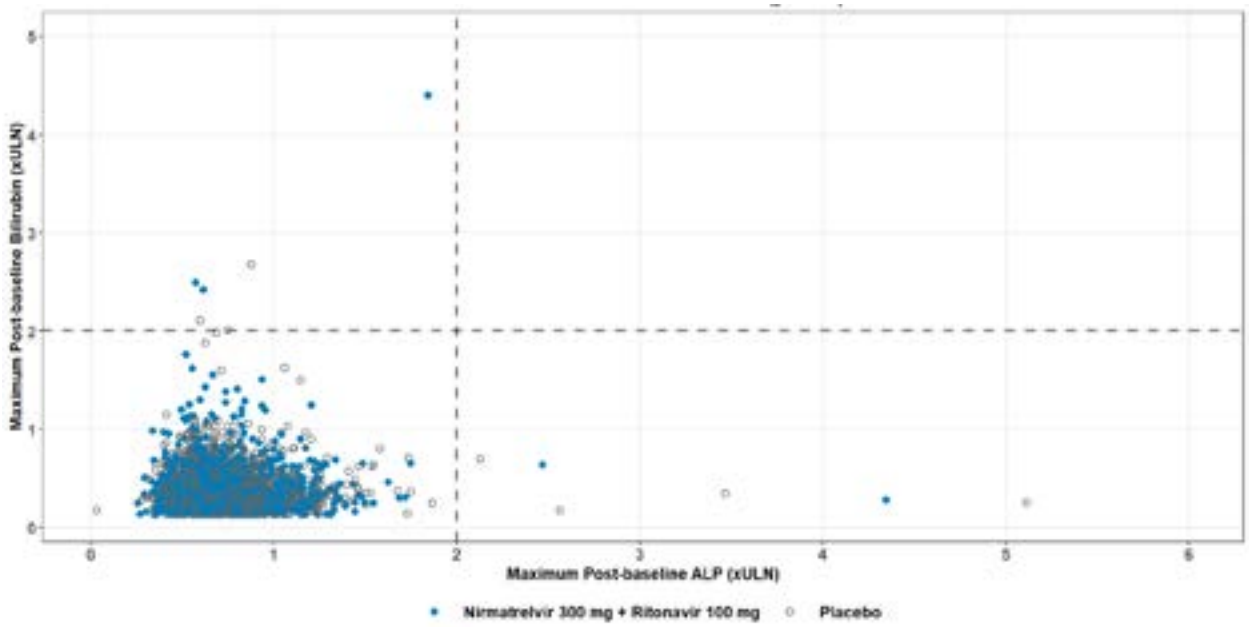
17.6. Assessment of Drug-Induced Liver Injury, EPIC-HR and EPIC-SR

As previously discussed in Section 7.6.1.7, there were two cases of potential hepatocellular drug induced liver injury (DILI) in PAXLOVID group in the EPIC-HR and EPIC-SR trials (one in each). As demonstrated in Figure 64 and Table 156, there were no cases of cholestatic drug-induced liver injury.

Figure 64. Cholestatic Drug-Induced Liver Injury Screening Plot, Safety Population, EPIC-HR and EPIC-SR



Source: adlb.xpt; Software: R.
Note: Each data point represents a patient plotted by their maximum ALP versus their maximum total bilirubin values in the post-baseline period.
Note: A potential cholestatic DILI case (red circled) was defined as having a maximum post-baseline total bilirubin equal to or exceeding 2X ULN within 30 days after post-baseline ALP became equal to or exceeding 2X ULN.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
Abbreviations: ALP, alkaline phosphatase; DILI, drug-induced liver injury; ULN, upper limit of normal

Table 156. Patients in Each Quadrant for Cholestatic DILI Screening Plot, Safety Population, EPIC-HR and EPIC-SR

	EPIC-HR		EPIC-SR		Pooled	
Quadrant	PAXLOVID N=1038 n/N_w (%)	Placebo N=1053 n/N_w (%)	PAXLOVID N=540 n/N_w (%)	Placebo N=528 n/N_w (%)	PAXLOVID N=1578 n/N_w (%)	Placebo N=1581 n/N_w (%)
Bilirubin ≥2X ULN and ALP ≥2X ULN (right upper)	0/984 (0)	0/996 (0)	0/515 (0)	0/506 (0)	0/1499 (0)	0/1502 (0)
Bilirubin ≥2X ULN and ALP <2X ULN (left upper)	2/984 (0.2)	0/996 (0)	1/515 (0.2)	3/506 (0.6)	3/1499 (0.2)	3/1502 (0.2)

Quadrant	EPIC-HR PAXLOVID N=1038 n/N_w (%)	EPIC-HR Placebo N=1053 n/N_w (%)	EPIC-SR PAXLOVID N=540 n/N_w (%)	EPIC-SR Placebo N=528 n/N_w (%)	Pooled PAXLOVID N=1578 n/N_w (%)	Pooled Placebo N=1581 n/N_w (%)
Bilirubin <2X ULN and ALP ≥2X ULN (right lower)	1/984 (0.1)	4/996 (0.4)	1/515 (0.2)	0/506 (0)	2/1499 (0.1)	4/1502 (0.3)
Total	3/984 (0.3)	4/996 (0.4)	2/515 (0.4)	3/506 (0.6)	5/1499 (0.3)	7/1502 (0.5)

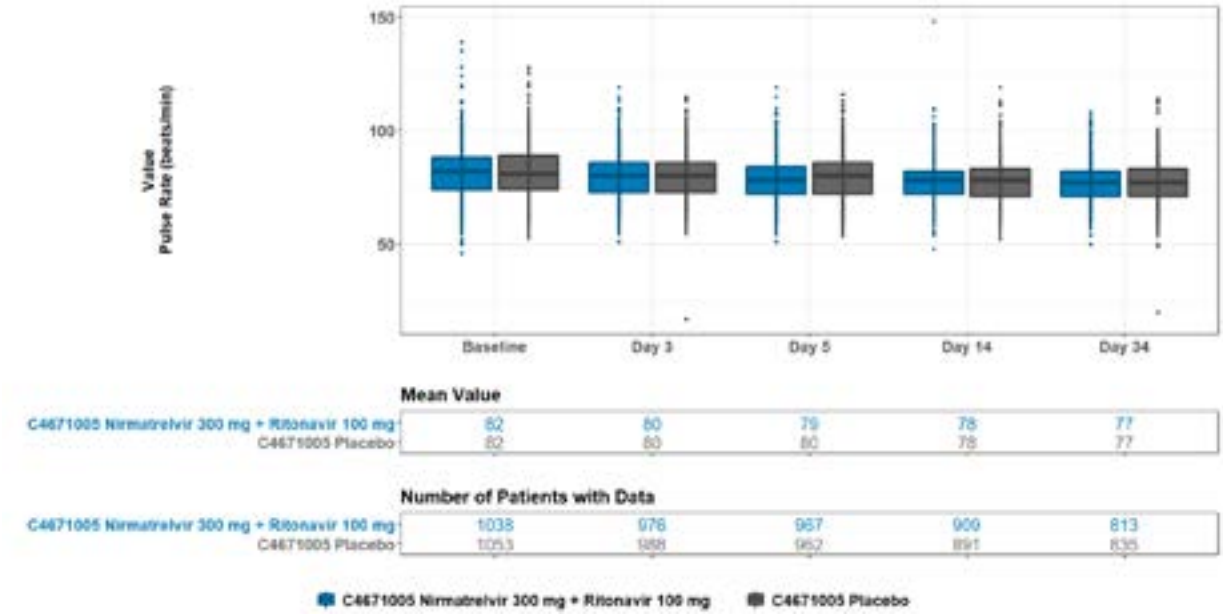
Source: adlb.xpt; Software: R.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
Abbreviations: ALP, alkaline phosphatase; DILI, drug-induced liver injury; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of patients with data; ULN, upper limit of normal

17.7. Vital Sign Assessment, EPIC-HR and EPIC-SR

An overview of vital sign assessment was provided in Section 7.6.1.8. Figure 65, Figure 66, and Figure 67 describe pulse, respiration rate, and body temperature in EPIC-HR and EPIC-SR.

Figure 65. Median and Interquartile Range of Pulse Rate Over Time by Treatment Arm, Safety Population, EPIC-HR and EPIC-SR

EPIC-HR

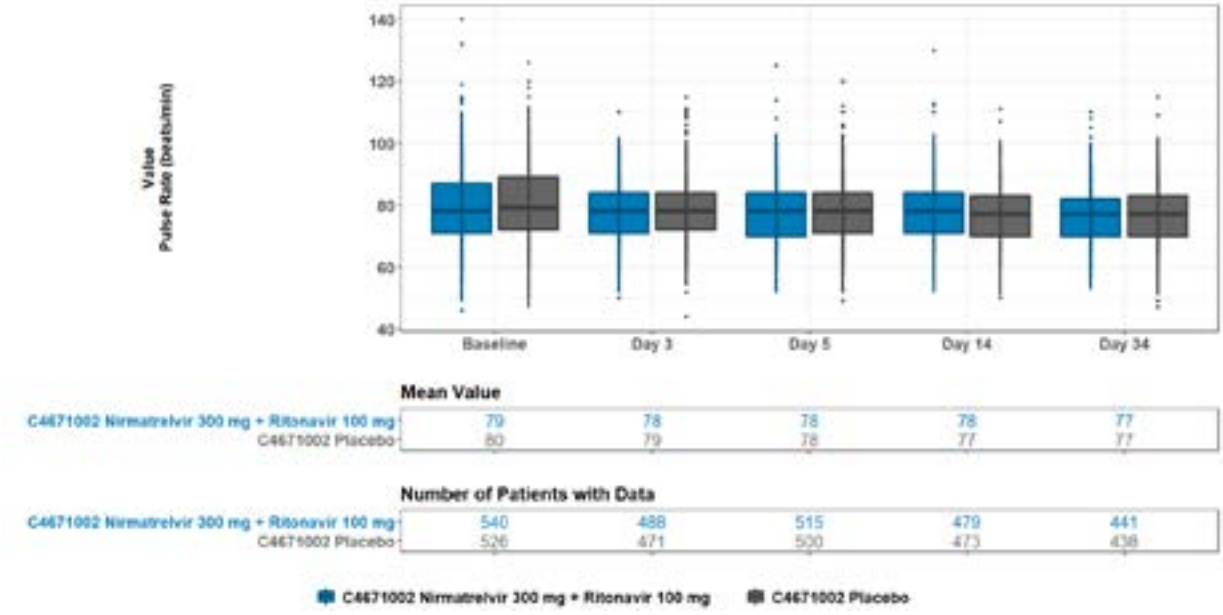


Mean Value					
C4671005 Nirmatrelvir 300 mg + Ritonavir 100 mg	82	80	79	78	77
C4671005 Placebo	82	80	80	78	77

Number of Patients with Data					
C4671005 Nirmatrelvir 300 mg + Ritonavir 100 mg	1038	976	957	909	813
C4671005 Placebo	1053	988	962	891	835

C4671005 Nirmatrelvir 300 mg + Ritonavir 100 mg C4671005 Placebo

EPIC-SR

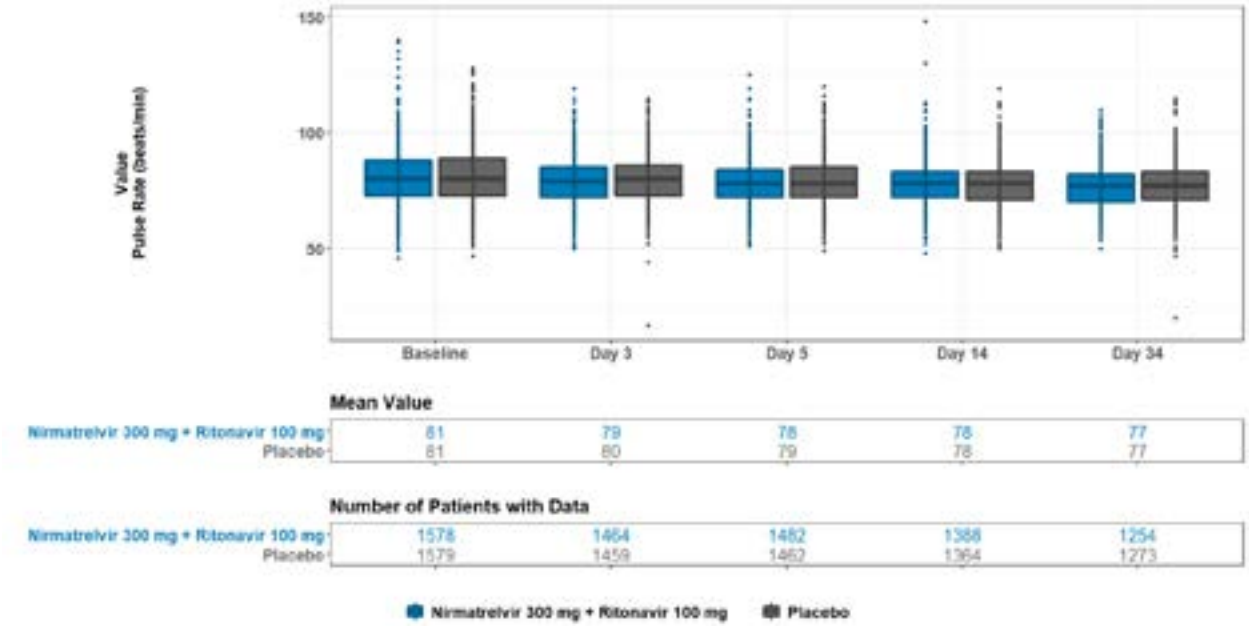


Mean Value					
C4671002 Nirmatrelvir 300 mg + Ritonavir 100 mg	79	78	78	78	77
C4671002 Placebo	80	79	78	77	77

Number of Patients with Data					
C4671002 Nirmatrelvir 300 mg + Ritonavir 100 mg	540	488	515	479	441
C4671002 Placebo	526	471	500	473	438

C4671002 Nirmatrelvir 300 mg + Ritonavir 100 mg C4671002 Placebo

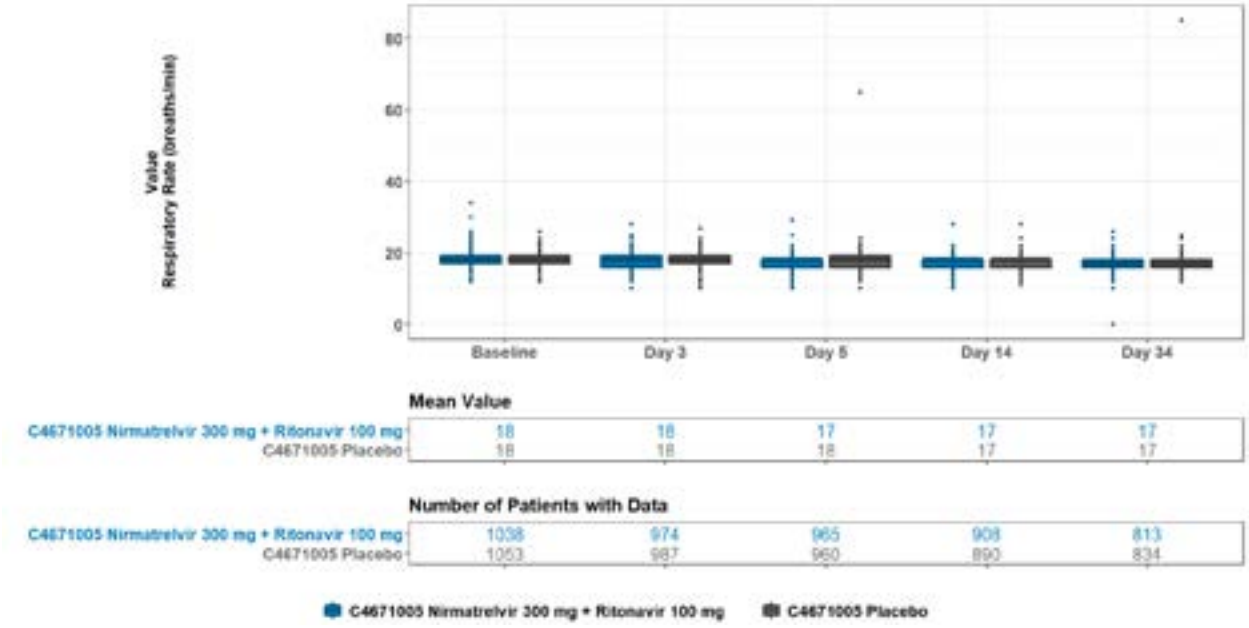
EPIC-HR and EPIC-SR



Source: advs.xpt; Software: R.
Note: Boxes span the interquartile range (25th to 75th percentile); horizontal lines indicate median; whiskers indicate 1.5X the interquartile range; individual outliers are those beyond this range.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
Note: C4671002 = EPIC-SR, C4671005 = EPIC-HR.

Figure 66. Median and Interquartile Range of Respiratory Rate Over Time by Treatment Arm, Safety Population, EPIC-HR and EPIC-SR

EPIC-HR



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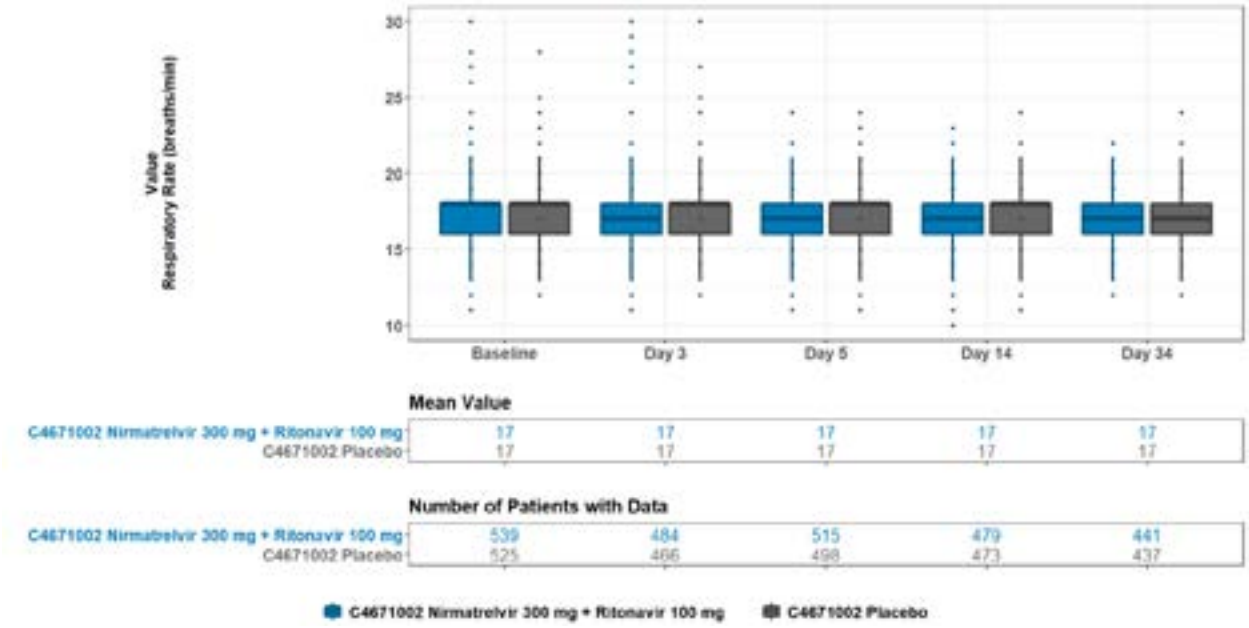
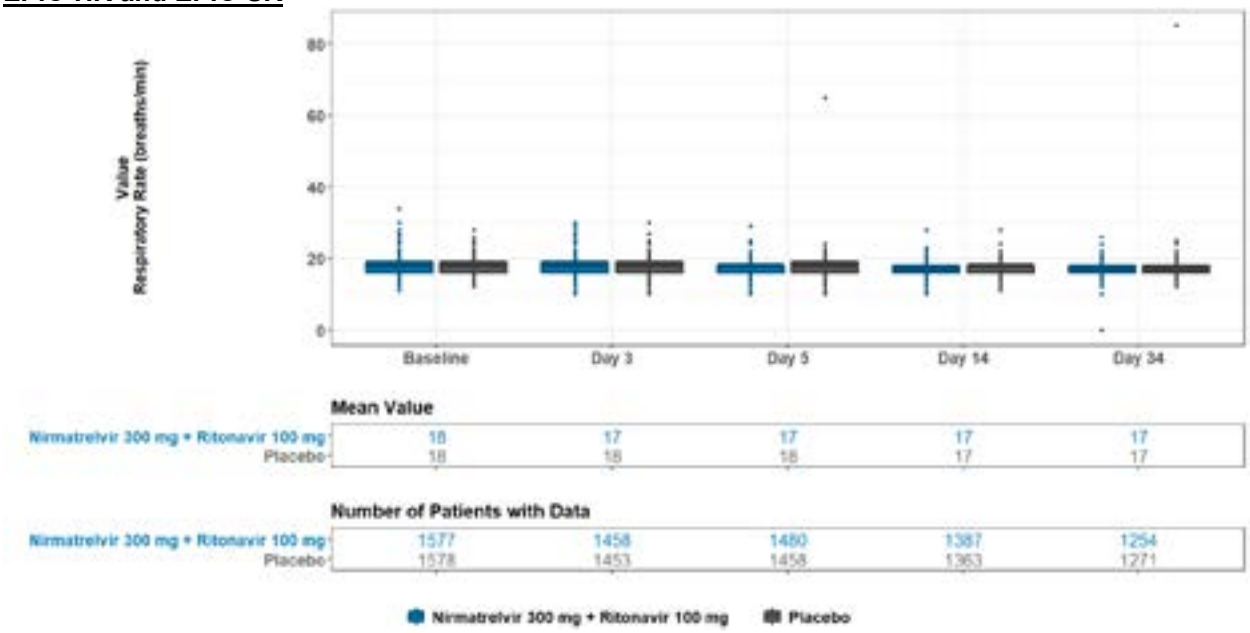
EPIC-SR



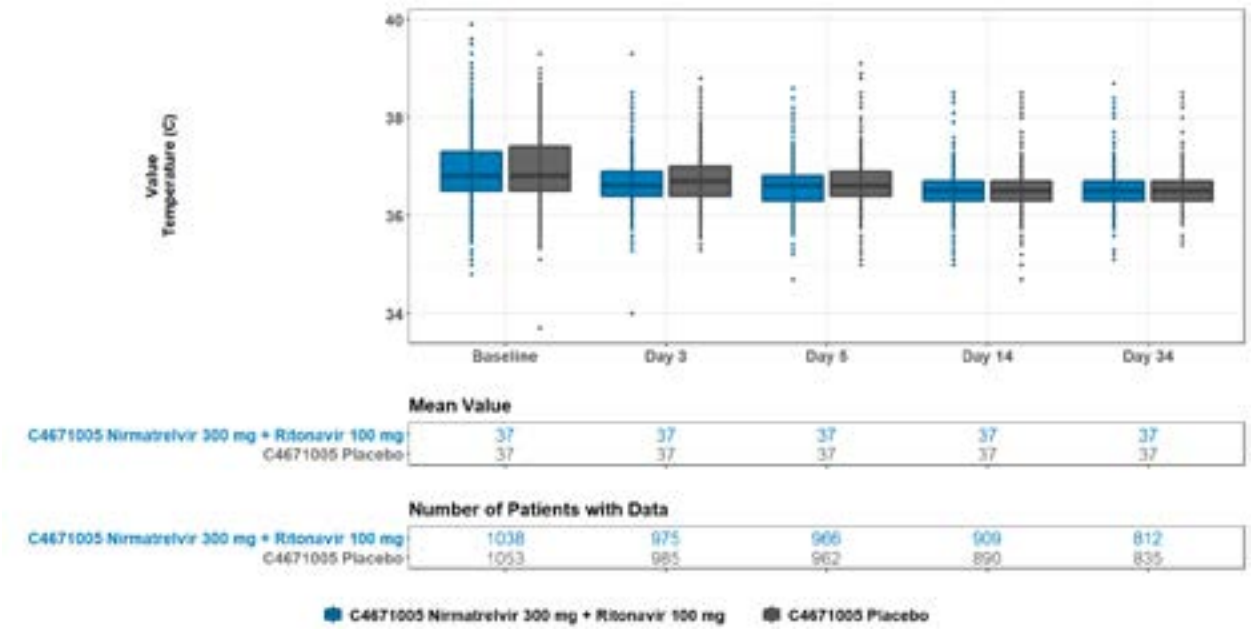
EPIC-HR and EPIC-SR



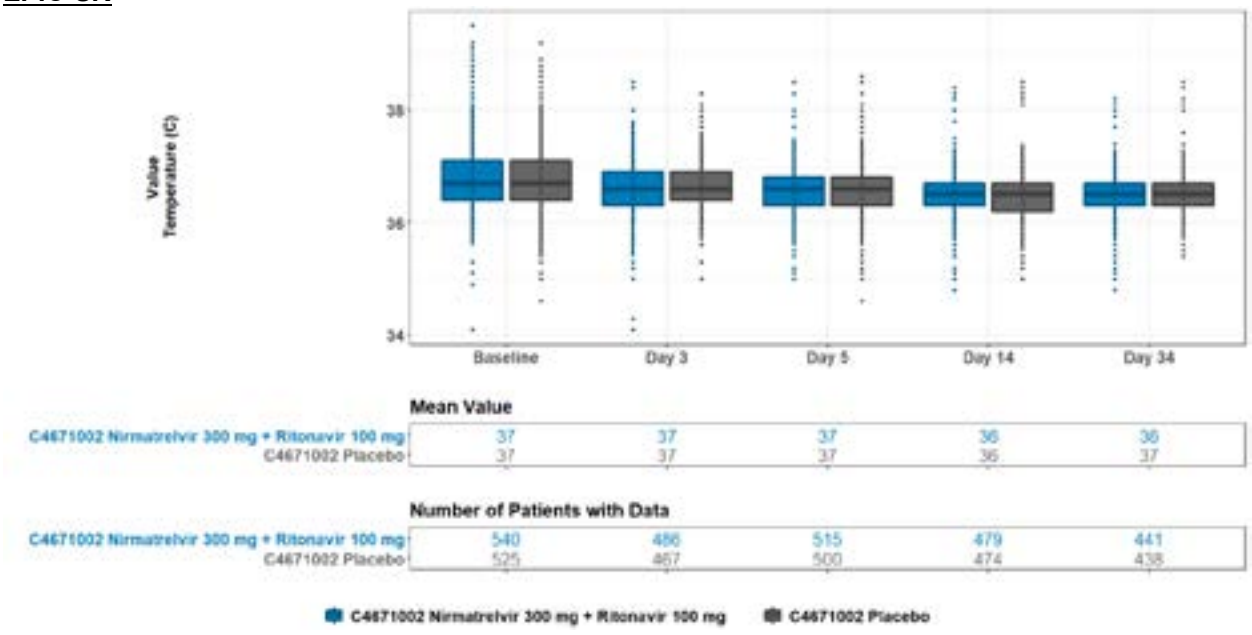
Source: advs.xpt; Software: R.
Note: Boxes span the interquartile range (25th to 75th percentile); horizontal lines indicate median; whiskers indicate 1.5X the interquartile range; individual outliers are those beyond this range.
Note: Participants enrolled in EPIC-SR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-HR at sites 1281 and 1488 (including those switched to 1282) are excluded.
Note: C4671002 = EPIC-SR, C4671005 = EPIC-HR.

Figure 67. Median and Interquartile Range of Body Temperature Over Time by Treatment Arm, Safety Population, EPIC-HR and EPIC-SR

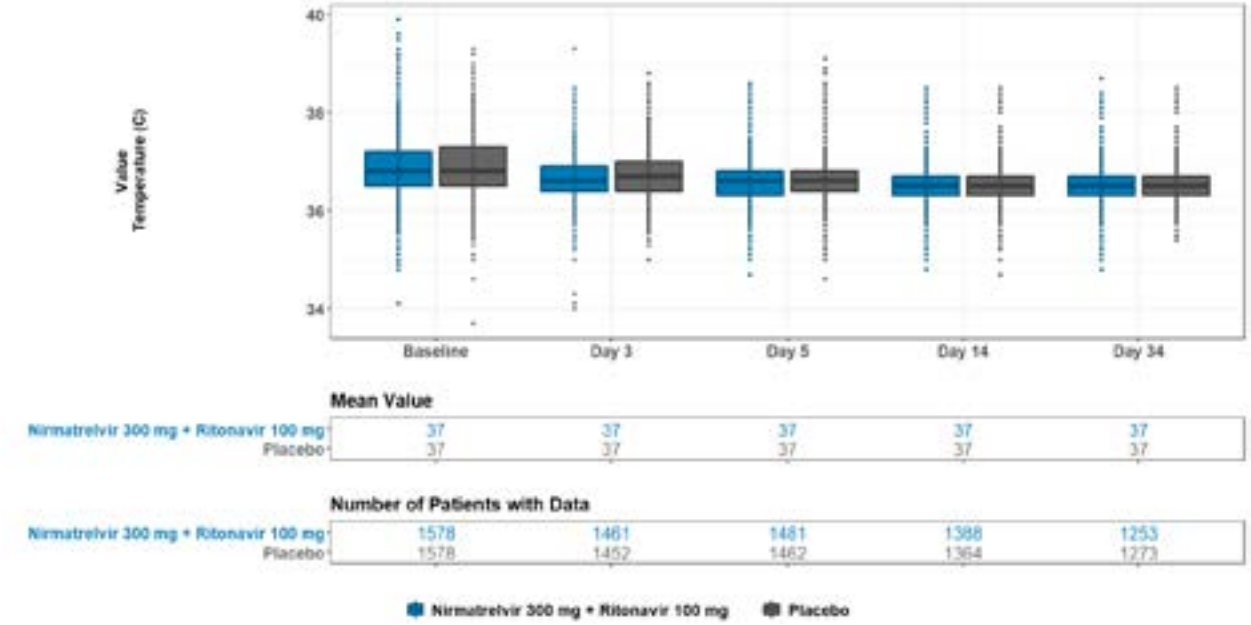
EPIC-HR



EPIC-SR



EPIC-HR and EPIC-SR



Source: advs.xpt; Software: R.
Note: Boxes span the interquartile range (25th to 75th percentile); horizontal lines indicate median; whiskers indicate 1.5X the interquartile range; individual outliers are those beyond this range.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
Note: Extreme outlier values are excluded.
Note: C4671002 = EPIC-SR, C4671005 = EPIC-HR.

17.8. Demographic Subgroup Analysis, EPIC-HR and EPIC-SR

An overview of adverse events by demographic subgroups in EPIC-HR and EPIC-SR was presented in Section 7.6.1.9. Table 157 and Table 158 describe adverse events by demographic subgroups in EPIC-HR and EPIC-SR.

Table 157. Overview of Adverse Events by Demographic Subgroup, Safety Population, EPIC-HR and EPIC-SR

	EPIC-HR			EPIC-SR			Pooled		
Characteristic	PAXLOVID N=1038 n/N_S (%)	Placebo N=1053 n/N_S (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n/N_S (%)	Placebo N=528 n/N_S (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n/N_S (%)	Placebo N=1581 n/N_S (%)	Risk Difference (%) (95% CI)
Sex, n (%)									
Female	125/522 (23.9)	131/515 (25.4)	-1.5 (-6.7, 3.8)	56/275 (20.4)	75/284 (26.4)	-6.0 (-13.0, 1.0)	181/797 (22.7)	206/799 (25.8)	-3.1 (-7.3, 1.1)
Male	103/516 (20.0)	125/538 (23.2)	-3.3 (-8.2, 1.7)	70/265 (26.4)	51/244 (20.9)	5.5 (-1.8, 12.9)	173/781 (22.2)	176/782 (22.5)	-0.4 (-4.5, 3.8)
Age group, years, n (%)									
18 to 44	93/534 (17.4)	89/499 (17.8)	-0.4 (-5.1, 4.2)	65/328 (19.8)	65/310 (21.0)	-1.2 (-7.4, 5.1)	158/862 (18.3)	154/809 (19.0)	-0.7 (-4.4, 3.0)
45 to 59	62/306 (20.3)	82/316 (25.9)	-5.7 (-12.3, 0.9)	39/157 (24.8)	45/169 (26.6)	-1.8 (-11.3, 7.7)	101/463 (21.8)	127/485 (26.2)	-4.4 (-9.8, 1.1)
60 to 64	19/69 (27.5)	36/104 (34.6)	-7.1 (-21.0, 6.9)	6/19 (31.6)	6/24 (25.0)	6.6 (-20.6, 33.7)	25/88 (28.4)	42/128 (32.8)	-4.4 (-16.9, 8.0)
65 to 74	35/96 (36.5)	35/103 (34.0)	2.5 (-10.8, 15.8)	13/30 (43.3)	6/15 (40.0)	3.3 (-27.1, 33.8)	48/126 (38.1)	41/118 (34.7)	3.3 (-8.7, 15.4)
≥75	19/33 (57.6)	14/31 (45.2)	12.4 (-11.9, 36.7)	3/6 (50.0)	4/10 (40.0)	10.0 (-40.2, 60.2)	22/39 (56.4)	18/41 (43.9)	12.5 (-9.2, 34.3)
Age group ≥65, years, n (%)									
≥65	54/129 (41.9)	49/134 (36.6)	5.3 (-6.5, 17.1)	16/36 (44.4)	10/25 (40.0)	4.4 (-20.7, 29.6)	70/165 (42.4)	59/159 (37.1)	5.3 (-5.3, 16.0)
Race, n (%)									
American Indian or Alaska Native	18/95 (18.9)	19/94 (20.2)	-1.3 (-12.6, 10.0)	2/23 (8.7)	9/18 (50.0)	-41.3 (-67.1, -15.5)	20/118 (16.9)	28/112 (25.0)	-8.1 (-18.5, 2.4)
Asian	43/153 (28.1)	30/156 (19.2)	8.9 (-0.6, 18.3)	14/67 (20.9)	14/70 (20.0)	0.9 (-12.6, 14.4)	57/220 (25.9)	44/226 (19.5)	6.4 (-1.3, 14.2)
Black or African American	8/52 (15.4)	8/35 (22.9)	-7.5 (-24.5, 9.5)	4/19 (21.1)	4/18 (22.2)	-1.2 (-27.7, 25.4)	12/71 (16.9)	12/53 (22.6)	-5.7 (-20.0, 8.5)
Multiple	0/1 (0)	0/2 (0)	0 (0, 0)	0/0 (NA)	0/0 (NA)	NA	0/1 (0)	0/2 (0)	0 (0, 0)
Unknown	0/1 (0)	1/1 (100)	-100.0 (-100.0, -100.0)	1/1 (100)	1/2 (50.0)	50.0 (-19.3, 119.3)	1/2 (50.0)	2/3 (66.7)	-16.7 (-104.1, 70.8)
White	158/728 (21.7)	195/756 (25.8)	-4.1 (-8.4, 0.2)	102/425 (24.0)	95/413 (23.0)	1.0 (-4.7, 6.7)	260/1153 (22.5)	290/1169 (24.8)	-2.3 (-5.7, 1.2)
Missing	1/8 (12.5)	3/9 (33.3)	-20.8 -59.2, 17.6)	3/5 (60.0)	3/7 (42.9)	17.1 (-39.3, 73.6)	4/13 (30.8)	6/16 (37.5)	-6.7 (-41.3, 27.8)

Characteristic	EPIC-HR PAXLOVID N=1038 n/N_s (%)	EPIC-HR Placebo N=1053 n/N_s (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n/N_s (%)	EPIC-SR Placebo N=528 n/N_s (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n/N_s (%)	Pooled Placebo N=1581 n/N_s (%)	Pooled Risk Difference (%) (95% CI)
Ethnicity, n (%)									
Hispanic or Latino	51/425 (12.0)	71/439 (16.2)	-4.2 (-8.8, 0.5)	28/233 (12.0)	43/224 (19.2)	-7.2 (-13.8, -0.5)	79/658 (12.0)	114/663 (17.2)	-5.2 (-9.0, -1.4)
Not Hispanic or Latino	174/608 (28.6)	182/607 (30.0)	-1.4 (-6.5, 3.8)	96/304 (31.6)	81/299 (27.1)	4.5 (-2.8, 11.7)	270/912 (29.6)	263/906 (29.0)	0.6 (-3.6, 4.8)
Not Reported	3/5 (60.0)	3/7 (42.9)	17.1 (-39.3, 73.6)	2/3 (66.7)	2/5 (40.0)	26.7 (-41.8, 95.1)	5/8 (62.5)	5/12 (41.7)	20.8 (-22.8, 64.5)

Source: adae.xpt; Software: R.
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event; N_s, total number of patients for each specific subgroup and were assigned to that specific arm

Table 158. Overview of Serious Adverse Events by Demographic Subgroup, Safety Population, EPIC-HR and EPIC-SR

Characteristic	EPIC-HR PAXLOVID N=1038 n/N_s (%)	EPIC-HR Placebo N=1053 n/N_s (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n/N_s (%)	EPIC-SR Placebo N=528 n/N_s (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n/N_s (%)	Pooled Placebo N=1581 n/N_s (%)	Pooled Risk Difference (%) (95% CI)
Sex, n (%)									
Female	8/522 (1.5)	29/515 (5.6)	-4.1 (-6.4, -1.8)	3/275 (1.1)	7/284 (2.5)	-1.4 (-3.6, 0.8)	11/797 (1.4)	36/799 (4.5)	-3.1 (-4.8, -1.5)
Male	10/516 (1.9)	42/538 (7.8)	-5.9 (-8.4, -3.3)	5/265 (1.9)	4/244 (1.6)	0.2 (-2.0, 2.5)	15/781 (1.9)	46/782 (5.9)	-4.0 (-5.9, -2.1)
Age group, years, n (%)									
18 to 44	3/534 (0.6)	13/499 (2.6)	-2.0 (-3.6, -0.5)	1/328 (0.3)	5/310 (1.6)	-1.3 (-2.8, 0.2)	4/862 (0.5)	18/809 (2.2)	-1.8 (-2.9, -0.6)
45 to 59	10/306 (3.3)	27/316 (8.5)	-5.3 (-8.9, -1.6)	5/157 (3.2)	3/169 (1.8)	1.4 (-2.0, 4.8)	15/463 (3.2)	30/485 (6.2)	-2.9 (-5.6, -0.3)
60 to 64	1/69 (1.4)	10/104 (9.6)	-8.2 (-14.5, -1.8)	1/19 (5.3)	0/24 (0)	5.3 (-4.8, 15.3)	2/88 (2.3)	10/128 (7.8)	-5.5 (-11.1, 0.1)
65 to 74	3/96 (3.1)	15/103 (14.6)	-11.4 (-19.1, -3.8)	1/30 (3.3)	2/15 (13.3)	-10.0 (-28.4, 8.4)	4/126 (3.2)	17/118 (14.4)	-11.2 (-18.3, -4.2)
≥75	1/33 (3.0)	6/31 (19.4)	-16.3 (-31.4, -1.2)	0/6 (0)	1/10 (10.0)	-10.0 (-28.6, 8.6)	1/39 (2.6)	7/41 (17.1)	-14.5 (-27.0, -2.0)
Age group ≥65, years, n (%)									
≥65	4/129 (3.1)	21/134 (15.7)	-12.6 (-19.4, -5.7)	1/36 (2.8)	3/25 (12.0)	-9.2 (-23.0, 4.6)	5/165 (3.0)	24/159 (15.1)	-12.1 (-18.2, -5.9)
Race, n (%)									
American Indian or Alaska Native	1/95 (1.1)	5/94 (5.3)	-4.3 (-9.2, 0.7)	0/23 (0)	2/18 (11.1)	-11.1 (-25.6, 3.4)	1/118 (0.8)	7/112 (6.2)	-5.4 (-10.2, -0.6)
Asian	2/153 (1.3)	7/156 (4.5)	-3.2 (-6.9, 0.5)	1/67 (1.5)	0/70 (0)	1.5 (-1.4, 4.4)	3/220 (1.4)	7/226 (3.1)	-1.7 (-4.5, 1.0)
Black or African American	1/52 (1.9)	2/35 (5.7)	-3.8 (-12.3, 4.8)	0/19 (0)	0/18 (0)	0 (0, 0)	1/71 (1.4)	2/53 (3.8)	-2.4 (-8.2, 3.5)
Multiple	0/1 (0)	0/2 (0)	0 (0, 0)	0/0 (NA)	0/0 (NA)	NA	0/1 (0)	0/2 (0)	0 (0, 0)
Unknown	0/1 (0)	0/1 (0)	0 (0, 0)	0/1 (0)	0/2 (0)	0 (0, 0)	0/2 (0)	0/3 (0)	0 (0, 0)
White	14/728 (1.9)	56/756 (7.4)	-5.5 (-7.6, -3.4)	7/425 (1.6)	9/413 (2.2)	-0.5 (-2.4, 1.3)	21/1153 (1.8)	65/1169 (5.6)	-3.7 (-5.3, -2.2)
Missing	0/8 (0)	1/9 (11.1)	-11.1 (-31.6, 9.4)	0/5 (0)	0/7 (0)	0 (0, 0)	0/13 (0)	1/16 (6.2)	-6.2 (-18.1, 5.6)
Ethnicity, n (%)									

	EPIC-HR			EPIC-SR			Pooled		
Characteristic	PAXLOVID N=1038 n/N_s (%)	Placebo N=1053 n/N_s (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n/N_s (%)	Placebo N=528 n/N_s (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n/N_s (%)	Placebo N=1581 n/N_s (%)	Risk Difference (%) (95% CI)
Hispanic or Latino	3/425 (0.7)	13/439 (3.0)	-2.3 (-4.0, -0.5)	1/233 (0.4)	5/224 (2.2)	-1.8 (-3.9, 0.3)	4/658 (0.6)	18/663 (2.7)	-2.1 (-3.5, -0.7)
Not Hispanic or Latino	15/608 (2.5)	57/607 (9.4)	-6.9 (-9.6, -4.3)	7/304 (2.3)	6/299 (2.0)	0.3 (-2.0, 2.6)	22/912 (2.4)	63/906 (7.0)	-4.5 (-6.5, -2.6)
Not Reported	0/5 (0)	1/7 (14.3)	-14.3 (-40.2, 11.6)	0/3 (0)	0/5 (0)	0 (0, 0)	0/8 (0)	1/12 (8.3)	-8.3 (-24.0, 7.3)

Source: adae.xpt; Software: R.
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event; N_s, total number of patients for each specific subgroup and were assigned to that specific arm

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17.9. Adverse Event Assessment, EPIC-PEP

Overviews of adverse events in EPIC-PEP were provided in Sections 7.6.2.3, 7.6.2.4, and 7.6.2.5. Assessment of adverse using FMQs to evaluate SAEs (Table 159), AEs leading to treatment discontinuation (Table 160), and patients with adverse events (Table 161 and Table 162) were similar to the respective assessments using preferred terms.

Table 159. Patients With Serious Adverse Events[1] by System Organ Class and FDA Medical Query (Narrow), Safety Population, EPIC-PEP[2]

System Organ Class FMQ (Narrow)[4]	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Hepatobiliary disorders (SOC)						
Cholecystitis	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Infections and infestations (SOC)						
Bacterial Infection	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Viral Infection	1 (0.1)	1 (0.1)	1 (0.1)	-0.0 (-0.3, 0.3)	-0.0 (-0.3, 0.3)	-0.0 (-0.3, 0.3)
Musculoskeletal and connective tissue disorders (SOC)						
Fracture	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)

Source: adae.xpt; Software: R.
Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
[1]Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 38 visit. Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
[2]Duration of treatment is 5 or 10 days.
[3]Difference is shown between PAXLOVID vs placebo
[4]Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC. Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.
Abbreviations: FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Table 160. Patients With Adverse Events[1] Leading to Treatment Discontinuation by System Organ Class and FDA Medical Query (Narrow), Safety Population, EPIC-PEP[2]

System Organ Class FMQ (Narrow)[4]	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Gastrointestinal disorders (SOC)						
Nausea	2 (0.2)	1 (0.1)	0	0.2 (-0.1, 0.5)	0.1 (-0.1, 0.3)	0.1 (-0.3, 0.5)
Dyspepsia	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Hepatobiliary disorders (SOC)						
Hepatic Injury	0	1 (0.1)	2 (0.2)	-0.2 (-0.5, 0.1)	-0.1 (-0.5, 0.3)	-0.1 (-0.3, 0.1)
Infections and infestations (SOC)						
Viral Infection	0	1 (0.1)	2 (0.2)	-0.2 (-0.5, 0.1)	-0.1 (-0.5, 0.3)	-0.1 (-0.3, 0.1)

System Organ Class FMQ (Narrow)[4]	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Nervous system disorders (SOC)						
Headache	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Dysgeusia	2 (0.2)	2 (0.2)	1 (0.1)	0.1 (-0.3, 0.5)	0.1 (-0.3, 0.5)	-0.0 (-0.4, 0.4)
Respiratory, thoracic and mediastinal disorders (SOC)						
Cough	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Skin and subcutaneous tissue disorders (SOC)						
Rash	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Vascular disorders (SOC)						
Hemorrhage	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)

Source: adae.xpt; Software: R.
Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
[1]Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 38 visit.
[2]Duration of treatment is 5 or 10 days.
[3]Difference is shown between PAXLOVID vs placebo
[4]Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC. Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table. For specific preferred terms under each FMQ, see the table "Serious Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…"
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Table 161. Patients With Adverse Events[1] by System Organ Class and FDA Medical Query (Narrow), Safety Population, EPIC-PEP[2]

System Organ Class FMQ[4] (Narrow)	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Blood and lymphatic system disorders (SOC)						
Anemia	5 (0.5)	3 (0.3)	3 (0.3)	0.2 (-0.4, 0.8)	-0.0 (-0.5, 0.5)	0.2 (-0.4, 0.8)
Thrombocytopenia	1 (0.1)	0	1 (0.1)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.1)	0.1 (-0.1, 0.3)
Leukopenia	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Cardiac disorders (SOC)						
Arrhythmia	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Systemic Hypertension	2 (0.2)	3 (0.3)	1 (0.1)	0.1 (-0.3, 0.5)	0.2 (-0.2, 0.6)	-0.1 (-0.6, 0.4)
Endocrine disorders (SOC)						
Hyperglycemia	5 (0.5)	2 (0.2)	4 (0.4)	0.1 (-0.5, 0.8)	-0.2 (-0.8, 0.3)	0.3 (-0.2, 0.9)

System Organ Class FMQ[4] (Narrow)	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Gastrointestinal disorders (SOC)						
Diarrhea	23 (2.5)	22 (2.4)	15 (1.7)	0.9 (-0.5, 2.2)	0.7 (-0.6, 2.0)	0.1 (-1.3, 1.5)
Vomiting	7 (0.8)	3 (0.3)	3 (0.3)	0.4 (-0.2, 1.1)	-0.0 (-0.5, 0.5)	0.4 (-0.2, 1.1)
Nausea	16 (1.8)	12 (1.3)	14 (1.6)	0.2 (-1.0, 1.4)	-0.2 (-1.3, 0.9)	0.4 (-0.7, 1.6)
Dry Mouth	1 (0.1)	1 (0.1)	0	0.1 (-0.1, 0.3)	0.1 (-0.1, 0.3)	-0.0 (-0.3, 0.3)
Dyspepsia	3 (0.3)	5 (0.5)	2 (0.2)	0.1 (-0.4, 0.6)	0.3 (-0.2, 0.9)	-0.2 (-0.8, 0.4)
Abdominal Pain	2 (0.2)	1 (0.1)	2 (0.2)	-0.0 (-0.4, 0.4)	-0.1 (-0.5, 0.3)	0.1 (-0.3, 0.5)
General disorders and administration site conditions (SOC)						
Dizziness	2 (0.2)	0	1 (0.1)	0.1 (-0.3, 0.5)	-0.1 (-0.3, 0.1)	0.2 (-0.1, 0.5)
Pyrexia	1 (0.1)	3 (0.3)	6 (0.7)	-0.6 (-1.1, 0.0)	-0.3 (-1.0, 0.3)	-0.2 (-0.6, 0.2)
Fatigue	13 (1.4)	10 (1.1)	18 (2.0)	-0.6 (-1.8, 0.6)	-0.9 (-2.0, 0.2)	0.3 (-0.7, 1.4)
Hepatobiliary disorders (SOC)						
Cholecystitis	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Hepatic Injury	3 (0.3)	7 (0.8)	12 (1.3)	-1.0 (-1.8, -0.2)*	-0.6 (-1.5, 0.4)	-0.4 (-1.1, 0.2)
Infections and infestations (SOC)						
Nasopharyngitis	16 (1.8)	11 (1.2)	7 (0.8)	1.0 (-0.1, 2.0)	0.4 (-0.5, 1.3)	0.5 (-0.6, 1.7)
Bacterial Infection	2 (0.2)	0	1 (0.1)	0.1 (-0.3, 0.5)	-0.1 (-0.3, 0.1)	0.2 (-0.1, 0.5)
Pneumonia	0	1 (0.1)	1 (0.1)	-0.1 (-0.3, 0.1)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.1)
Viral Infection	35 (3.8)	32 (3.5)	45 (5.0)	-1.2 (-3.1, 0.7)	-1.5 (-3.4, 0.4)	0.3 (-1.4, 2.1)
Metabolism and nutrition disorders (SOC)						
Lipid Disorder	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Musculoskeletal and connective tissue disorders (SOC)						
Fracture	2 (0.2)	0	0	0.2 (-0.1, 0.5)	0 (0, 0)	0.2 (-0.1, 0.5)
Back Pain	1 (0.1)	2 (0.2)	1 (0.1)	-0.0 (-0.3, 0.3)	0.1 (-0.3, 0.5)	-0.1 (-0.5, 0.3)
Myalgia	3 (0.3)	2 (0.2)	9 (1.0)	-0.7 (-1.4, 0.1)	-0.8 (-1.5, -0.1)*	0.1 (-0.4, 0.6)
Nervous system disorders (SOC)						
Dysgeusia	54 (5.9)	63 (6.9)	6 (0.7)	5.3 (3.6, 6.9)*	6.2 (4.5, 8.0)*	-1.0 (-3.2, 1.3)
Somnolence	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Syncope	0	1 (0.1)	1 (0.1)	-0.1 (-0.3, 0.1)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.1)
Headache	15 (1.6)	17 (1.9)	29 (3.2)	-1.6 (-3.0, -0.2)*	-1.4 (-2.8, 0.1)	-0.2 (-1.4, 1.0)
Psychiatric disorders (SOC)						
Study Agent Abuse Potential	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Arthritis	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Insomnia	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)

System Organ Class FMQ[4] (Narrow)	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Renal and urinary disorders (SOC)						
Renal and Urinary Tract Infection	1 (0.1)	0	1 (0.1)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.1)	0.1 (-0.1, 0.3)
Acute Kidney Injury	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Reproductive system and breast disorders (SOC)						
Abnormal Uterine Bleeding	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Excessive Menstrual Bleeding	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Respiratory, thoracic and mediastinal disorders (SOC)						
Dyspnea	4 (0.4)	2 (0.2)	3 (0.3)	0.1 (-0.5, 0.7)	-0.1 (-0.6, 0.4)	0.2 (-0.3, 0.7)
Bronchospasm	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Cough	10 (1.1)	2 (0.2)	12 (1.3)	-0.2 (-1.3, 0.8)	-1.1 (-1.9, -0.3)*	0.9 (0.1, 1.6)*
Skin and subcutaneous tissue disorders (SOC)						
Rash	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Erythema	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Pruritus	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Vascular disorders (SOC)						
Hemorrhage	3 (0.3)	3 (0.3)	0	0.3 (-0.0, 0.7)	0.3 (-0.0, 0.7)	-0.0 (-0.5, 0.5)

Source: adae.xpt; Software: R.
Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
[1]Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 38 visit.
[2]Duration of treatment is 5 or 10 days.
[3]Difference is shown between PAXLOVID vs placebo
[4]Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC. For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…"
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Table 162. Patients With Adverse Events[1] by System Organ Class and FDA Medical Query (Broad), Safety Population, EPIC-PEP[2]

System Organ Class FMQ (Broad)[4]	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs. PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Blood and lymphatic system disorders (SOC)						
Anemia	5 (0.5)	3 (0.3)	3 (0.3)	0.2 (-0.4, 0.8)	-0.0 (-0.5, 0.5)	0.2 (-0.4, 0.8)
Thrombocytopenia	1 (0.1)	0	1 (0.1)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.1)	0.1 (-0.1, 0.3)
Leukopenia	2 (0.2)	3 (0.3)	2 (0.2)	-0.0 (-0.4, 0.4)	0.1 (-0.4, 0.6)	-0.1 (-0.6, 0.4)

System Organ Class FMQ (Broad)[4]	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs. PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Cardiac disorders (SOC)						
Systemic hypertension	2 (0.2)	3 (0.3)	1 (0.1)	0.1 (-0.3, 0.5)	0.2 (-0.2, 0.6)	-0.1 (-0.6, 0.4)
Arrhythmia	3 (0.3)	2 (0.2)	2 (0.2)	0.1 (-0.4, 0.6)	-0.0 (-0.4, 0.4)	0.1 (-0.4, 0.6)
Heart failure	4 (0.4)	2 (0.2)	3 (0.3)	0.1 (-0.5, 0.7)	-0.1 (-0.6, 0.4)	0.2 (-0.3, 0.7)
Acute coronary syndrome	12 (1.3)	15 (1.6)	13 (1.4)	-0.1 (-1.2, 0.9)	0.2 (-0.9, 1.3)	-0.3 (-1.4, 0.8)
Ear and labyrinth disorders (SOC)						
Vertigo	2 (0.2)	0	1 (0.1)	0.1 (-0.3, 0.5)	-0.1 (-0.3, 0.1)	0.2 (-0.1, 0.5)
Endocrine disorders (SOC)						
Hyperglycemia	5 (0.5)	2 (0.2)	5 (0.6)	-0.0 (-0.7, 0.7)	-0.3 (-0.9, 0.2)	0.3 (-0.2, 0.9)
Diabetic ketoacidosis	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Hypoglycemia	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Gastrointestinal disorders (SOC)						
Diarrhea	24 (2.6)	23 (2.5)	16 (1.8)	0.8 (-0.5, 2.2)	0.7 (-0.6, 2.1)	0.1 (-1.3, 1.6)
Vomiting	17 (1.9)	16 (1.8)	15 (1.7)	0.2 (-1.0, 1.4)	0.1 (-1.1, 1.3)	0.1 (-1.1, 1.3)
Dry mouth	1 (0.1)	1 (0.1)	0	0.1 (-0.1, 0.3)	0.1 (-0.1, 0.3)	-0.0 (-0.3, 0.3)
Nausea	16 (1.8)	15 (1.6)	15 (1.7)	0.1 (-1.1, 1.3)	-0.0 (-1.2, 1.2)	0.1 (-1.1, 1.3)
Abdominal pain	2 (0.2)	1 (0.1)	2 (0.2)	-0.0 (-0.4, 0.4)	-0.1 (-0.5, 0.3)	0.1 (-0.3, 0.5)
Dyspepsia	5 (0.5)	7 (0.8)	6 (0.7)	-0.1 (-0.8, 0.6)	0.1 (-0.7, 0.9)	-0.2 (-1.0, 0.5)
General disorders and administration site conditions (SOC)						
Dizziness	2 (0.2)	0	1 (0.1)	0.1 (-0.3, 0.5)	-0.1 (-0.3, 0.1)	0.2 (-0.1, 0.5)
Fall	2 (0.2)	2 (0.2)	2 (0.2)	-0.0 (-0.4, 0.4)	-0.0 (-0.4, 0.4)	-0.0 (-0.4, 0.4)
Pyrexia	5 (0.5)	3 (0.3)	8 (0.9)	-0.3 (-1.1, 0.4)	-0.6 (-1.3, 0.2)	0.2 (-0.4, 0.8)
Fatigue	14 (1.5)	10 (1.1)	18 (2.0)	-0.5 (-1.7, 0.7)	-0.9 (-2.0, 0.2)	0.4 (-0.6, 1.5)
Hepatobiliary disorders (SOC)						
Cholecystitis	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Hepatic failure	2 (0.2)	0	1 (0.1)	0.1 (-0.3, 0.5)	-0.1 (-0.3, 0.1)	0.2 (-0.1, 0.5)
Hepatic injury	4 (0.4)	8 (0.9)	14 (1.6)	-1.1 (-2.0, -0.2)*	-0.7 (-1.7, 0.3)	-0.4 (-1.2, 0.3)
Immune system disorders (SOC)						
Hypersensitivity	1 (0.1)	3 (0.3)	2 (0.2)	-0.1 (-0.5, 0.3)	0.1 (-0.4, 0.6)	-0.2 (-0.6, 0.2)
Infections and infestations (SOC)						
Nasopharyngitis	16 (1.8)	11 (1.2)	7 (0.8)	1.0 (-0.1, 2.0)	0.4 (-0.5, 1.3)	0.5 (-0.6, 1.7)
Bacterial infection	2 (0.2)	1 (0.1)	2 (0.2)	-0.0 (-0.4, 0.4)	-0.1 (-0.5, 0.3)	0.1 (-0.3, 0.5)
Pneumonia	3 (0.3)	4 (0.4)	8 (0.9)	-0.6 (-1.3, 0.2)	-0.5 (-1.2, 0.3)	-0.1 (-0.7, 0.5)
Viral infection	56 (6.1)	51 (5.6)	67 (7.5)	-1.3 (-3.6, 1.0)	-1.9 (-4.1, 0.4)	0.5 (-1.6, 2.7)

System Organ Class FMQ (Broad)[4]	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs. PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Metabolism and nutrition disorders (SOC)						
Lipid disorder	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Musculoskeletal and connective tissue disorders (SOC)						
Fracture	2 (0.2)	0	0	0.2 (-0.1, 0.5)	0 (0, 0)	0.2 (-0.1, 0.5)
Arthralgia	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Back Pain	1 (0.1)	2 (0.2)	2 (0.2)	-0.1 (-0.5, 0.3)	-0.0 (-0.4, 0.4)	-0.1 (-0.5, 0.3)
Rhabdomyolysis	12 (1.3)	15 (1.6)	13 (1.4)	-0.1 (-1.2, 0.9)	0.2 (-0.9, 1.3)	-0.3 (-1.4, 0.8)
Myalgia	3 (0.3)	3 (0.3)	9 (1.0)	-0.7 (-1.4, 0.1)	-0.7 (-1.4, 0.1)	-0.0 (-0.5, 0.5)
Nervous system disorders (SOC)						
Dysgeusia	55 (6.0)	63 (6.9)	7 (0.8)	5.3 (3.6, 6.9)*	6.1 (4.4, 7.9)*	-0.9 (-3.1, 1.4)
Somnolence	3 (0.3)	3 (0.3)	1 (0.1)	0.2 (-0.2, 0.6)	0.2 (-0.2, 0.6)	-0.0 (-0.5, 0.5)
Confusional state	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Syncope	2 (0.2)	2 (0.2)	2 (0.2)	-0.0 (-0.4, 0.4)	-0.0 (-0.4, 0.4)	-0.0 (-0.4, 0.4)
Headache	15 (1.6)	17 (1.9)	29 (3.2)	-1.6 (-3.0, -0.2)*	-1.4 (-2.8, 0.1)	-0.2 (-1.4, 1.0)
Psychiatric disorders (SOC)						
Anxiety	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Study agent abuse potential	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Depression	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Insomnia	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Self-harm	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Arthritis	0	0	2 (0.2)	-0.2 (-0.5, 0.1)	-0.2 (-0.5, 0.1)	0 (0, 0)
Renal and urinary disorders (SOC)						
Acute kidney injury	10 (1.1)	7 (0.8)	8 (0.9)	0.2 (-0.7, 1.1)	-0.1 (-1.0, 0.7)	0.3 (-0.6, 1.2)
Urinary retention	0	1 (0.1)	1 (0.1)	-0.1 (-0.3, 0.1)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.1)
Renal and urinary tract infection	1 (0.1)	1 (0.1)	2 (0.2)	-0.1 (-0.5, 0.3)	-0.1 (-0.5, 0.3)	-0.0 (-0.3, 0.3)
Reproductive system and breast disorders (SOC)						
Abnormal uterine bleeding	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Excessive menstrual bleeding	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)

System Organ Class FMQ (Broad)[4]	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs. PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Respiratory, thoracic and mediastinal disorders (SOC)						
Bronchospasm	4 (0.4)	3 (0.3)	3 (0.3)	0.1 (-0.5, 0.7)	-0.0 (-0.5, 0.5)	0.1 (-0.5, 0.7)
Dyspnea	4 (0.4)	2 (0.2)	3 (0.3)	0.1 (-0.5, 0.7)	-0.1 (-0.6, 0.4)	0.2 (-0.3, 0.7)
Respiratory failure	4 (0.4)	2 (0.2)	3 (0.3)	0.1 (-0.5, 0.7)	-0.1 (-0.6, 0.4)	0.2 (-0.3, 0.7)
Pneumonitis	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Cough	10 (1.1)	2 (0.2)	13 (1.4)	-0.4 (-1.4, 0.7)	-1.2 (-2.1, -0.4)*	0.9 (0.1, 1.6)*
Skin and subcutaneous tissue disorders (SOC)						
Rash	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Urticaria	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Erythema	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Pruritus	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Vascular disorders (SOC)						
Hemorrhage	3 (0.3)	3 (0.3)	0	0.3 (-0.0, 0.7)	0.3 (-0.0, 0.7)	-0.0 (-0.5, 0.5)

Source: adae.xpt; Software: R.
Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 38 visit.
[2.] Duration of treatment is 5 or 10 days.
[3.] Difference is shown between PAXLOVID vs placebo
[4.] Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC. For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Broad) and Preferred Term…"
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Table 163 includes the AEs considered by the investigator to be related to study drug in EPIC-PEP. These AEs were previously discussed in Section 7.6.2.5.

Table 163. Patients With Adverse Events Assessed by Investigator as Treatment-Related, Safety Population, Trial EPIC-PEP

Preferred Term	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)
Any treatment-related AE	86 (9.4)	107 (11.7)	49 (5.5)	4.0 (1.6, 6.4)*	6.3 (3.7, 8.9)*	-2.3 (-5.1, 0.5)
Dysgeusia	54 (5.9)	62 (6.8)	6 (0.7)	5.3 (3.6, 6.9)*	6.1 (4.4, 7.9)*	-0.9 (-3.1, 1.4)
Vomiting	6 (0.7)	0	1 (0.1)	0.5 (-0.0, 1.1)	-0.1 (-0.3, 0.1)	0.7 (0.1, 1.2)*
Diarrhea	11 (1.2)	14 (1.5)	7 (0.8)	0.4 (-0.5, 1.3)	0.8 (-0.2, 1.7)	-0.3 (-1.4, 0.7)
Oropharyngeal pain	2 (0.2)	1 (0.1)	0	0.2 (-0.1, 0.5)	0.1 (-0.1, 0.3)	0.1 (-0.3, 0.5)
Blood fibrinogen decreased	3 (0.3)	1 (0.1)	1 (0.1)	0.2 (-0.2, 0.6)	-0.0 (-0.3, 0.3)	0.2 (-0.2, 0.6)
Blood calcium decreased	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Dry mouth	1 (0.1)	1 (0.1)	0	0.1 (-0.1, 0.3)	0.1 (-0.1, 0.3)	-0.0 (-0.3, 0.3)
Dyspnea	1 (0.1)	1 (0.1)	0	0.1 (-0.1, 0.3)	0.1 (-0.1, 0.3)	-0.0 (-0.3, 0.3)
Fibrin D dimer increased	1 (0.1)	4 (0.4)	0	0.1 (-0.1, 0.3)	0.4 (0.0, 0.9)*	-0.3 (-0.8, 0.2)
Gastroesophageal reflux disease	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
International normalized ratio increased	1 (0.1)	1 (0.1)	0	0.1 (-0.1, 0.3)	0.1 (-0.1, 0.3)	-0.0 (-0.3, 0.3)
Pain	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Serum ferritin increased	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Dizziness	2 (0.2)	0	1 (0.1)	0.1 (-0.3, 0.5)	-0.1 (-0.3, 0.1)	0.2 (-0.1, 0.5)
Blood thyroid stimulating hormone increased	6 (0.7)	5 (0.5)	5 (0.6)	0.1 (-0.6, 0.8)	-0.0 (-0.7, 0.7)	0.1 (-0.6, 0.8)
Back pain	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Blood lactate dehydrogenase increased	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Dysuria	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Eosinophilia	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Gastritis	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Gastroenteritis	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Hyperkalemia	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Rash	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Abdominal pain upper	1 (0.1)	1 (0.1)	1 (0.1)	-0.0 (-0.3, 0.3)	-0.0 (-0.3, 0.3)	-0.0 (-0.3, 0.3)
Cough	1 (0.1)	0	1 (0.1)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.1)	0.1 (-0.1, 0.3)
Neutropenia	1 (0.1)	0	1 (0.1)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.1)	0.1 (-0.1, 0.3)
Prothrombin time prolonged	1 (0.1)	1 (0.1)	1 (0.1)	-0.0 (-0.3, 0.3)	-0.0 (-0.3, 0.3)	-0.0 (-0.3, 0.3)
Nausea	12 (1.3)	11 (1.2)	12 (1.3)	-0.0 (-1.1, 1.0)	-0.1 (-1.2, 0.9)	0.1 (-0.9, 1.1)
Chills	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Dyspepsia	0	3 (0.3)	1 (0.1)	-0.1 (-0.3, 0.1)	0.2 (-0.2, 0.6)	-0.3 (-0.7, 0.0)
Fatigue	0	2 (0.2)	1 (0.1)	-0.1 (-0.3, 0.1)	0.1 (-0.3, 0.5)	-0.2 (-0.5, 0.1)
Hepatic enzyme increased	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Platelet count increased	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Pruritus	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)

Preferred Term	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)
Thrombocytopenia	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
White blood cell count decreased	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Aspartate aminotransferase increased	1 (0.1)	4 (0.4)	2 (0.2)	-0.1 (-0.5, 0.3)	0.2 (-0.3, 0.7)	-0.3 (-0.8, 0.2)
Nasal congestion	1 (0.1)	0	2 (0.2)	-0.1 (-0.5, 0.3)	-0.2 (-0.5, 0.1)	0.1 (-0.1, 0.3)
Activated partial thromboplastin time prolonged	7 (0.8)	8 (0.9)	8 (0.9)	-0.1 (-1.0, 0.7)	-0.0 (-0.9, 0.9)	-0.1 (-0.9, 0.7)
Pyrexia	0	0	2 (0.2)	-0.2 (-0.5, 0.1)	-0.2 (-0.5, 0.1)	0 (0, 0)
Alanine aminotransferase increased	1 (0.1)	2 (0.2)	3 (0.3)	-0.2 (-0.7, 0.2)	-0.1 (-0.6, 0.4)	-0.1 (-0.5, 0.3)
Myalgia	1 (0.1)	0	3 (0.3)	-0.2 (-0.7, 0.2)	-0.3 (-0.7, 0.0)	0.1 (-0.1, 0.3)
Headache	4 (0.4)	4 (0.4)	6 (0.7)	-0.2 (-0.9, 0.5)	-0.2 (-0.9, 0.5)	-0.0 (-0.6, 0.6)
Blood creatine phosphokinase increased	2 (0.2)	8 (0.9)	5 (0.6)	-0.3 (-0.9, 0.2)	0.3 (-0.5, 1.1)	-0.7 (-1.3, 0.0)
Asthenia	1 (0.1)	0	5 (0.6)	-0.4 (-1.0, 0.1)	-0.6 (-1.0, -0.1)*	0.1 (-0.1, 0.3)

Source: adae.xpt; Software: R.
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
Note: Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 38 visit.
Note: Duration of treatment is 5 or 10 days.
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with adverse event

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17.10. Laboratory Findings, EPIC-PEP

Table 164, Table 165, and Table 166 describe laboratory outliers assessed by the Safety Standard & Figures Integrated Guide (August 2022). An overview was previously provided in Section 7.6.2.6.

Table 164. Patients With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels[1], Safety Population, EPIC-PEP[2]

Laboratory Parameter	PAXLOVID 5 Days N=912 n/N_w (%)	PAXLOVID 10 Days N=911 n/N_w (%)	Placebo N=898 n/N_w (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Sodium, low (mEq/L)						
Level 1 (<132)	11/893 (1.2)	9/891 (1.0)	5/882 (0.6)	0.7 (-0.2, 1.5)	0.4 (-0.4, 1.3)	0.2 (-0.8, 1.2)
Level 2 (<130)	3/893 (0.3)	2/891 (0.2)	2/882 (0.2)	0.1 (-0.4, 0.6)	-0.0 (-0.4, 0.4)	0.1 (-0.4, 0.6)
Level 3 (<125)	2/893 (0.2)	1/891 (0.1)	1/882 (0.1)	0.1 (-0.3, 0.5)	-0.0 (-0.3, 0.3)	0.1 (-0.3, 0.5)
Sodium, high (mEq/L)						
Level 1 (>150)	4/893 (0.4)	1/891 (0.1)	5/882 (0.6)	-0.1 (-0.8, 0.5)	-0.5 (-1.0, 0.1)	0.3 (-0.2, 0.8)
Level 2 (>155)	1/893 (0.1)	0/891 (0)	1/882 (0.1)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.1)	0.1 (-0.1, 0.3)
Level 3 (>160)	0/893 (0)	0/891 (0)	0/882 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Potassium, low (mEq/L)						
Level 1 (<3.6)	60/892 (6.7)	54/891 (6.1)	73/882 (8.3)	-1.6 (-4.0, 0.9)	-2.2 (-4.6, 0.2)	0.7 (-1.6, 2.9)
Level 2 (<3.4)	20/892 (2.2)	17/891 (1.9)	18/882 (2.0)	0.2 (-1.1, 1.5)	-0.1 (-1.4, 1.2)	0.3 (-1.0, 1.7)
Level 3 (<3)	0/892 (0)	1/891 (0.1)	0/882 (0)	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Potassium, high (mEq/L)						
Level 1 (>5.5)	21/892 (2.4)	32/891 (3.6)	37/882 (4.2)	-1.8 (-3.5, -0.2)	-0.6 (-2.4, 1.2)	-1.2 (-2.8, 0.3)
Level 2 (>6)	3/892 (0.3)	9/891 (1.0)	10/882 (1.1)	-0.8 (-1.6, -0.0)	-0.1 (-1.1, 0.8)	-0.7 (-1.4, 0.1)
Level 3 (>6.5)	0/892 (0)	2/891 (0.2)	4/882 (0.5)	-0.5 (-0.9, -0.0)	-0.2 (-0.8, 0.3)	-0.2 (-0.5, 0.1)
Chloride, low (mEq/L)						
Level 1 (<95)	56/893 (6.3)	45/891 (5.1)	32/882 (3.6)	2.6 (0.6, 4.7)	1.4 (-0.5, 3.3)	1.2 (-0.9, 3.4)
Level 2 (<88)	2/893 (0.2)	1/891 (0.1)	1/882 (0.1)	0.1 (-0.3, 0.5)	-0.0 (-0.3, 0.3)	0.1 (-0.3, 0.5)
Level 3 (<80)	0/893 (0)	1/891 (0.1)	1/882 (0.1)	-0.1 (-0.3, 0.1)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.1)
Chloride, high (mEq/L)						
Level 1 (>108)	11/893 (1.2)	10/891 (1.1)	12/882 (1.4)	-0.1 (-1.2, 0.9)	-0.2 (-1.3, 0.8)	0.1 (-0.9, 1.1)
Level 2 (>112)	1/893 (0.1)	1/891 (0.1)	0/882 (0)	0.1 (-0.1, 0.3)	0.1 (-0.1, 0.3)	-0.0 (-0.3, 0.3)
Level 3 (>115)	1/893 (0.1)	0/891 (0)	0/882 (0)	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Bicarbonate, low (mEq/L)						
Level 1 (<20)	182/893 (20.4)	175/891 (19.6)	205/882 (23.2)	-2.9 (-6.7, 1.0)	-3.6 (-7.4, 0.2)	0.7 (-3.0, 4.5)
Level 2 (<18)	54/893 (6.0)	40/891 (4.5)	57/882 (6.5)	-0.4 (-2.7, 1.8)	-2.0 (-4.1, 0.1)	1.6 (-0.5, 3.6)
Level 3 (<15)	4/893 (0.4)	1/891 (0.1)	6/882 (0.7)	-0.2 (-0.9, 0.5)	-0.6 (-1.2, 0.0)	0.3 (-0.2, 0.8)
Bicarbonate, high (mEq/L)						
Level 3 (>30)	10/893 (1.1)	11/891 (1.2)	15/882 (1.7)	-0.6 (-1.7, 0.5)	-0.5 (-1.6, 0.7)	-0.1 (-1.1, 0.9)

Laboratory Parameter	PAXLOVID 5 Days N=912 n/N_w (%)	PAXLOVID 10 Days N=911 n/N_w (%)	Placebo N=898 n/N_w (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Glucose, low (mg/dL)						
Level 1 (<70)	112/893 (12.5)	127/891 (14.3)	122/882 (13.8)	-1.3 (-4.4, 1.9)	0.4 (-2.8, 3.7)	-1.7 (-4.9, 1.4)
Level 2 (<54)	18/893 (2.0)	24/891 (2.7)	30/882 (3.4)	-1.4 (-2.9, 0.1)	-0.7 (-2.3, 0.9)	-0.7 (-2.1, 0.7)
Level 3 (<40)	1/893 (0.1)	3/891 (0.3)	3/882 (0.3)	-0.2 (-0.7, 0.2)	-0.0 (-0.5, 0.5)	-0.2 (-0.7, 0.2)
Glucose, fasting, high (mg/dL)						
Missing	NA	NA	NA	NA	NA	NA
Glucose, random, high (mg/dL)						
Level 2 (≥200)	52/893 (5.8)	43/891 (4.8)	42/882 (4.8)	1.1 (-1.0, 3.1)	0.1 (-1.9, 2.1)	1.0 (-1.1, 3.1)
Level 3 (>250)	31/893 (3.5)	25/891 (2.8)	23/882 (2.6)	0.9 (-0.7, 2.5)	0.2 (-1.3, 1.7)	0.7 (-1.0, 2.3)
Calcium, low (mg/dL)						
Level 1 (<8.4)	33/893 (3.7)	31/890 (3.5)	36/882 (4.1)	-0.4 (-2.2, 1.4)	-0.6 (-2.4, 1.2)	0.2 (-1.5, 1.9)
Level 2 (<8)	14/893 (1.6)	12/890 (1.3)	14/882 (1.6)	-0.0 (-1.2, 1.1)	-0.2 (-1.4, 0.9)	0.2 (-0.9, 1.3)
Level 3 (<7.5)	6/893 (0.7)	9/890 (1.0)	7/882 (0.8)	-0.1 (-0.9, 0.7)	0.2 (-0.7, 1.1)	-0.3 (-1.2, 0.5)
Calcium, high (mg/dL)						
Level 1 (>10.5)	24/893 (2.7)	17/890 (1.9)	12/882 (1.4)	1.3 (0.0, 2.6)	0.5 (-0.6, 1.7)	0.8 (-0.6, 2.2)
Level 2 (>11)	4/893 (0.4)	1/890 (0.1)	0/882 (0)	0.4 (0.0, 0.9)	0.1 (-0.1, 0.3)	0.3 (-0.2, 0.8)
Level 3 (>12)	0/893 (0)	0/890 (0)	0/882 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Magnesium, low (mg/dL)						
Missing	NA	NA	NA	NA	NA	NA
Magnesium, high (mg/dL)						
Missing	NA	NA	NA	NA	NA	NA
Phosphate, low (mg/dL)						
Missing	NA	NA	NA	NA	NA	NA
Protein, total, low (g/dL)						
Level 1 (<6)	5/893 (0.6)	7/891 (0.8)	5/882 (0.6)	-0.0 (-0.7, 0.7)	0.2 (-0.5, 1.0)	-0.2 (-1.0, 0.5)
Level 2 (<5.4)	0/893 (0)	0/891 (0)	0/882 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Level 3 (<5)	0/893 (0)	0/891 (0)	0/882 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Albumin, low (g/dL)						
Level 1 (<3.1)	0/894 (0)	0/891 (0)	2/882 (0.2)	-0.2 (-0.5, 0.1)	-0.2 (-0.5, 0.1)	0 (0, 0)
Level 2 (<2.5)	0/894 (0)	0/891 (0)	0/882 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Level 3 (<2)	0/894 (0)	0/891 (0)	0/882 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
CPK, high (U/L)						
Level 1 (>3X ULN)	51/893 (5.7)	41/891 (4.6)	46/882 (5.2)	0.5 (-1.6, 2.6)	-0.6 (-2.6, 1.4)	1.1 (-0.9, 3.2)
Level 2 (>5X ULN)	24/893 (2.7)	19/891 (2.1)	21/882 (2.4)	0.3 (-1.2, 1.8)	-0.2 (-1.6, 1.1)	0.6 (-0.9, 2.0)
Level 3 (>10X ULN)	11/893 (1.2)	5/891 (0.6)	8/882 (0.9)	0.3 (-0.6, 1.3)	-0.3 (-1.1, 0.4)	0.7 (-0.2, 1.5)

Laboratory Parameter	PAXLOVID 5 Days N=912 n/N_w (%)	PAXLOVID 10 Days N=911 n/N_w (%)	Placebo N=898 n/N_w (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Amylase, high (U/L)						
Missing	NA	NA	NA	NA	NA	NA
Lipase, high (U/L)						
Missing	NA	NA	NA	NA	NA	NA
Blood urea nitrogen, high (mg/dL)						
Level 1 (>23)	46/893 (5.2)	26/891 (2.9)	41/882 (4.6)	0.5 (-1.5, 2.5)	-1.7 (-3.5, 0.0)	2.2 (0.4, 4.1)
Level 2 (>27)	17/893 (1.9)	12/891 (1.3)	9/882 (1.0)	0.9 (-0.2, 2.0)	0.3 (-0.7, 1.3)	0.6 (-0.6, 1.7)
Level 3 (>31)	8/893 (0.9)	5/891 (0.6)	6/882 (0.7)	0.2 (-0.6, 1.0)	-0.1 (-0.9, 0.6)	0.3 (-0.5, 1.1)
Creatinine, high (mg/dL)						
Level 1 (≥1.5X baseline)	57/885 (6.4)	45/872 (5.2)	44/869 (5.1)	1.4 (-0.8, 3.6)	0.1 (-2.0, 2.2)	1.3 (-0.9, 3.5)
Level 2 (≥2X baseline)	14/885 (1.6)	10/872 (1.1)	5/869 (0.6)	1.0 (0.0, 2.0)	0.6 (-0.3, 1.4)	0.4 (-0.6, 1.5)
Level 3 (≥3X baseline)	0/885 (0)	1/872 (0.1)	0/869 (0)	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
eGFR, low (ml/min/1.73 m^2)						
Level 1 (≥25% decrease)	93/885 (10.5)	78/872 (8.9)	68/868 (7.8)	2.7 (-0.0, 5.4)	1.1 (-1.5, 3.7)	1.6 (-1.2, 4.3)
Level 2 (≥50% decrease)	9/885 (1.0)	4/872 (0.5)	3/868 (0.3)	0.7 (-0.1, 1.4)	0.1 (-0.5, 0.7)	0.6 (-0.2, 1.4)
Level 3 (≥75% decrease)	0/885 (0)	0/872 (0)	0/868 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)

Source: adlb.xpt; Software: R
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
Note: Glucose values for hyperglycemia do not follow a nested format l ke the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.
[1.] Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (August 2022).
[2.] Duration of treatment is 5 or 10 days.
[3.] Difference is shown between PAXLOVID vs placebo
Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; ULN, upper limit of normal

Table 165. Patients With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels[1], Safety Population, Trial EPIC-PEP[2]

Laboratory Parameter	PAXLOVID 5 Days N=912 n/N_w (%)	PAXLOVID 10 Days N=911 n/N_w (%)	Placebo N=898 n/N_w (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Alkaline phosphatase, high (U/L)						
Level 1 (>1.5X ULN)	4/893 (0.4)	7/891 (0.8)	11/882 (1.2)	-0.8 (-1.7, 0.1)	-0.5 (-1.4, 0.5)	-0.3 (-1.1, 0.4)
Level 2 (>2X ULN)	1/893 (0.1)	4/891 (0.4)	5/882 (0.6)	-0.5 (-1.0, 0.1)	-0.1 (-0.8, 0.5)	-0.3 (-0.8, 0.2)
Level 3 (>3X ULN)	0/893 (0)	0/891 (0)	0/882 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Alanine aminotransferase, high (U/L)						
Level 1 (>3X ULN)	12/893 (1.3)	8/891 (0.9)	8/882 (0.9)	0.4 (-0.5, 1.4)	-0.0 (-0.9, 0.9)	0.4 (-0.5, 1.4)
Level 2 (>5X ULN)	1/893 (0.1)	2/891 (0.2)	1/882 (0.1)	-0.0 (-0.3, 0.3)	0.1 (-0.3, 0.5)	-0.1 (-0.5, 0.3)
Level 3 (>10X ULN)	1/893 (0.1)	1/891 (0.1)	0/882 (0)	0.1 (-0.1, 0.3)	0.1 (-0.1, 0.3)	-0.0 (-0.3, 0.3)
Aspartate aminotransferase, high (U/L)						
Level 1 (>3X ULN)	3/893 (0.3)	7/891 (0.8)	2/882 (0.2)	0.1 (-0.4, 0.6)	0.6 (-0.1, 1.2)	-0.4 (-1.1, 0.2)
Level 2 (>5X ULN)	0/893 (0)	3/891 (0.3)	2/882 (0.2)	-0.2 (-0.5, 0.1)	0.1 (-0.4, 0.6)	-0.3 (-0.7, 0.0)
Level 3 (>10X ULN)	0/893 (0)	1/891 (0.1)	0/882 (0)	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Bilirubin, total, high (mg/dL)						
Level 1 (>1.5X ULN)	4/893 (0.4)	1/891 (0.1)	5/882 (0.6)	-0.1 (-0.8, 0.5)	-0.5 (-1.0, 0.1)	0.3 (-0.2, 0.8)
Level 2 (>2X ULN)	1/893 (0.1)	0/891 (0)	2/882 (0.2)	-0.1 (-0.5, 0.3)	-0.2 (-0.5, 0.1)	0.1 (-0.1, 0.3)
Level 3 (>3X ULN)	1/893 (0.1)	0/891 (0)	0/882 (0)	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)

Source: adlb.xpt; Software: R
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
[1.] Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (August 2022).
[2.] Duration of treatment is 5 or 10 days.
[3.] Difference is shown between PAXLOVID vs placebo.
Abbreviations: N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; ULN, upper limit of normal

Table 166. Patients With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population[1], EPIC-PEP[2]

Laboratory Parameter	PAXLOVID 5 Days N=912 n/N_w (%)	PAXLOVID 10 Days N=911 n/N_w (%)	Placebo N=898 n/N_w (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Complete Blood Count						
WBC, low (cells/uL)						
Level 1 (<3500)	45/871 (5.2)	50/863 (5.8)	54/859 (6.3)	-1.1 (-3.3, 1.1)	-0.5 (-2.7, 1.8)	-0.6 (-2.8, 1.5)
Level 2 (<3000)	26/871 (3.0)	23/863 (2.7)	28/859 (3.3)	-0.3 (-1.9, 1.4)	-0.6 (-2.2, 1.0)	0.3 (-1.2, 1.9)
Level 3 (<1000)	0/871 (0)	0/863 (0)	0/859 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)

Laboratory Parameter	PAXLOVID 5 Days N=912 n/N_w (%)	PAXLOVID 10 Days N=911 n/N_w (%)	Placebo N=898 n/N_w (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
WBC, high (cells/uL)						
Level 1 (>10800)	79/871 (9.1)	75/863 (8.7)	61/859 (7.1)	2.0 (-0.6, 4.5)	1.6 (-1.0, 4.1)	0.4 (-2.3, 3.1)
Level 2 (>13000)	24/871 (2.8)	17/863 (2.0)	19/859 (2.2)	0.5 (-0.9, 2.0)	-0.2 (-1.6, 1.1)	0.8 (-0.6, 2.2)
Level 3 (>15000)	7/871 (0.8)	2/863 (0.2)	7/859 (0.8)	-0.0 (-0.9, 0.8)	-0.6 (-1.3, 0.1)	0.6 (-0.1, 1.2)
Hemoglobin, low (g/dL)						
Level 2 (>1.5 dec. from BL)	78/707 (11.0)	67/668 (10.0)	74/662 (11.2)	-0.1 (-3.5, 3.2)	-1.1 (-4.5, 2.2)	1.0 (-2.2, 4.2)
Level 3 (>2 dec. from BL)	32/707 (4.5)	31/668 (4.6)	28/662 (4.2)	0.3 (-1.9, 2.5)	0.4 (-1.8, 2.6)	-0.1 (-2.3, 2.1)
Hemoglobin, high (g/dL)						
Level 2 (>2 inc. from BL)	7/707 (1.0)	16/668 (2.4)	13/662 (2.0)	-1.0 (-2.3, 0.3)	0.4 (-1.1, 2.0)	-1.4 (-2.8, -0.0)
Level 3 (>3 inc. from BL)	4/707 (0.6)	7/668 (1.0)	10/662 (1.5)	-0.9 (-2.0, 0.1)	-0.5 (-1.7, 0.7)	-0.5 (-1.4, 0.5)
Platelets, low (cells/uL)						
Level 1 (<140000)	15/870 (1.7)	26/862 (3.0)	31/858 (3.6)	-1.9 (-3.4, -0.4)	-0.6 (-2.3, 1.1)	-1.3 (-2.7, 0.1)
Level 2 (<125000)	9/870 (1.0)	14/862 (1.6)	18/858 (2.1)	-1.1 (-2.2, 0.1)	-0.5 (-1.8, 0.8)	-0.6 (-1.7, 0.5)
Level 3 (<100000)	2/870 (0.2)	3/862 (0.3)	5/858 (0.6)	-0.4 (-1.0, 0.2)	-0.2 (-0.9, 0.4)	-0.1 (-0.6, 0.4)
WBC Differential						
Lymphocytes, low (cells/uL)						
Level 1 (<1000)	34/870 (3.9)	33/861 (3.8)	45/857 (5.3)	-1.3 (-3.3, 0.6)	-1.4 (-3.4, 0.6)	0.1 (-1.7, 1.9)
Level 2 (<750)	9/870 (1.0)	5/861 (0.6)	13/857 (1.5)	-0.5 (-1.5, 0.6)	-0.9 (-1.9, 0.0)	0.5 (-0.4, 1.3)
Level 3 (<500)	1/870 (0.1)	0/861 (0)	2/857 (0.2)	-0.1 (-0.5, 0.3)	-0.2 (-0.6, 0.1)	0.1 (-0.1, 0.3)
Lymphocytes, high (cells/uL)						
Level 1 (>4000)	18/870 (2.1)	18/861 (2.1)	23/857 (2.7)	-0.6 (-2.1, 0.8)	-0.6 (-2.0, 0.9)	-0.0 (-1.4, 1.3)
Level 2 (>10000)	0/870 (0)	1/861 (0.1)	0/857 (0)	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Level 3 (>20000)	0/870 (0)	1/861 (0.1)	0/857 (0)	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Neutrophils, low (cells/uL)						
Level 1 (<2000)	117/870 (13.4)	125/860 (14.5)	107/857 (12.5)	1.0 (-2.2, 4.1)	2.0 (-1.2, 5.3)	-1.1 (-4.4, 2.2)
Level 2 (<1000)	21/870 (2.4)	26/860 (3.0)	23/857 (2.7)	-0.3 (-1.8, 1.2)	0.3 (-1.2, 1.9)	-0.6 (-2.1, 0.9)
Level 3 (<500)	3/870 (0.3)	7/860 (0.8)	10/857 (1.2)	-0.8 (-1.6, -0.0)	-0.4 (-1.3, 0.6)	-0.5 (-1.2, 0.2)
Eosinophils, high (cells/uL)						
Level 1 (>650)	19/870 (2.2)	26/861 (3.0)	29/857 (3.4)	-1.2 (-2.8, 0.4)	-0.4 (-2.0, 1.3)	-0.8 (-2.3, 0.7)
Level 2 (>1500)	2/870 (0.2)	3/861 (0.3)	2/857 (0.2)	-0.0 (-0.5, 0.4)	0.1 (-0.4, 0.6)	-0.1 (-0.6, 0.4)
Level 3 (>5000)	0/870 (0)	0/861 (0)	0/857 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Coagulation Studies						
PT, high (sec)						
Level 1 (>1.1X ULN)	96/889 (10.8)	114/887 (12.9)	110/880 (12.5)	-1.7 (-4.7, 1.3)	0.4 (-2.8, 3.5)	-2.1 (-5.1, 0.9)
Level 2 (>1.3X ULN)	13/889 (1.5)	14/887 (1.6)	11/880 (1.2)	0.2 (-0.9, 1.3)	0.3 (-0.8, 1.4)	-0.1 (-1.3, 1.0)
Level 3 (>1.5X ULN)	7/889 (0.8)	2/887 (0.2)	7/880 (0.8)	-0.0 (-0.8, 0.8)	-0.6 (-1.2, 0.1)	0.6 (-0.1, 1.2)

Laboratory Parameter	PAXLOVID 5 Days N=912 n/N_w (%)	PAXLOVID 10 Days N=911 n/N_w (%)	Placebo N=898 n/N_w (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
PTT, high (sec)						
Level 1 (>1X ULN)	557/888 (62.7)	523/888 (58.9)	541/878 (61.6)	1.1 (-3.4, 5.6)	-2.7 (-7.3, 1.8)	3.8 (-0.7, 8.4)
Level 2 (>1.21X ULN)	161/888 (18.1)	156/888 (17.6)	161/878 (18.3)	-0.2 (-3.8, 3.4)	-0.8 (-4.3, 2.8)	0.6 (-3.0, 4.1)
Level 3 (>1.41X ULN)	44/888 (5.0)	50/888 (5.6)	43/878 (4.9)	0.1 (-2.0, 2.1)	0.7 (-1.3, 2.8)	-0.7 (-2.8, 1.4)

Source: adlb.xpt; Software: R.
Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
[1.] Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (August 2022).
[2.] Duration of treatment is 5 or 10 days.
[3.] Difference is shown between PAXLOVID vs placebo.
Abbreviations: BL, baseline; CI, confidence interval; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; PT, prothrombin time; PTT, partial thromboplastin time; ULN, upper limit of normal; WBC, white blood cell

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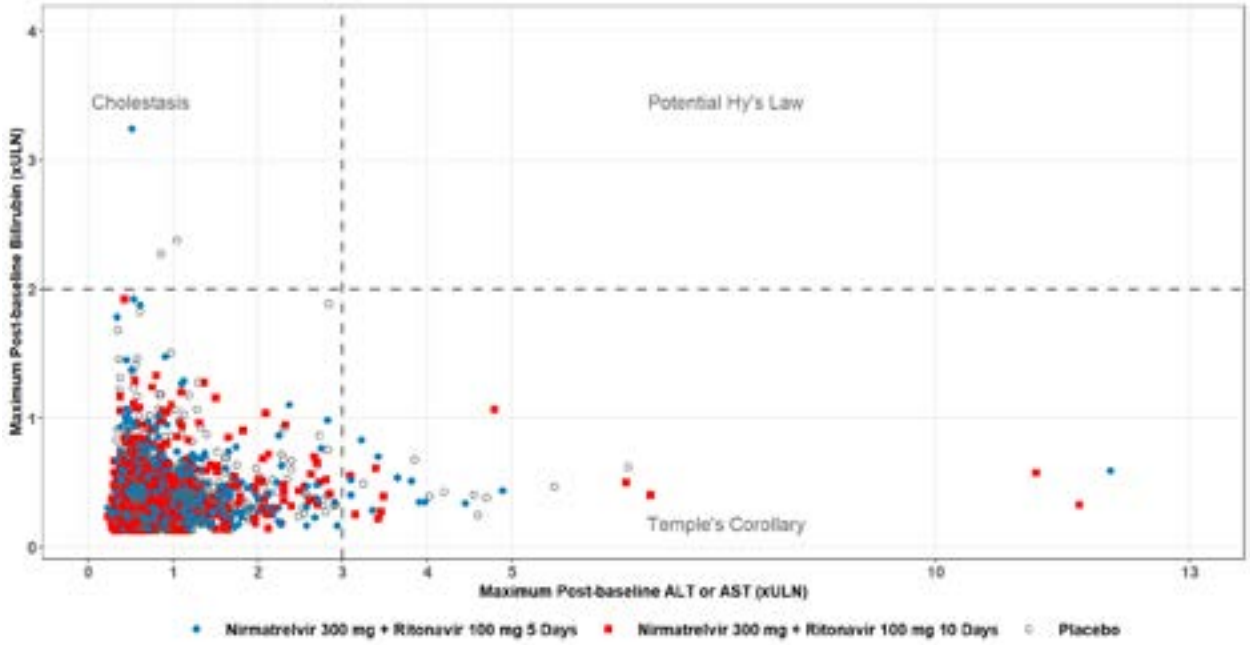
17.11. Assessment of Drug-Induced Liver Injury, EPIC-PEP

An assessment of DILI for EPIC-PEP was provided in Section 7.6.2.7. Figure 68 and Figure 69 shows a screening assessment for potential cases of serious DILI, whereas Table 167 and Table 168 provide analyses by quadrant for each screening assessment.

Figure 68. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, EPIC-PEP



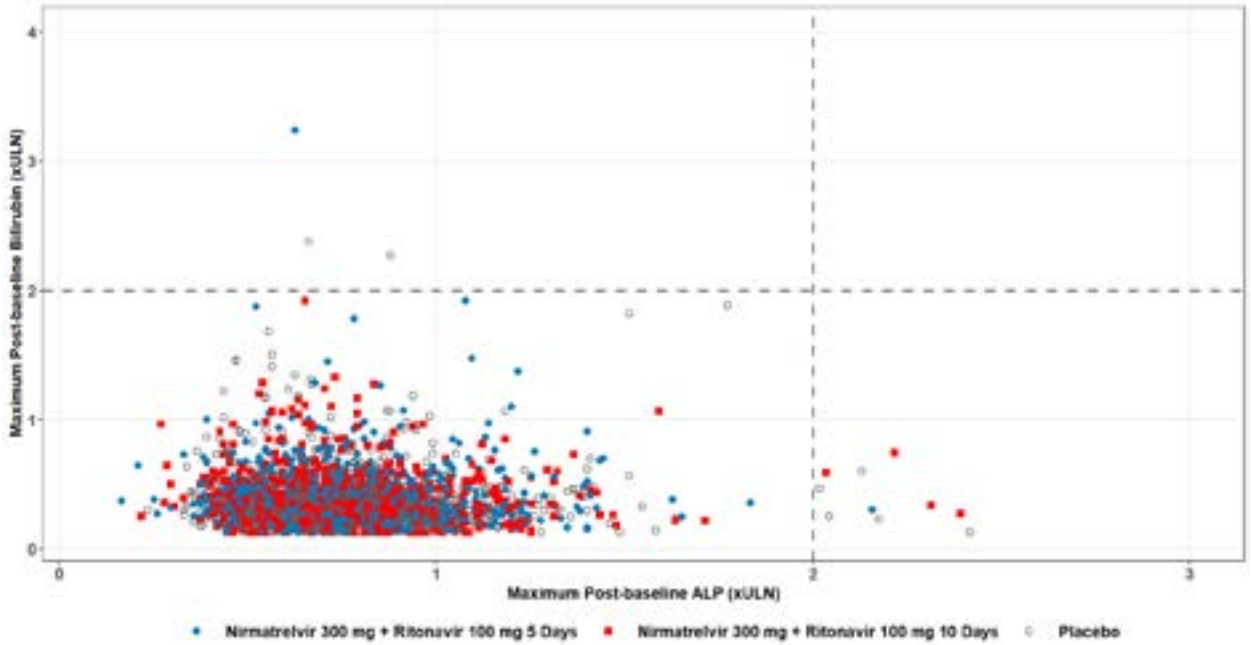
Source: adlb.xpt; Software: R.
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
Note: Each data point represents a patient plotted by their maximum ALT or AST versus their maximum total bilirubin values in the post-baseline period.
Note: A potential Hy's Law case (red circle) was defined as having any post-baseline total bilirubin equal to or exceeding 2X ULN within 30 days after a post-baseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN (note ALP values are not circled). All patients with at least one post-baseline ALT or AST and bilirubin are plotted.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; TB, total bilirubin; ULN, upper limit of normal

Table 167. Patients in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, EPIC-PEP

Quadrant	PAXLOVID 5 Days N=912 n/N_w (%)	PAXLOVID 10 Days N=911 n/N_w (%)	Placebo N=898 n/N_w (%)
Potential Hy's Law (right upper)	0/893 (0)	0/891 (0)	0/882 (0)
Cholestasis (left upper)	1/893 (0.1)	0/891 (0)	2/882 (0.2)
Temple's corollary (right lower)	12/893 (1.3)	11/891 (1.2)	9/882 (1)
Total	13/893 (1.5)	11/891 (1.2)	11/882 (1.2)

Source: adlb.xpt; Software: R.
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
Abbreviations: DILI, drug-induced liver injury; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of patients with data

Figure 69. Cholestatic Drug-Induced Liver Injury Screening Plot, Safety Population, EPIC-PEP



Source: adlb.xpt; Software: R.
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
Note: Each data point represents a patient plotted by their maximum ALP versus their maximum total bilirubin values in the post-baseline period.
Note: A potential cholestatic DILI case (red circled) was defined as having a maximum post-baseline total bilirubin equal to or exceeding 2X ULN within 30 days after post-baseline ALP became equal to or exceeding 2X ULN.
Abbreviations: ALP, alkaline phosphatase; DILI, drug-induced liver injury; ULN, upper limit of normal

Table 168. Patients in Each Quadrant for Cholestatic DILI Screening Plot, Safety Population, EPIC-PEP

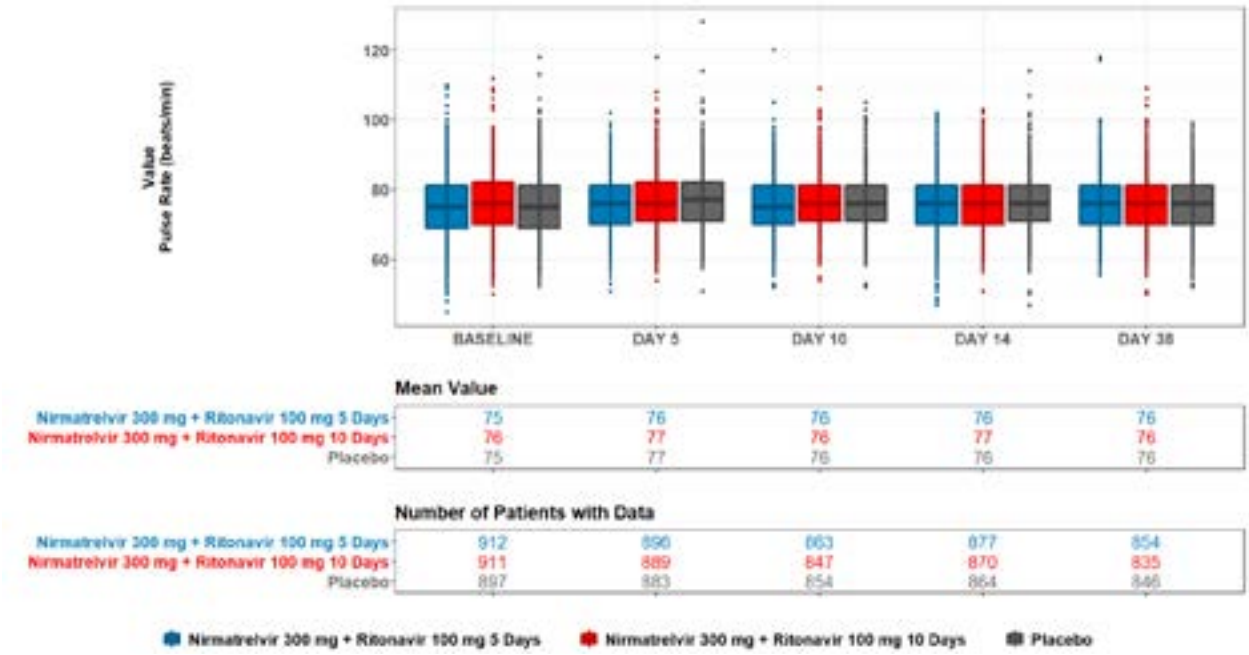
Quadrant	PAXLOVID 5 Days N=912 n/N_w (%)	PAXLOVID 10 Days N=911 n/N_w (%)	Placebo N=898 n/N_w (%)
Bilirubin ≥2X ULN and ALP ≥2X ULN (right upper)	0/893 (0)	0/891 (0)	0/882 (0)
Bilirubin ≥2X ULN and ALP <2X ULN (left upper)	1/893 (0.1)	0/891 (0)	2/882 (0.2)
Bilirubin <2X ULN and ALP ≥2X ULN (right lower)	1/893 (0.1)	4/891 (0.4)	5/882 (0.6)
Total	2/893 (0.2)	4/891 (0.4)	7/882 (0.8)

Source: adlb.xpt; Software: R.
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
Abbreviations: ALP, alkaline phosphatase; DILI, drug-induced liver injury; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of patients with data; ULN, upper limit of normal

17.12. Vital Sign Assessment, EPIC-PEP

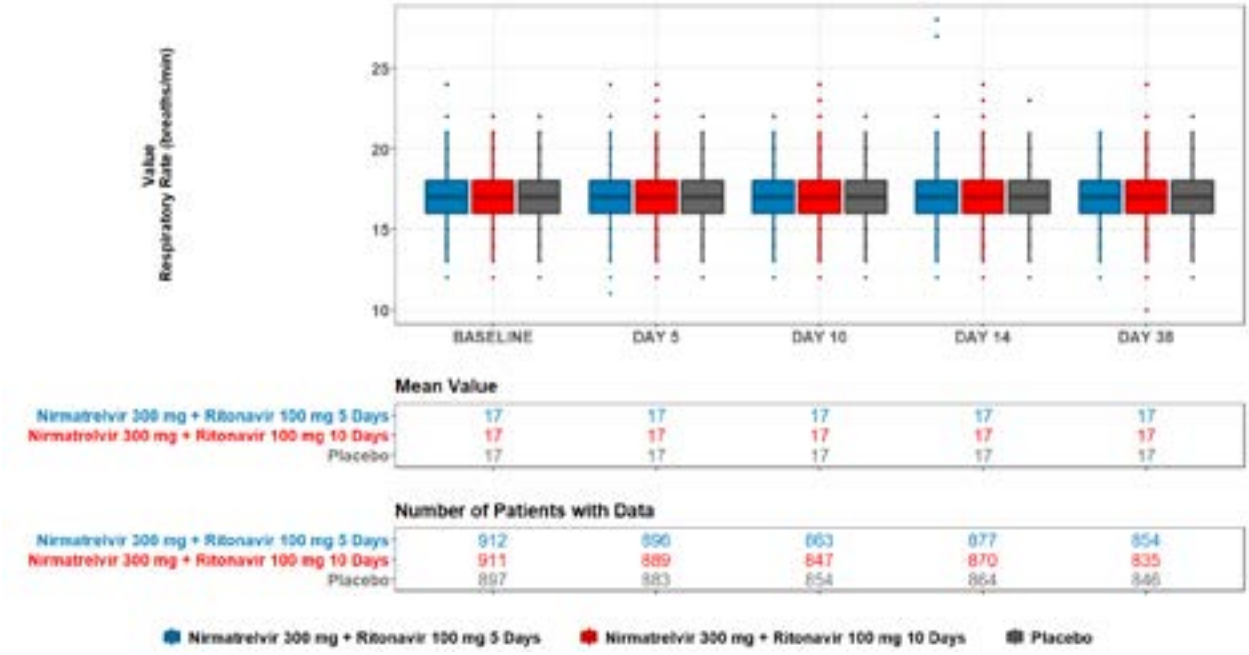
An overview of vital signs was provided in Section 7.6.2.8. Figure 70, Figure 71, and Figure 72 describe pulse rate, temperature, and respiratory rate in EPIC-PEP.

Figure 70. Median and Interquartile Range of Pulse Rate Over Time by Treatment Arm, Safety Population, EPIC-PEP



Source: advs.xpt; Software: R.
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
Note: Boxes span the interquartile range (25th to 75th percentile); horizontal lines indicate median; whiskers indicate 1.5X the interquartile range; individual outliers are those beyond this range.

Figure 71. Median and Interquartile Range of Respiratory Rate Over Time by Treatment Arm, Safety Population, EPIC-PEP



Source: advs.xpt; Software: R.
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
Note: Boxes span the interquartile range (25th to 75th percentile); horizontal lines indicate median; whiskers indicate 1.5X the interquartile range; individual outliers are those beyond this range.

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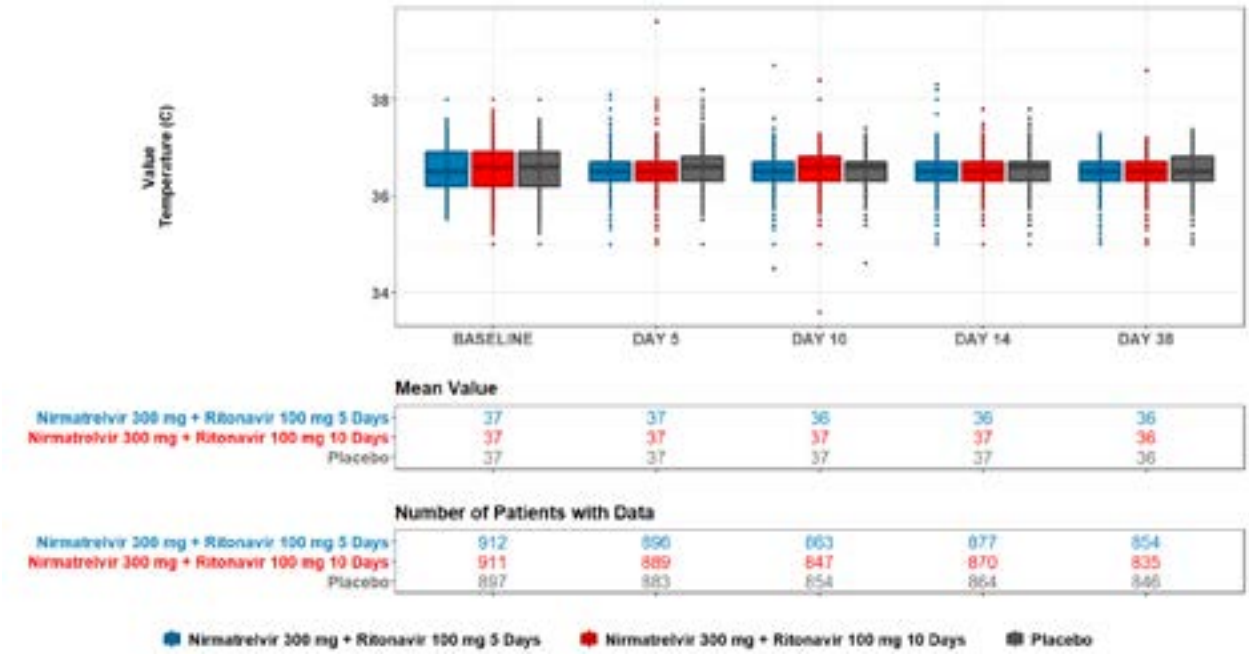
Figure 72. Median and Interquartile Range of Body Temperature Over Time by Treatment Arm, Safety Population, EPIC-PEP



Source: advs.xpt; Software: R.
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
Note: Boxes span the interquartile range (25th to 75th percentile); horizontal lines indicate median; whiskers indicate 1.5X the interquartile range; individual outliers are those beyond this range.

17.13. Demographic Subgroup Analysis, EPIC-PEP

An overview of adverse events by demographic subgroups in EPIC-PEP was presented in Section 7.6.2.9. Table 169 summarizes the AEs of demographic subgroups and Table 170 summarizes the SAEs.

Table 169. Overview of Adverse Events by Demographic Subgroup, Safety Population, Trial EPIC-PEP

Characteristic	PAXLOVID 5 Days N=912 n/N_s (%)	PAXLOVID 10 Days N=911 n/N_s (%)	Placebo N=898 n/N_s (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)
Sex, n (%)						
Female	118/499 (23.6)	112/478 (23.4)	104/473 (22.0)	1.7 (-3.6, 6.9)	1.4 (-3.9, 6.8)	0.2 (-5.1, 5.5)
Male	100/413 (24.2)	100/433 (23.1)	91/425 (21.4)	2.8 (-2.9, 8.5)	1.7 (-3.9, 7.2)	1.1 (-4.6, 6.8)
Age group, years, n (%)						
18 to 44	119/475 (25.1)	118/526 (22.4)	109/509 (21.4)	3.6 (-1.6, 8.9)	1.0 (-4.0, 6.1)	2.6 (-2.7, 7.9)
45 to 59	74/297 (24.9)	62/249 (24.9)	61/279 (21.9)	3.1 (-3.9, 10.0)	3.0 (-4.2, 10.3)	0.0 (-7.3, 7.3)
60 to 64	7/61 (11.5)	9/53 (17.0)	8/44 (18.2)	-6.7 (-20.6, 7.2)	-1.2 (-16.4, 14.0)	-5.5 (-18.4, 7.4)
65 to 74	11/50 (22.0)	16/58 (27.6)	13/49 (26.5)	-4.5 (-21.4, 12.3)	1.1 (-15.8, 17.9)	-5.6 (-21.8, 10.7)
≥75	7/29 (24.1)	7/25 (28.0)	4/17 (23.5)	0.6 (-24.9, 26.1)	4.5 (-22.3, 31.2)	-3.9 (-27.4, 19.6)
Age group ≥65, years, n (%)						
≥65	18/79 (22.8)	23/83 (27.7)	17/66 (25.8)	-3.0 (-17.0, 11.1)	2.0 (-12.3, 16.2)	-4.9 (-18.3, 8.4)
Race, n (%)						
American Indian or Alaska Native	16/58 (27.6)	13/52 (25.0)	8/49 (16.3)	11.3 (-4.2, 26.7)	8.7 (-7.0, 24.3)	2.6 (-13.9, 19.0)
Asian	4/8 (50.0)	3/15 (20.0)	7/11 (63.6)	-13.6 (-58.5, 31.2)	-43.6 (-78.5, -8.7) *	30.0 (-10.1, 70.1)
Black or African American	32/137 (23.4)	34/134 (25.4)	36/131 (27.5)	-4.1 (-14.5, 6.3)	-2.1 (-12.7, 8.5)	-2.0 (-12.2, 8.2)
Multiple	0/1 (0)	0/1 (0)	0/1 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Unknown	0/1 (0)	1/1 (100)	0/0 (NA)	NA	NA	-100.0 (-100.0, -100.0)
White	166/707 (23.5)	160/707 (22.6)	144/705 (20.4)	3.1 (-1.3, 7.4)	2.2 (-2.1, 6.5)	0.8 (-3.5, 5.2)
Missing	0/0 (NA)	1/1 (100)	0/1 (0)	NA	100.0 (100.0, 100.0)	NA
Ethnicity, n (%)						
Hispanic or Latino	118/657 (18.0)	109/638 (17.1)	104/642 (16.2)	1.8 (-2.3, 5.9)	0.9 (-3.2, 5.0)	0.9 (-3.3, 5.0)
Not Hispanic or Latino	100/255 (39.2)	103/273 (37.7)	91/256 (35.5)	3.7 (-4.7, 12.1)	2.2 (-6.0, 10.4)	1.5 (-6.8, 9.8)

Source: adae.xpt; Software: R.
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event; N_s, total number of patients for each specific subgroup and were assigned to that specific arm

Table 170. Overview of Serious Adverse Events by Demographic Subgroup, Safety Population, Trial EPIC-PEP

Characteristic	PAXLOVID 5 Days N=912 n/N_s (%)	PAXLOVID 10 Days N=911 n/N_s (%)	Placebo N=898 n/N_s (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)
Sex, n (%)						
Female	3/499 (0.6)	1/478 (0.2)	0/473 (0)	0.6 (-0.1, 1.3)	0.2 (-0.2, 0.6)	0.4 (-0.4, 1.2)
Male	0/413 (0)	0/433 (0)	2/425 (0.5)	-0.5 (-1.1, 0.2)	-0.5 (-1.1, 0.2)	0 (0, 0)
Age group, years, n (%)						
18 to 44	1/475 (0.2)	0/526 (0)	1/509 (0.2)	0.0 (-0.5, 0.6)	-0.2 (-0.6, 0.2)	0.2 (-0.2, 0.6)
45 to 59	1/297 (0.3)	0/249 (0)	0/279 (0)	0.3 (-0.3, 1.0)	0 (0, 0)	0.3 (-0.3, 1.0)
60 to 64	0/61 (0)	0/53 (0)	1/44 (2.3)	-2.3 (-6.7, 2.1)	-2.3 (-6.7, 2.1)	0 (0, 0)
65 to 74	0/50 (0)	1/58 (1.7)	0/49 (0)	0 (0, 0)	1.7 (-1.6, 5.1)	-1.7 (-5.1, 1.6)
≥75	1/29 (3.4)	0/25 (0)	0/17 (0)	3.4 (-3.2, 10.1)	0 (0, 0)	3.4 (-3.2, 10.1)
Age group ≥65, years, n (%)						
≥65	1/79 (1.3)	1/83 (1.2)	0/66 (0)	1.3 (-1.2, 3.7)	1.2 (-1.1, 3.6)	0.1 (-3.3, 3.5)
Race, n (%)						
American Indian or Alaska Native	0/58 (0)	0/52 (0)	0/49 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Asian	0/8 (0)	0/15 (0)	0/11 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Black or African American	0/137 (0)	0/134 (0)	0/131 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Multiple	0/1 (0)	0/1 (0)	0/1 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Unknown	0/1 (0)	0/1 (0)	0/0 (NA)	NA	NA	0 (0, 0)
White	3/707 (0.4)	1/707 (0.1)	2/705 (0.3)	0.1 (-0.5, 0.8)	-0.1 (-0.6, 0.3)	0.3 (-0.3, 0.8)
Missing	0/0 (NA)	0/1 (0)	0/1 (0)	NA	0 (0, 0)	NA
Ethnicity, n (%)						
Hispanic or Latino	2/657 (0.3)	0/638 (0)	0/642 (0)	0.3 (-0.1, 0.7)	0 (0, 0)	0.3 (-0.1, 0.7)
Not Hispanic or Latino	1/255 (0.4)	1/273 (0.4)	2/256 (0.8)	-0.4 (-1.7, 0.9)	-0.4 (-1.7, 0.9)	0.0 (-1.0, 1.1)

Source: adae.xpt; Software: R.
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event; N_s, total number of patients for each specific subgroup and were assigned to that specific arm

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17.14. Adverse Events of Special Interest

17.14.1. Thyroid-related events

This section provides additional details for the adverse events of special interest (AESI) of thyroid-related events. As summarized in Section 7.6.3.1, frequencies of any thyroid-related AEs were similar between the PAXLOVID and placebo groups in EPIC-HR and EPIC-SR (Table 171).

There was one severe (Grade 3) event of blood thyroid stimulating hormone increase in subject (b) (6) in EPIC-PEP who was a 20-year-old male in the PAXLOVID 5-day group who had a thyrotropin within reference range at baseline. This AE was reported on Day 5 with a thyrotropin of 4.81 mIU/L (reference range: 0.53 to 3.59 mIU/L) and was reported resolved on Day 10. The investigator assessed the causality of this AE as not related to study intervention; however, it was reported to be related to "other: unknown".

Abnormalities in the laboratory test for thyrotropin (>1.2x ULN) were more frequent in the PAXLOVID 5-day (38/829, 4.6%) and 10-day (35/827, 4.2%) groups when compared to the placebo group (33/843, 3.9%).

Table 171. Thyroid-Related Adverse Event Assessment[1], Safety Population, Trials EPIC-HR and EPIC-SR[2]

	EPIC-HR		EPIC-SR		Pooled	
Thyroid-Related AE Assessment	**PAXLOVID N=1038 n(%)**	**Placebo N=1053 n(%)**	**PAXLOVID N=540 n(%)**	**Placebo N=528 n(%)**	**PAXLOVID N=1578 n(%)**	**Placebo N=1581 n(%)**
Any thyroid-related AE	6 (0.6)	7 (0.7)	3 (0.6)	5 (0.9)	9 (0.6)	12 (0.8)
Blood thyroid stimulating hormone increased	5 (0.5)	7 (0.7)	2 (0.4)	5 (0.9)	7 (0.4)	12 (0.8)
Thyroxine free increased	0	1 (0.1)	1 (0.2)	0	1 (0.1)	1 (0.1)
Thyroxine increased	1 (0.1)	0	0	1 (0.2)	1 (0.1)	1 (0.1)
Maximum severity						
Moderate	0	3 (0.3)	0	0	0	3 (0.2)
Mild	6 (0.6)	5 (0.5)	3 (0.6)	6 (1.1)	9 (0.6)	11 (0.7)
Serious event	0	0	0	0	0	0
Resulted in discontinuation	0	0	0	0	0	0
Relatedness[3]	1 (0.1)	3 (0.3)	2 (0.4)	4 (0.8)	3 (0.2)	7 (0.4)

Source: adae.xpt; Software: JMP.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
[2.] Duration of treatment is 5 days.
[3.] Relatedness is determined by investigator.
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with adverse event

In EPIC-PEP, the frequencies of thyroid-related AEs of blood thyroid stimulating hormone increased and thyroxine free decreased were similar between all groups (1.2% in the 5-day PAXLOVID group, 0.9% in the 10-day group, and 1.1% in the placebo group).

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17.14.2. Inflammatory Events

This section provides additional details for the AESI of inflammatory events. As summarized in Section 7.6.3.2, any inflammatory-related AE was similar between the PAXLOVID group and placebo group in EPIC-HR and EPIC-SR (Table 172). Frequencies of inflammatory related AEs graded as severe or life-threatening were also similar between the PAXLOVID and placebo groups in EPIC-HR and EPIC-SR (Table 172). Details regarding these events are described in Table 173. Table 174 describes inflammatory-related laboratory outliers.

The incidence of all-causality AEs was comparable between treatment groups, except for Fibrin D dimer increases and activated partial thromboplastin time prolongation, which occurred at greater frequencies (≥5 subjects) in the placebo group compared with the PAXLOVID group in EPIC-HR and the pooled trials. Severe or life-threatening events were reported infrequently (0.6% in the pooled PAXLOVID groups) and none of these resulted in death. The SAE of D-dimer increase was reported in Subject (b) (6) in EPIC-HR who received placebo. This event occurred on Day 8 and resolved. In terms of laboratory outliers, leukocytes >1.5x ULN and neutrophils >1.2x ULN occurred at greater frequency (≥5 subjects) in the PAXLOVID group when compared to placebo in EPIC-HR. Neutrophils >1.2x ULN and lymphocytes >1.2x ULN occurred at greater frequencies (≥5 subjects) in the PAXLOVID group compared to placebo in the pooled analysis. Other hematology related laboratory outliers were similar or occurred at a higher frequency in the placebo group when compared to the PAXLOVID group. In EPIC-PEP, events were similar except for fibrin D dimer increases which occurred at greater frequency (≥5 subjects) in the PAXLOVID group when compared to placebo. Few subjects had severe (Grade 3) or higher inflammatory-related AEs. Frequency of inflammatory-related laboratory outliers were similar between all treatment groups.

Table 172. Inflammatory-Related Adverse Events Assessment[1], Safety Population, EPIC-HR and EPIC-SR[2]

	EPIC-HR		EPIC-SR		Pooled	
Inflammatory-Related AE Assessment	PAXLOVID N=1038 n(%)	Placebo N=1053 n(%)	PAXLOVID N=540 n(%)	Placebo N=528 n(%)	PAXLOVID N=1578 n(%)	Placebo N=1581 n(%)
Any inflammatory-related AE	42 (4.0)	45 (4.3)	14 (2.6)	14 (2.7)	56 (3.5)	59 (3.7)
Activated partial thromboplastin time prolonged	9 (0.9)	12 (1.1)	3 (0.6)	6 (1.1)	12 (0.8)	18 (1.1)
Blood fibrinogen increased	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
C-reactive protein increased	10 (1.0)	13 (1.2)	3 (0.6)	2 (0.4)	13 (0.8)	15 (0.9)
Fibrin D dimer increased	22 (2.2)	30 (2.8)	6 (1.1)	6 (1.1)	28 (1.8)	36 (2.3)
Haptoglobin increased	4 (0.4)	3 (0.3)	0	0	4 (0.3)	3 (0.2)
Leukocytosis	2 (0.2)	0	0	0	2 (0.1)	0
Platelet count increased	2 (0.2)	1 (0.1)	0	0	2 (0.1)	1 (0.1)
Prothrombin time prolonged	3 (0.3)	5 (0.5)	2 (0.4)	0	5 (0.3)	5 (0.3)
White blood cell count increased	2 (0.2)	0	0	0	2 (0.1)	0
Maximum severity						
Life-threatening	2 (0.2)	2 (0.2)	0	0	2 (0.1)	2 (0.1)
Severe	7 (0.7)	8 (0.8)	0	0	7 (0.4)	8 (0.5)
Moderate	13 (1.3)	15 (1.4)	2 (0.4)	5 (0.9)	15 (1.0)	20 (1.3)
Mild	32 (3.1)	39 (3.7)	13 (2.4)	10 (1.9)	45 (2.9)	49 (3.1)
Serious	0	1(0.1)	0	0	0	1(0.1)
Deaths	0	1(0.1)	0	0	0	1(0.1)

Inflammatory-Related AE Assessment	EPIC-HR PAXLOVID N=1038 n(%)	EPIC-HR Placebo N=1053 n(%)	EPIC-SR PAXLOVID N=540 n(%)	EPIC-SR Placebo N=528 n(%)	Pooled PAXLOVID N=1578 n(%)	Pooled Placebo N=1581 n(%)
Resulting in discontinuation	0	0	0	0	0	0
Relatedness[3]	1 (0.1)	3 (0.3)	2 (0.4)	0	3 (0.2)	3 (0.2)

Source: adae.xpt; Software: JMP
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
[2.] Duration of treatment is 5 days.
[3.] Relatedness is determined by investigator
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with adverse event

Table 173. Subjects With Severe (Grade 3) or Life-Threatening (Grade 4) Inflammatory-Related AE[1], EPIC-HR and EPIC-SR[2]

Subject Identifier	Treatment	Age	Sex	Dictionary-Derived Term	Study Day of AE Onset	Outcome of AE	Related[3]	SAE
(b) (6)	Placebo	49	F	Fibrin D dimer increased	15	Recovered/resolved	N	N
	Placebo	49	F	Fibrin D dimer increased	20	Recovered/resolved	N	N
	PAXLOVID	43	M	Fibrin D dimer increased	5	Recovered/resolved	N	N
	PAXLOVID	73	M	Prothrombin time prolonged	6	Recovered/resolved	N	N
	Placebo	39	M	Fibrin D dimer increased	5	Recovered/resolved	N	N
	PAXLOVID	70	F	C-reactive protein increased	1	Recovered/resolved	N	N
	Placebo	46	M	C-reactive protein increased	1	Recovered/resolved	N	N
	Placebo	47	M	Activated partial thromboplastin time prolonged	1	Recovering/resolving	N	N
	PAXLOVID	40	M	C-reactive protein increased	6	Recovered/resolved	N	N
	Placebo	68	F	Prothrombin time prolonged	6	Recovering/resolving	N	N
	PAXLOVID	72	F	Activated partial thromboplastin time prolonged	1	Recovering/resolving	N	N
	PAXLOVID	79	F	Fibrin D dimer increased	14	Recovering/resolving	N	N
	Placebo	62	M	Prothrombin time prolonged	14	Recovering/resolving	N	N
	Placebo	61	M	Activated partial thromboplastin time prolonged	1	Recovered/resolved	N	N
	Placebo	68	F	Fibrin D dimer increased	1	Recovered/resolved	N	N
	PAXLOVID	69	F	Prothrombin time prolonged	1	Recovered/resolved	N	N
	Placebo	70	F	Fibrin D dimer increased	8	Recovered/resolved	N	Y
	PAXLOVID	76	F	Fibrin D dimer increased	1	Recovered/resolved	N	N
	PAXLOVID	81	F	Fibrin D dimer increased	1	Recovered/resolved	N	N

Source: adae.xpt; Software: JMP.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
[2.] Duration of treatment is 5 days.
[3.] Relatedness is determined by investigator.
Abbreviations: AE, adverse event; F, female; M, male; N, no; SAE, serious adverse event; Y, yes

Table 174. Inflammatory Related Laboratory Outliers, Safety Population, EPIC-HR and EPIC-SR[1]

		EPIC-HR		EPIC-SR		Pooled	
Parameter	**Outlier**	**PAXLOVID N=1038 n/N_w (%)**	**Placebo N=1053 n/N_w (%)**	**PAXLOVID N=540 n/N_w (%)**	**Placebo N=528 n/N_w (%)**	**PAXLOVID N=1578 n/N_w (%)**	**Placebo N=1581 n/N_w (%)**
Activated partial thromboplastin time (sec)	>1.1x ULN	183/928 (19.7)	181/942 (19.2)	88/513 (17.2)	88/498 (17.7)	271/1441 (18.8)	269/1440 (18.7)
D-Dimer (ng/mL)	>1.5x ULN	120/975 (12.3)	186/988 (18.8)	39/522 (7.5)	47/520 (9.0)	159/1497 (10.6)	233/1508 (15.5)
Eosinophils (10^9/L)	>1.2x ULN	7/870 (0.8)	9/882 (1.0)	0/547 (0.0)	2/441 (0.5)	7/1417 (0.5)	11/1323 (0.8)
Leukocytes (10^9/L)	<0.6x LLN	1/873 (0.1)	9/890 (1.0)	1/461 (0.2)	2/446 (0.4)	2/1334 (0.1)	11/1336 (0.8)
	>1.5x ULN	13/873 (1.5)	10/890 (1.1)	2/461 (0.4)	4/446 (0.9)	15/1334 (1.1)	13/1336 (1.0)
Lymphocytes (10^9/L)	<0.8x LLN	18/870 (2.1)	42/882 (4.8)	5/457 (1.1)	7/441 (1.6)	23/1327 (1.7)	49/1323 (3.7)
	>1.2x ULN	9/870 (1.0)	8/882 (0.9)	4/457 (0.9)	0/441 (0.0)	13/1327 (1.0)	8/1323 (0.6)
Neutrophils (10^9/L)	<0.8x LLN	24/866 (2.8)	43/881 (4.9)	14/455 (3.1)	19/439 (4.3)	38/1321 (2.9)	62/1320 (4.7)
	>1.2x ULN	55/866 (6.4)	33/881 (3.7)	12/455 (2.6)	9/439 (2.1)	67/1321 (5.1)	41/1320 (3.1)
Platelets (10^9/L)	<0.5x LLN	0/864 (0.0)	4/884 (0.5)	0/456 (0.0)	0/439 (0.0)	0/1320 (0.0)	4/1323 (0.3)
	>1.75x ULN	5/864 (0.6)	10/884 (1.1)	0/456 (0.0)	1/439 (0.2)	5/1320 (0.4)	11/1323 (0.8)
Prothrombin intl. normalized ratio	>1.1x ULN	49/931 (5.3)	51/942 (5.4)	13/513 (2.5)	12/498 (2.4)	62/1444 (4.3)	63/1440 (4.4)
Prothrombin time (sec)	>1.1x ULN	92/931 (9.9)	106/942 (11.3)	14/513 (2.7)	12/498 (2.4)	106/1444 (7.3)	118/1440 (8.2)
Fibrinogen (mg/dL)	<0.75x Baseline	311/974 (31.9)	284/997 (28.5)	160/524 (30.5)	138/504 (27.4)	471/1498 (31.4)	422/1501 (28.1)
	>1.25x Baseline	160/974 (16.4)	238/988 (24.1)	78/524 (14.9)	87/504 (17.3)	238/1498 (15.9)	325/1492 (21.8)

Source: adlb.xpt; Software: JMP
[1]Duration of treatment is 5 days
Abbreviations: N, number of patients in treatment arm; n, number of patients meeting criteria; N_w: number of patients with data; ULN, upper limit of normal; LLN, lower limit of normal

As summarized in Section 7.6.3.2, any inflammatory-related AE was similar between the PAXLOVID groups and placebo group in EPIC-PEP (Table 175). Frequencies of inflammatory related AEs graded as severe or life-threatening were also similar between the PAXLOVID and placebo groups in EPIC-PEP (Table 175). Details regarding these events are described in Table 176. Table 177 describes inflammatory-related laboratory outliers in EPIC-PEP.

Table 175. Inflammatory-Related Adverse Events Assessment[1], Safety Population, EPIC-PEP[2]

Inflammatory-related AE assessment	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)
Any Inflammatory-related AE	31 (3.4)	31 (3.4)	31 (3.5)
Activated partial thromboplastin time prolonged	11 (1.2)	14 (1.5)	22 (2.4)
C-reactive protein increased	0	1 (0.1)	4 (0.4)
Eosinophilia	1 (0.1)	1 (0.1)	0
Fibrin D dimer increased	18 (2.0)	13 (1.4)	4 (0.4)
Haptoglobin increased	0	0	1 (0.1)
Platelet count increased	0	0	1 (0.1)
Prothrombin time prolonged	3 (0.3)	4 (0.4)	3 (0.3)
Maximum Severity			
Severe	2 (0.2)	0	2 (0.2)
Moderate	8 (0.9)	8 (0.9)	4 (0.4)
Mild	23 (2.5)	25 (2.7)	29 (3.2)
Serious	0	0	0
Resulting in discontinuation	1 (0.1)	0	1 (0.1)
Relatedness[3]	7 (0.8)	13 (1.4)	9 (1.0)

Source: adae.xpt; Software: JMP.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 38 visit.
[2.] Duration of treatment is 5 or 10 days.
[3.] Relatedness is determined by investigator.
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with adverse event

Table 176. Subjects With Severe (Grade 3) or Life-Threatening (Grade 4) Inflammatory-Related Adverse Events[1], EPIC-PEP[2]

Unique Subject Identifier	Treatment	Age	Sex	Dictionary-Derived Term	Study Day of AE Onset	Outcome of AE	Related[3]	SAE
(b) (6)	Placebo	67	M	Fibrin D dimer increased	1	Recovered/resolved	N	N
	Placebo	40	F	C-reactive protein increased	1	Recovered/resolved	N	N
	PAXLOVID 5 Days	34	F	Fibrin D dimer increased	1	Recovering/resolving	N	N
	PAXLOVID 10 Days	82	F	Activated partial thromboplastin time prolonged	8	Recovered/resolved	Y	N

Source: adae.xpt; Software: JMP.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
[2.] Duration of treatment is 5 days.
[3.] Relatedness is determined by investigator.
Abbreviations: F, female; M, male; N, no; SAE, serious adverse event; Y, yes

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Table 177. Inflammatory Related Laboratory Outliers, Safety Population, Trial EPIC-PEP[1]

Parameter	PAXLOVID 5 Days N=912 n/N_w (%)	PAXLOVID 10 Days N=911 n/N_w (%)	Placebo N=898 n/N_w (%)
Activated Partial Thromboplastin Time (sec)			
>1.1x ULN	337/888 (38.0)	319/888 (35.9)	318/878 (36.2)
Basophils (10^9/L)			
>1.2x ULN	1/870 (0.1)	0/861	0/857
D-Dimer (ng/mL)			
>1.5x ULN	74/893 (8.3)	62/889 (7.0)	71/879 (8.1)
Eosinophils (10^9/L)			
>1.2x ULN	7/870 (0.8)	11/861 (1.3)	9/857 (1.1)
Fibrinogen (mg/dL)			
>1.25x Baseline	184/894 (20.6)	195/889 (21.9)	195/880 (22.2)
<0.75x Baseline	227/894 (25.4)	239/889 (26.9)	220/880 (25.0)
Leukocytes (10^9/L)			
>1.5x ULN	2/871 (0.2)	0/863	2/859 (0.2)
<0.6x LLN	5/871 (0.6)	4/863 (0.5)	6/859 (0.7)
Lymphocytes (10^9/L)			
>1.2x ULN	9/871 (1.0)	9/863 (1.0)	10/859 (1.2)
<0.8x LLN	7/870 (0.8)	5/861 (0.6)	11/857 (1.3)
Monocytes (10^9/L)			
>1.2x ULN	3/870 (0.3)	2/861 (0.2)	0/857
Neutrophils (10^9/L)			
>1.2x ULN	18/870 (2.1)	13/860 (1.5)	14/857 (1.6)
<0.8x LLN	40/870 (4.6)	49/860 (5.7)	39/857 (4.6)
Platelets (10^9/L)			
>1.75x ULN	0/870	1/862 (0.1)	2/858 (0.2)
<0.5x LLN	0/870	2/862 (0.2)	2/858 (0.2)
Prothrombin Intl. Normalized Ratio			
>1.1x ULN	41/889 (4.6)	47/887 (5.3)	37/880 (4.2)
Prothrombin Time (sec)			
>1.1x ULN	96/889 (10.8)	114/887 (12.9)	110/880 (12.5)

Source: adlb.xpt; Software: JMP.
[1.] Duration of treatment is 5 or 10 days.
Abbreviations: Intl, international; N, number of patients in treatment arm; n, number of patients meeting criteria; Nw: number of patients with data; ULN, upper limit of normal; LLN, lower limit of normal

17.14.1. Hypersensitivity Events

The instances of rash in EPIC-HR and EPIC-SR are described below:

- Subject (b) (6): in EPIC-HR received PAXLOVID experienced severe (Grade 3) rash maculo-papular on Day 2 and the study drug was subsequently discontinued. This event was reported as resolved on Day 3 and the investigator assessed this event as related to study intervention.
- Subject (b) (6): in EPIC-HR received PAXLOVID and experienced mild (Grade 1) rash on Day 2 and subsequently treated with hydroxyzine hydrochloride. No modifications were

made to study intervention and the event was reported as resolved on Day 3. The investigator assessed this event was related to study intervention.

- Subject (b) (6): in EPIC-HR received PAXLOVID and experienced mild (Grade 1) rash and mild (Grade 1) pruritus on Day 2. The participant continued study intervention and these adverse events were reported as resolved on Day 54.

17.14.2. Hepatoxicity

This section provides additional details for the AESI of hepatotoxicity. As summarized in Section 7.6.3.4, frequencies of hepatic related AEs were low and comparable between the PAXLOVID and placebo groups in all three trials. Table 178 describes hepatobiliary AEs in EPIC-HR and EPIC-SR, Table 179 describes drug-induced liver injury assessment in EPIC-HR and EPIC-SR, and Table 180 describes hepatobiliary AEs in the subset of vaccinated participants with at least one risk factor for progression to severe disease in EPIC-SR.

Table 178. Hepatobiliary SOC Adverse Events Assessment[1], Safety Population, EPIC-HR and EPIC-SR[2]

	EPIC-HR		EPIC-SR		Pooled	
Hepatobiliary Disorders AE Assessment	**PAXLOVID N=1038 n(%)**	**Placebo N=1053 n(%)**	**PAXLOVID N=540 n(%)**	**Placebo N=528 n(%)**	**PAXLOVID N=1578 n(%)**	**Placebo N=1581 n(%)**
Any Hepatobiliary disorders AE	4 (0.4)	2 (0.2)	1 (0.2)	1 (0.2)	5 (0.3)	3 (0.2)
Cholestasis	1 (0.1)	0	0	0	1 (0.1)	0
Hepatic function abnormal	1 (0.1)	1 (0.1)	0	1 (0.2)	1 (0.1)	2 (0.1)
Hepatic mass	0	0	1 (0.2)	0	1 (0.1)	0
Hepatitis toxic	1 (0.1)	0	0	0	1 (0.1)	0
Hyperbilirubinemia	1 (0.1)	0	0	0	1 (0.1)	0
Liver injury	0	1 (0.1)	0	0	0	1 (0.1)
Maximum severity						
Severe	1 (0.1)	0	0	0	1 (0.1)	0
Moderate	2 (0.2)	1 (0.1)	1 (0.2)	1 (0.2)	3 (0.2)	2 (0.1)
Mild	1 (0.1)	1 (0.1)	0	0	1 (0.1)	1 (0.1)
Serious	0	0	1 (0.2)	0	1 (0.1)	0
Deaths	0	0	0	0	0	0
Resulting in discontinuation	0	0	0	0	0	0
Relatedness[3]	0	0	0	0	0	0

Source: adae.xpt; Software: JMP.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
[2.] Duration of treatment is 5 days.
[3.] Relatedness is determined by investigator.
Abbreviations: AE, adverse event; AESI, adverse events of special interest; N, number of patients in treatment arm; n, number of patients with adverse event

Table 179. Drug-Induced Liver Injury Assessment[1], Safety Population, EPIC-HR and EPIC-SR[2]

	EPIC-HR		EPIC-SR		Pooled	
Drug-Induced Liver Injury Assessment	**PAXLOVID N=1038 n (%)**	**Placebo N=1053 n (%)**	**PAXLOVID N=540 n (%)**	**Placebo N=528 n (%)**	**PAXLOVID N=1578 n (%)**	**Placebo N=1581 n (%)**
AE grouping related to AESI	17 (1.6)	30 (2.8)	13 (2.4)	9 (1.7)	30 (1.9)	39 (2.5)
Alanine aminotransferase inc.	17 (1.6)	27 (2.6)	13 (2.4)	8 (1.5)	30 (1.9)	35 (2.2)
Aspartate aminotransferase inc.	10 (1.0)	14 (1.3)	7 (1.3)	4 (0.8)	17 (1.1)	18 (1.1)
Cholestasis	1 (0.1)	0	0	0	1 (0.06)	0
Liver injury	0	1 (0.09)	0	0	0	1 (0.06)
Maximum severity						
Life-threatening	0	1 (0.09)	1 (0.2)	0	1 (0.06)	1 (0.06)
Severe	2 (0.2)	5 (0.5)	1 (0.2)	0	3 (0.2)	5 (0.3)
Moderate	15 (1.4)	20 (1.9)	7 (1.3)	6 (1.1)	22 (1.4)	26 (1.6)
Mild	0	4 (0.4)	4 (0.7)	3 (0.6)	4 (0.3)	7 (0.4)
Serious	0	1 (0.09)	0	0	0	1 (0.06)
Deaths	0	0	0	0	0	0
Resulting in discontinuation	1 (0.1)	1 (0.09)	0	0	1 (0.06)	1 (0.06)
Relatedness[3]	5 (0.5)	2 (0.2)	4 (0.7)	1 (0.2)	9 (0.6)	3 (0.2)

Source: adae.xpt; Software: R.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
1. Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
2. Duration of treatment is 5 days.
3. Relatedness is determined by investigator.
Abbreviations: AE, adverse event; AESI, adverse events of special interest; inc, increased; N, number of patients in treatment arm; n, number of patients with adverse event

Table 180. Adverse Events[1] of Drug-Induced Liver Injury Assessment, Vaccinated Participants With Risk Factors Assessed by the Applicant, Safety Population, EPIC-SR[2]

Drug-Induced Liver Injury Assessment	**PAXLOVID N=317 n (%)**	**Placebo N=314 n (%)**	**Risk Difference (%) (95% CI)[3]**
AE grouping related to AESI	6 (1.9)	4 (1.3)	0.6 (-1.3, 2.6)
Alanine aminotransferase inc.	6 (1.9)	4 (1.3)	0.6 (-1.3, 2.6)
Aspartate aminotransferase inc.	4 (1.3)	1 (0.3)	0.9 (-0.4, 2.3)
Maximum severity			
Death	0	0	0 (0, 0)
Life-threatening	0	0	0 (0, 0)
Severe	1 (0.3)	0	0.3 (-0.3, 0.9)
Moderate	4 (1.3)	4 (1.3)	-0.0 (-1.8, 1.7)
Mild	1 (0.3)	0	0.3 (-0.3, 0.9)
Serious	0	0	0 (0, 0)
Deaths	0	0	0 (0, 0)
Resulting in discontinuation	0	0	0 (0, 0)
Relatedness	2 (0.6)	1 (0.3)	0.3 (-0.8, 1.4)

Source: adae.xpt; Software: R.
Note: Participants enrolled at sites 1281 and 1488 (including those switched to 1282) are excluded.
1. Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
2. Duration of treatment is 5 days.
3. Relatedness is determined by investigator.
Abbreviations: AE, adverse event; AESI, adverse events of special interest; inc, increased; N, number of patients in treatment arm; n, number of patients with adverse event

In EPIC-PEP there were three AEs in the hepatobiliary disorders system organ class (SOC). This included one SAE of severe (Grade 3) acute cholecystitis in subject (b) (6), a 47-year-old

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female who was in the PAXLOVID 5-day group. This subject experienced the SAE of acute cholecystitis on Day 14. This subject was reported resolved on Day 34 and the subject was subsequently discharged from the hospital. This AE was considered not related to study intervention. The remainder of AEs in the hepatobiliary SOC were mild in severity.

The remainder AEs were one each of mild (Grade 1) non-alcoholic steatohepatitis in the PAXLOVID 5-day group and mild (Grade 1) nonalcoholic fatty liver disease in the PAXLOVID 10-day group. None of the AEs were considered related to study intervention and none resulted in discontinuation of study drug.

In terms of drug-induced liver injury, severe and life-threatening AEs were infrequent, and none were considered SAEs (Table 181). There were no deaths and few cases resulted in discontinuation of study drug.

Table 181. Drug-Induced Liver Injury Assessment[1], Safety Population, EPIC-PEP[2]

Drug-Induced Liver Injury Assessment	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)
AE grouping related to AESI	2 (0.2)	7 (0.8)	12 (1.3)
Alanine aminotransferase increased	2 (0.2)	6 (0.7)	11 (1.2)
Aspartate aminotransferase increased	2 (0.2)	5 (0.5)	7 (0.8)
Maximum severity			
Death	0	0	0
Life-threatening	0	2 (0.2)	0
Severe	1 (0.1)	0	1 (0.1)
Moderate	1 (0.1)	2 (0.2)	5 (0.6)
Mild	0	3 (0.3)	6 (0.7)
Serious	0	0	0
Deaths	0	0	0
Resulting in discontinuation	0	1 (0.1)	2 (0.2)
Relatedness[3]	1 (0.1)	4 (0.4)	3 (0.3)

Source: adae.xpt; Software: R.
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 38 visit.
[2.] Duration of treatment is 5 or 10 days.
[3.] Relatedness is determined by investigator.
Abbreviations: AE, adverse event; AESI, adverse events of special interest; N, number of patients in treatment arm; n, number of patients with adverse event

17.14.3. Hemodynamic Events

This section provides additional details for the AESI of hemodynamic adverse events. As summarized in Section 7.6.3.4, the frequencies of any hemodynamic AE was similar between the PAXLOVID and placebo groups in EPIC-HR and EPIC-SR (Table 182). Additionally, the frequencies of systolic blood pressure ≥140 mm hg, ≥160 mm hg, and ≥180 mm hg were similar between PAXLOVID and placebo groups (Table 183). Frequencies of diastolic blood pressure ≥90 mm hg, ≥110 mm hg, and ≥120 mm hg were also similar between both groups (Table 184).

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Table 182. Hemodynamic Adverse Events Assessment[1], Safety Population, EPIC-SR and EPIC-HR[2]

	EPIC-HR		EPIC-SR		Pooled	
Hemodynamic AE Assessment	**PAXLOVID N=1038 n(%)**	**Placebo N=1053 n(%)**	**PAXLOVID N=540 n(%)**	**Placebo N=528 n(%)**	**PAXLOVID N=1578 n(%)**	**Placebo N=1581 n(%)**
Any hemodynamic AE	8 (0.8)	8 (0.8)	8 (1.5)	8 (1.5)	16 (1.0)	16 (1.0)
Blood pressure decreased	0	0	1 (0.2)	0	1 (0.1)	0
Blood pressure increased	1 (0.1)	1 (0.1)	0	2 (0.4)	1 (0.1)	3 (0.2)
Bradycardia	0	0	0	1 (0.2)	0	1 (0.1)
Heart rate decreased	0	0	1 (0.2)	0	1 (0.1)	0
Hypertension	6 (0.6)	2 (0.2)	2 (0.4)	2 (0.4)	8 (0.5)	4 (0.3)
Hypertensive crisis	1 (0.1)	0	0	0	1 (0.1)	0
Hypotension	1 (0.1)	4 (0.4)	2 (0.4)	0	3 (0.2)	4 (0.3)
Sinus bradycardia	0	1 (0.1)	0	1 (0.2)	0	2 (0.1)
Sinus tachycardia	0	1 (0.1)	0	0	0	1 (0.1)
Tachycardia	0	0	1 (0.2)	3 (0.6)	1 (0.1)	3 (0.2)
Maximum severity						
Life-threatening	1 (0.1)	0	0	0	1 (0.1)	0
Severe	1 (0.1)	1 (0.1)	0	0	1 (0.1)	1 (0.1)
Moderate	1 (0.1)	4 (0.4)	2 (0.4)	3 (0.6)	3 (0.2)	7 (0.4)
Mild	6 (0.6)	3 (0.3)	6 (1.1)	5 (0.9)	12 (0.8)	8 (0.5)
Serious	1 (0.1)	0	0	0	1 (0.1)	0
Deaths	0	0	0	0	0	0
Relatedness[3]	0	0	1 (0.2)	0	1 (0.1)	0
Resulting in discontinuation	1 (0.1)	0	0	0	1 (0.1)	0

Source: adae.xpt; Software: JMP.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
[2.] Duration of treatment is 5 days.
[3.] Relatedness is determined by investigator.
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with adverse event

Table 183. Percentage of Patients With Maximum Systolic Blood Pressure by Category of Blood Pressure Post-Baseline, Safety Population, EPIC-HR and EPIC-SR

	EPIC-HR			EPIC-SR			Pooled		
Systolic Blood Pressure (mmHg)	PAXLOVID N=1038 n/Nw (%)	Placebo N=1053 n/Nw (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n/Nw (%)	Placebo N=528 n/Nw (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n/Nw (%)	Placebo N=1581 n/Nw (%)	Risk Difference (%) (95% CI)
<90	0/1038 (0)	0/1052 (0)	0 (0, 0)	0/540 (0)	0/527 (0)	0 (0, 0)	0/1578 (0)	0/1579 (0)	0 (0, 0)
≥90	1038/1038 (100)	1052/1052 (100)	0 (0, 0)	540/540 (100)	527/527 (100)	0 (0, 0)	1578/1578 (100)	1579/1579 (100)	0 (0, 0)
≥120	933/1038 (89.9)	935/1052 (88.9)	1.0 (-1.6, 3.6)	459/540 (85.0)	450/527 (85.4)	-0.4 (-4.7, 3.9)	1392/1578 (88.2)	1385/1579 (87.7)	0.5 (-1.8, 2.8)
≥140	204/1038 (19.7)	201/1052 (19.1)	0.5 (-2.8, 3.9)	97/540 (18.0)	101/527 (19.2)	-1.2 (-5.9, 3.5)	301/1578 (19.1)	302/1579 (19.1)	-0.1 (-2.8, 2.7)
≥160	12/1038 (1.2)	19/1052 (1.8)	-0.7 (-1.7, 0.4)	8/540 (1.5)	10/527 (1.9)	-0.4 (-2.0, 1.1)	20/1578 (1.3)	29/1579 (1.8)	-0.6 (-1.4, 0.3)
≥180	1/1038 (0.1)	4/1052 (0.4)	-0.3 (-0.7, 0.1)	1/540 (0.2)	5/527 (0.9)	-0.8 (-1.7, 0.1)	2/1578 (0.1)	9/1579 (0.6)	-0.4 (-0.9, -0.0)

Source: advs.xpt; Software: R.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
Abbreviations: N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data

Table 184. Percentage of Patients With Maximum Diastolic Blood Pressure by Category of Blood Pressure Post-Baseline, Safety Population, EPIC-HR and EPIC-SR

	EPIC-HR			EPIC-SR			Pooled		
Diastolic Blood Pressure (mmHg)	PAXLOVID N=1038 n/Nw (%)	Placebo N=1053 n/Nw (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n/Nw (%)	Placebo N=528 n/Nw (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n/Nw (%)	Placebo N=1581 n/Nw (%)	Risk Difference (%) (95% CI)
<60	0/1038	0/1052	0	0/540	0/527	0	0/1578	0/1579	0
	(0)	(0)	(0, 0)	(0)	(0)	(0, 0)	(0)	(0)	(0, 0)
≥60	1038/1038	1052/1052	0	540/540	527/527	0	1578/1578	1579/1579	0
	(100)	(100)	(0, 0)	(100)	(100)	(0, 0)	(100)	(100)	(0, 0)
≥90	243/1038	238/1052	0.8	91/540	126/527	-7.1	334/1578	364/1579	-1.9
	(23.4)	(22.6)	(-2.8, 4.4)	(16.9)	(23.9)	(-11.9, -2.2)	(21.2)	(23.1)	(-4.8, 1.0)
≥110	3/1038	6/1052	-0.3	3/540	3/527	-0.0	6/1578	9/1579	-0.2
	(0.3)	(0.6)	(-0.8, 0.3)	(0.6)	(0.6)	(-0.9, 0.9)	(0.4)	(0.6)	(-0.7, 0.3)
≥120	0/1038	0/1052	0	0/540	1/527	-0.2	0/1578	1/1579	-0.1
	(0)	(0)	(0, 0)	(0)	(0.2)	(-0.6, 0.2)	(0)	(0.06)	(-0.2, 0.1)

Source: advs.xpt; Software: R
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
Abbreviations: N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data

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As described in Section 7.6.3.4, in EPIC-PEP, the AE of hypertension was infrequent and occurred at similar frequencies between the 5-day (0.2%), 10-day (0.2%), and placebo (0.1%) groups. One subject experienced moderate (Grade 2) hypertension in the PAXLOVID 10-day group. The remained of instances of hypertension were all mild (Grade 1) in severity. Other hemodynamic AEs in the PAXLOVID 5-day group included one AE of moderate (Grade 2) bradycardia. In the PAXLOVID 10-day group there was one each of loss of consciousness and syncope, all of which were mild (Grade 1) in severity. There were no severe (Grade 3) or higher AEs associated with hemodynamic events in the Safety Population in EPIC-PEP. When evaluating vital signs, frequencies of systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg were similar across all groups (Table 185 and Table 186).

Table 185. Percentage of Patients With Maximum Systolic Blood Pressure by Category of Blood Pressure Post-Baseline, Safety Population, EPIC-PEP

Systolic Blood Pressure (mmHg)	PAXLOVID 5 Days N=912 n/N_w (%)	PAXLOVID 10 Days N=911 n/N_w (%)	Placebo N=898 n/N_w (%)
<90	0/905 (0)	0/908 (0)	0/895 (0)
≥90	905/905 (100)	908/908 (100)	895/895 (100)
≥120	792/905 (87.5)	809/908 (89.1)	785/895 (87.7)
≥140	96/905 (10.6)	95/908 (10.5)	89/895 (9.9)
≥160	2/905 (0.2)	13/908 (1.4)	6/895 (0.7)
≥180	1/905 (0.1)	2/908 (0.2)	3/895 (0.3)

Source: advs.xpt; Software: R.
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
Abbreviations: N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data

Table 186. Percentage of Patients With Maximum Diastolic Blood Pressure by Category of Blood Pressure Post-Baseline, Safety Population, Trial EPIC-PEP

Diastolic Blood Pressure (mmHg)	PAXLOVID 5 Days N=912 n/N_w (%)	PAXLOVID 10 Days N=911 n/N_w (%)	Placebo N=898 n/N_w (%)
<60	1/862 (0.1)	0/863 (0)	0/851 (0)
≥60	861/862 (99.9)	863/863 (100)	851/851 (100)
≥90	101/862 (11.7)	93/863 (10.8)	106/851 (12.5)
≥110	2/862 (0.2)	3/863 (0.3)	0/851 (0)
≥120	0/862 (0)	0/863 (0)	0/851 (0)

Source: advs.xpt; Software: R.
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
Abbreviations: N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data

Overall, frequencies of AEs and maximum blood pressures were similar between the PAXLOVID and placebo groups in all three trials. Specific labeling will be added to address hypertension given post-authorization findings.

17.14.4. Dysgeusia

Narratives for severe (Grade 3) dysgeusia and higher are provided below:

- Subject (b) (6): in EPIC-SR was a 33-year-old female who received PAXLOVID. On Day 1 this individual experienced severe (Grade 3) dysgeusia and study intervention was

permanently discontinued on Day 3 in response to this event with last documented dose on Day 2. This AE was reported as resolved on Day 2.

- Subject [redacted]: in EPIC-HR was a 47-year-old male who received PAXLOVID. On Day 4 this individual experienced severe (Grade 3) dysgeusia which was reported as resolved on Day 6. No changes were made to study intervention.
- Subject [redacted]: in EPIC-PEP was a 51-year-old female in the PAXLOVID 10-day group who experienced severe (Grade 3) dysgeusia on Day 2 of study intervention and was reported resolved on Day 7.
- Subject [redacted]: in EPIC-PEP was a 38-year-old male in the PAXLOVID 5-day group who experienced severe (Grade 3) dysgeusia on Day 1 of study intervention. This was reported resolved on Day 6.

18. Clinical Virology

18.1. SARS-CoV-2 RNA Shedding and Rebound

18.1.1. Methods for Analyses of Viral RNA Shedding and Serology Testing

Nasopharyngeal (NP) swab samples (in some cases [~5%] collected as nasal mid-turbinate swab samples) for viral shedding and nucleotide sequencing analyses were collected at Baseline (Day 1), Day 3, Day 5 (End-of-Treatment), Day 10 and Day 14; a small number of subjects had additional unplanned samples collected after Day 14. Viral RNA levels were measured at a central laboratory [redacted] using the Abbott RealTime Quantitative SARS-CoV-2 assay, which is a quantitative real-time RT-PCR assay. The assay targets the viral RNA-dependent RNA polymerase (RdRp, i.e., nsp12) and nucleocapsid (N) genes, and utilizes the reagents and equivalent application specifications of the Abbott Real-Time SARS-CoV-2 Qualitative assay that is available under EUA (Abbott 2021). The assay has a lower limit of quantification (LLOQ) of 100 (2 $\log_{10}$) copies/mL. The limit of detection (LOD) of the assay, based on the ≥95% positive detection rate, is also considered to be 100 (2 $\log_{10}$) copies/mL. These and other assay performance parameters were validated at the [redacted] central laboratory [redacted] For quantitative viral RNA analysis purposes, results of SARS-CoV-2 RNA "<LLOQ/Detected" were assigned a quantitative value of 1.7 $\log_{10}$ copies/mL, while results of "Not Detected" were assigned a quantitative value of 0 $\log_{10}$ copies/mL.

Serology testing involved Elecsys® Anti-SARS-CoV-2 assays targeting the spike (S) or nucleocapsid (N) proteins. Both assays detected total antibody without distinguishing between IgG, IgM, and IgA. Participants were considered to be SARS-CoV-2 seropositive at baseline if they had evidence of antibodies to either the viral S or the viral N antigen.

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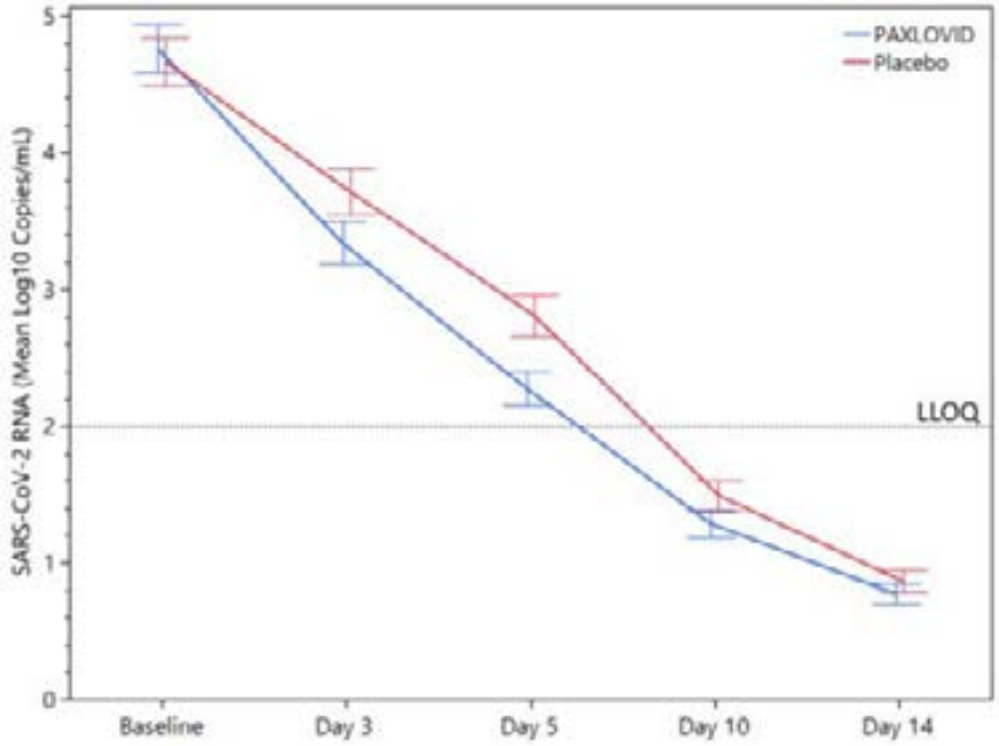
18.1.2. Effect of PAXLOVID Treatment on SARS-CoV-2 RNA Shedding

EPIC-HR

Analyses of SARS-CoV-2 RNA levels in NP samples in EPIC-HR are summarized in Figure 73. PAXLOVID treatment was associated with a mean 0.70 $\log_{10}$ copies/mL (median 0.97 $\log_{10}$ copies/mL) more rapid decline relative to placebo through Day 5/end-of-treatment. Similar results were observed in the mITT analysis (mean 0.71 $\log_{10}$ copies/mL, median 0.90 $\log_{10}$ copies/mL greater decline) and mITT1 (mean 0.68 $\log_{10}$ copies/mL, median 0.86 $\log_{10}$ copies/mL greater decline) analysis sets. Note that the Applicant's analyses of these data primarily focused on the mITT1 population and excluded subjects with a 'Not Detected' or a missing baseline viral RNA result, or subjects with non-validated/non-NP swab use. Based on these analysis parameters for the mITT1 population, PAXLOVID was associated with a mean 0.85 $\log_{10}$ copies/mL (median 0.83 $\log_{10}$ copies/mL) more rapid decline in viral RNA levels relative to placebo through Day 5/end-of-treatment.

Figure 73. EPIC-HR: Analysis of SARS-CoV-2 RNA levels (Log_{10} Copies/mL) in NP Samples

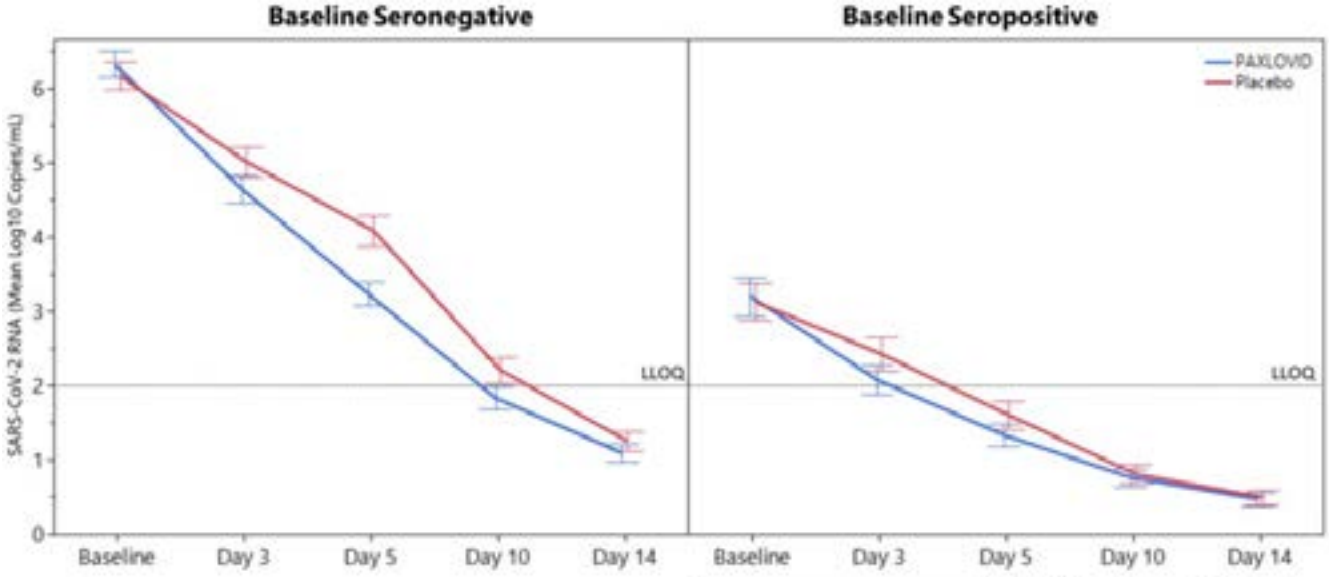


Day 5/EOT Analysis Visit	PAXLOVID	Placebo
Mean Change from BL (log_{10} cp/mL)	-2.48	-1.79
% (n/N) <LLOQ	47.8% (447/936)	44.1% (415/942)

Source: FDA analysis of ADMC and ADSL datasets.
Note: mITT2 analysis set, i.e., all subjects who took at least one dose of study intervention.
Note: Chart shows mean +/- 95% confidence intervals.
Abbreviations: BL, baseline; EOT, end of trial; LLOQ, lower limit of quantitation; log, logarithm; N, total number of subjects; n, number of subjects in sample; NP, nasopharyngeal; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Although viral RNA levels in NP samples at baseline were orders of magnitude lower among subjects who were baseline anti-SARS-CoV-2 seropositive, modest antiviral activity of PAXLOVID could be observed both in subjects who were baseline seronegative or baseline seropositive (Figure 74).

Figure 74. EPIC-HR: Analysis of SARS-CoV-2 RNA levels (Log_{10} Copies/mL) in NP Samples According to Baseline Serostatus



	PAXLOVID	Placebo
Day 5 Mean Change from BL (log_{10} cp/mL)	-3.13	-2.06
Day 5 % (n/N) <LLOQ	24.0% (103/429)	20.0% (87/435)

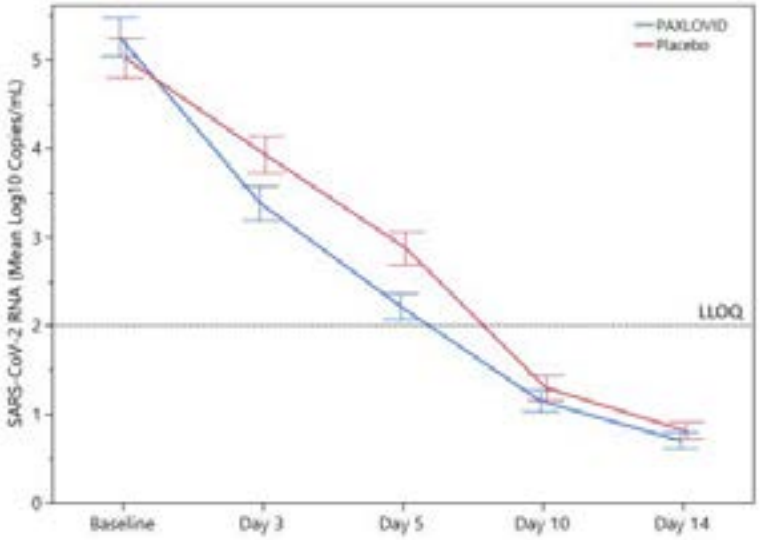
	PAXLOVID	Placebo
Day 3 Mean Change from BL (log_{10} cp/mL)	-1.11	-0.72
Day 3 % (n/N) <LLOQ	57.6% (266/462)	53.5% (242/452)
Day 5 % (n/N) <LLOQ	70.4% (311/442)	67.7% (296/437)

Source: FDA analysis of ADMC and ADSL datasets.
Note: mITT1 analysis set, i.e., subjects who did not receive nor were expected to receive COVID-19 therapeutic mAb treatment.
Note: Chart shows mean +/- 95% confidence intervals.
Abbreviations: BL, baseline; LLOQ, lower limit of quantitation; log, logarithm; N, total number of subjects; n, number of subjects in sample; NP, nasopharyngeal; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

EPIC-SR

Analyses of SARS-CoV-2 RNA levels in NP samples are summarized in Figure 75. PAXLOVID treatment was associated with a mean 0.87 log_{10} copies/mL (median 1.11 log_{10} copies/mL) more rapid decline relative to placebo through Day 5/End-of-Treatment. As noted above for EPIC-HR, the Applicant's analyses of these data excluded subjects with a 'Not Detected' or a missing baseline viral RNA result, or subjects with non-validated/non-NP swab use. Based on these analysis parameters for the mITT1 population, PAXLOVID was associated with a mean 0.97 log_{10} copies/mL (median 1.05 log_{10} copies/mL) more rapid decline in viral RNA levels relative to placebo through Day 5/end-of-treatment.

Figure 75. EPIC-SR: Analysis of SARS-CoV-2 RNA Levels (Log_{10} Copies/mL) in NP Samples



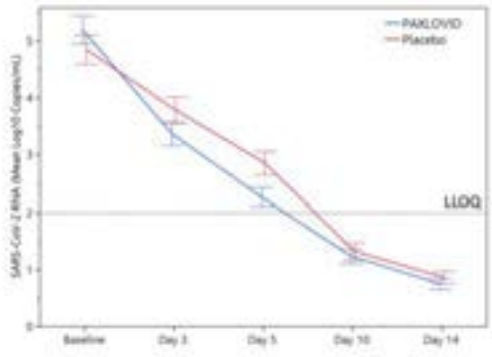
Day 5/EOT Analysis Visit	PAXLOVID	Placebo
Mean Change from BL (log_{10} cp/mL)	-3.03	-2.15
% (n/N) <LLOQ	50.6% (311/615)	39.8% (237/596)

Source: FDA analysis of ADMC and ADSL datasets.
Note: mITT1 analysis set i.e., all subjects who took at least one dose of study intervention.
Note: Chart shows mean +/- 95% confidence intervals.
Abbreviations: BL, baseline; EOT, end of trial; LLOQ, lower limit of quantitation; log, logarithm; N, total number of subjects; n, number of subjects in sample; NP, nasopharyngeal; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Antiviral activity of PAXLOVID was observed in both the 2021/Pre-Omicron and 2022/Omicron enrollment periods based on viral RNA shedding levels in NP samples (Figure 76).

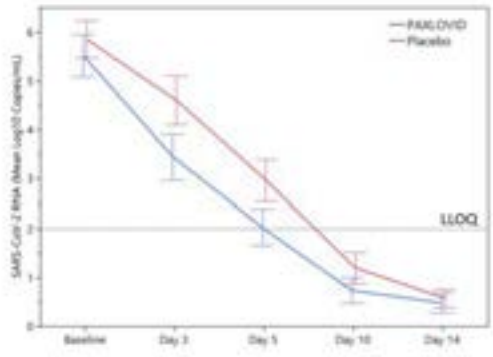
Figure 76. EPIC-SR: Analysis of SARS-CoV-2 RNA Levels (Log_{10} Copies/mL) in NP Samples, Pre- and Post-Omicron

2021: Pre-Omicron Period (n=539 PAXLOVID, n=528 Placebo)



Day 5/EOT Analysis Visit	PAXLOVID	Placebo
Mean Change from BL (log_{10} cp/mL)	-2.93	-2.01
% (n/N) <LLOQ	49.3% (251/509)	40.4% (199/492)

2022: Omicron Period* (n=114 PAXLOVID, n=106 Placebo)



Day 5/EOT Analysis Visit	PAXLOVID	Placebo
Mean Change from BL (log_{10} cp/mL)	-3.52	-2.85
% (n/N) <LLOQ	56.6% (60/106)	36.5% (38/104)

Source: FDA analysis of ADMC and ADSL datasets.
Note: Charts show mean +/- 95% confidence intervals.
Note: mITT1 analysis set i.e., all subjects who took at least one dose of study intervention
* Subjects enrolled in 2022 (March-June): Omicron variants detected in >99% (143/144) of subjects w/variant data
Abbreviations: BL, baseline; EOT, end of trial; LLOQ, lower limit of quantitation; log, logarithm; N, total number of subjects; n, number of subjects in sample; NP, nasopharyngeal; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

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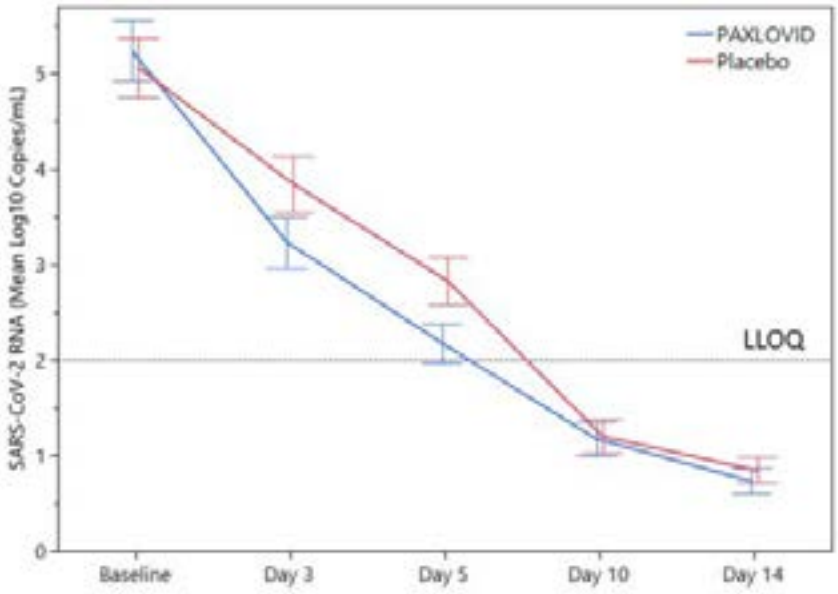
Antiviral activity of PAXLOVID was also observed among high-risk subjects who were enrolled in the EPIC-SR 2021 (Pre-Omicron) period and had previously received a SARS-CoV-2 vaccine (which was exclusionary in EPIC-HR) (Figure 77). Note that high-risk subjects were excluded from the 2022 enrollment period, regardless of vaccination status.

Figure 77. EPIC-SR: Analysis of SARS-CoV-2 RNA Levels (Log_{10} copies/mL) in NP Samples From High-Risk Subjects Who Had Received a SARS-CoV-2 Vaccine



Day 5/EOT Analysis Visit	PAXLOVID	Placebo
Mean Change from BL (log_{10} cp/mL)	-3.03	-2.27
% (n/N) <LLOQ	52.8% (163/309)	39.0% (114/292)

Source: FDA analysis of ADMC and ADSL datasets.
Note: mITT1 analysis set, 2021 enrollment period.
Note: Chart shows mean +/- 95% confidence intervals.
Abbreviations: BL, baseline; EOT, end of trial; LLOQ, lower limit of quantitation; log, logarithm; N, total number of subjects; n, number of subjects in sample; NP, nasopharyngeal; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

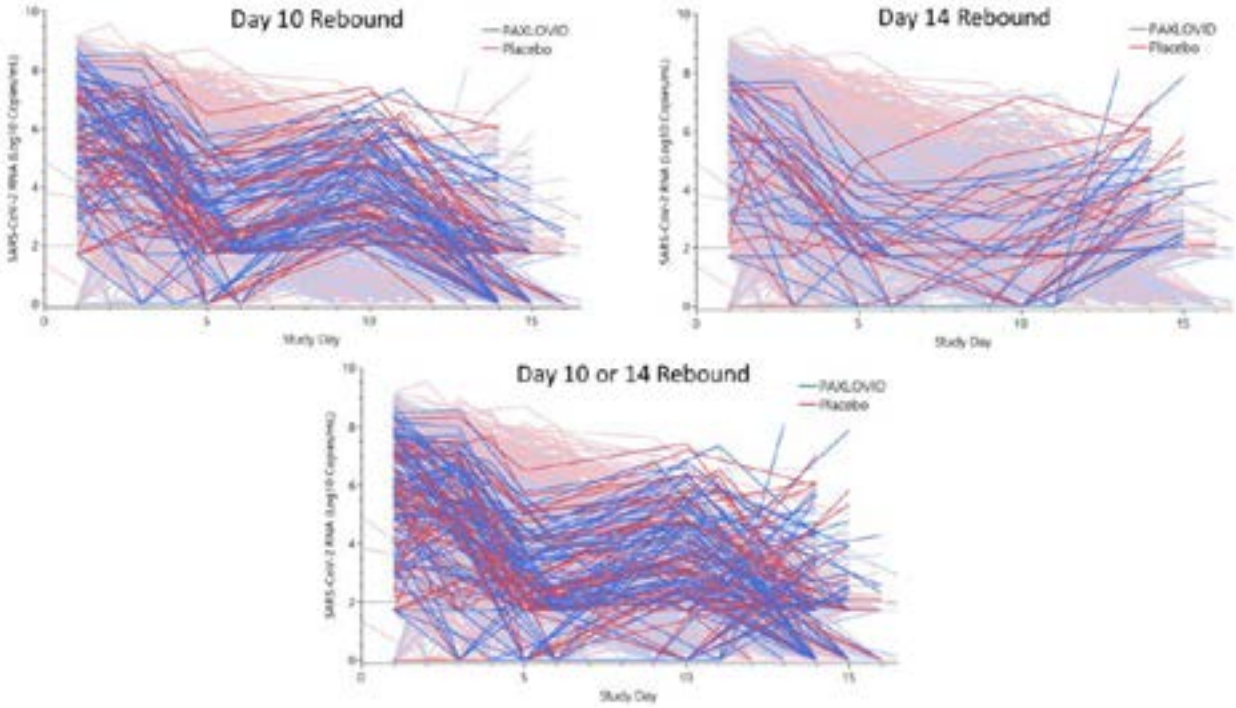
18.1.3. Additional Analyses of Viral RNA Rebound

FDA analyses of viral RNA rebound are summarized in the Integrated Review Section 6.3.6. The following section includes additional supporting analyses and details.

EPIC-HR

Viral RNA levels for individual subjects who met the definitions of viral RNA rebound are illustrated in Figure 78 and show substantial heterogeneity in the viral RNA patterns. No clear or consistent differences between PAXLOVID and placebo recipients in the RNA rebound patterns or magnitude of rebound are apparent.

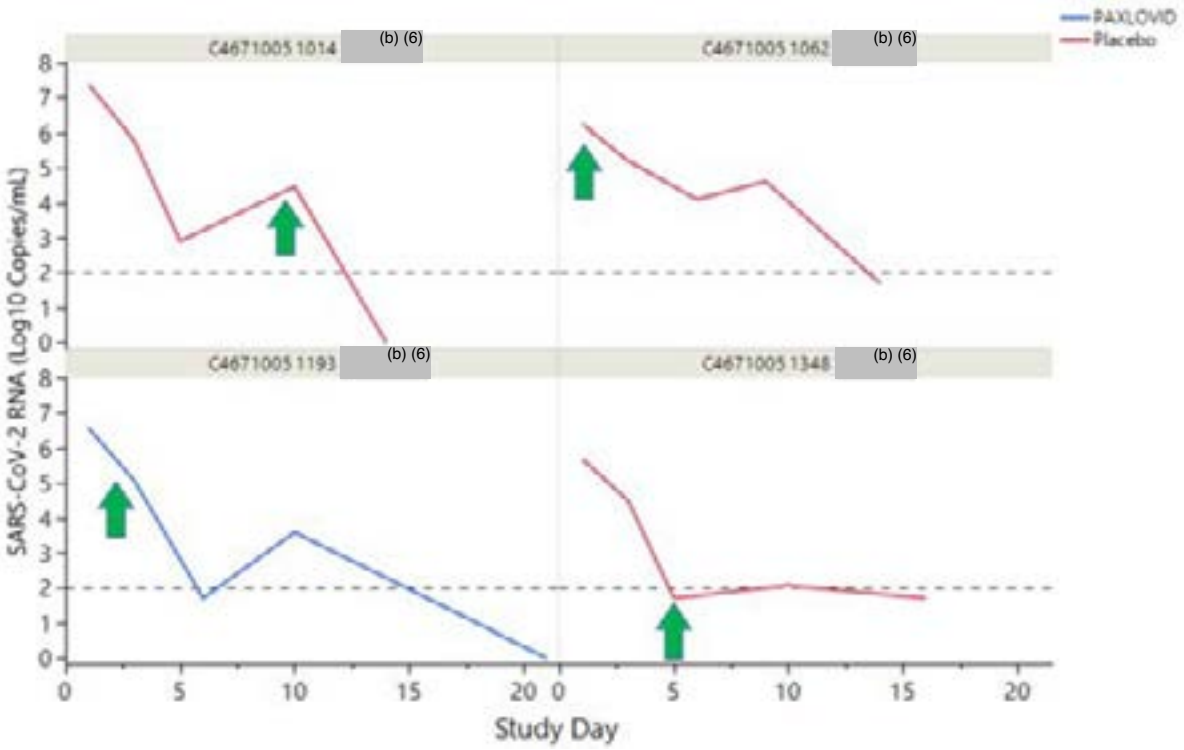
Figure 78. EPIC-HR: Viral RNA Levels Over Time for Individual Subjects Who Experienced Post-Treatment Viral RNA Rebound (Day 10, Day 14, or Day 10/14 [LLOQ/0.5 Combined])



Source: FDA analysis of ADMC and ADSL datasets.
Note: Lines in the foreground indicate subjects with viral RNA rebound. Results for all other subjects are in the background.
Note: The dashed lines indicate the assay LLOQ.
Abbreviations: LLOQ, lower limit of quantitation; log, logarithm; RNA, r bonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Post-treatment viral RNA rebound in EPIC-HR was not associated with the primary clinical outcome of COVID-19-related hospitalization or death from any cause through Day 28. Among the 130 subjects who experienced Day 10/14 viral RNA rebound, only 4 subjects (3%) reached the hospitalization or death endpoint (0 deaths), including 1 PAXLOVID recipient and 3 placebo recipients. Viral RNA results from these subjects are shown in Figure 79 and indicate there was not a consistent temporal relationship between post-Day 5 viral RNA rebound and the timing of hospitalization in these subjects. The hospitalization in the PAXLOVID recipient (Subject (b) (6)) occurred early during treatment and the subject was discharged from the hospital on Day 8 prior to the post-treatment viral RNA rebound on Day 10. One placebo treated subject (Subject (b) (6)) was admitted to the hospital on Day 9 around the time of viral RNA rebound observed on Day 10, but clearly this could not be attributed to a "post-treatment" viral RNA rebound and rather likely reflects natural COVID-19 disease progression.

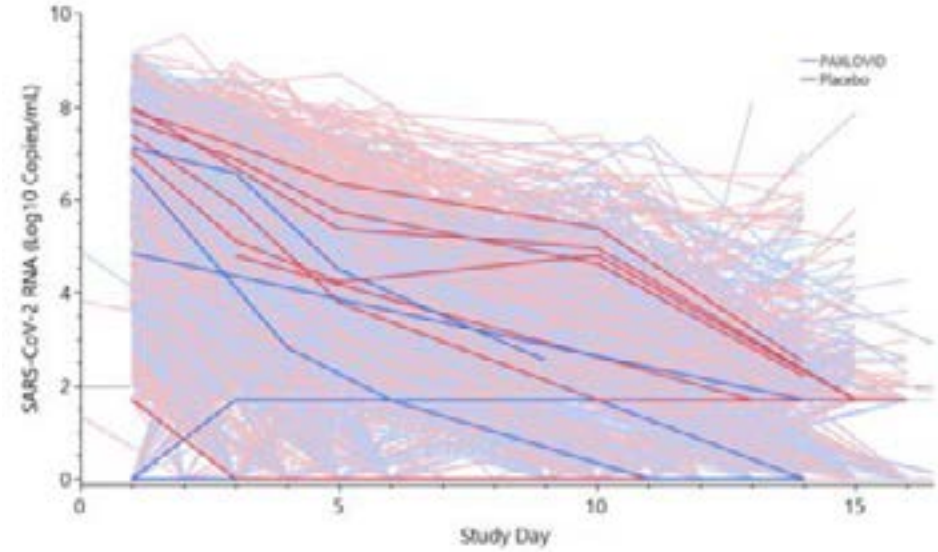
Figure 79. EPIC-HR: Viral RNA Levels in Subjects Who Experienced Post-Treatment Viral RNA Rebound (Day 10/14 [LLOQ/0.5 Combined]) and Reached the Primary Clinical Endpoint of COVID-19-Related Hospitalization or Death From Any Cause Through Day 28



Source: FDA analysis of ADMC and ADSL datasets.
Note: Arrows indicate timing of hospitalization.
Note: Dashed lines indicate the assay LLOQ.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; LLOQ, lower limit of quantitation; log, logarithm; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Post-treatment viral RNA rebound was not associated with baseline immunosuppression risk, although this was a small subgroup of subjects in the trial (n = 6 PAXLOVID, n = 7 placebo). Viral RNA results for the 13 subjects with baseline immunosuppression are shown in Figure 80. Only one of these subjects experienced post-treatment viral RNA rebound, and the subject received placebo. None of the subjects experienced the clinical endpoint of hospitalization or death. One additional subject not flagged for immunosuppression risk had HIV-1 infection, was treated with placebo, and did not have post-treatment viral RNA rebound.

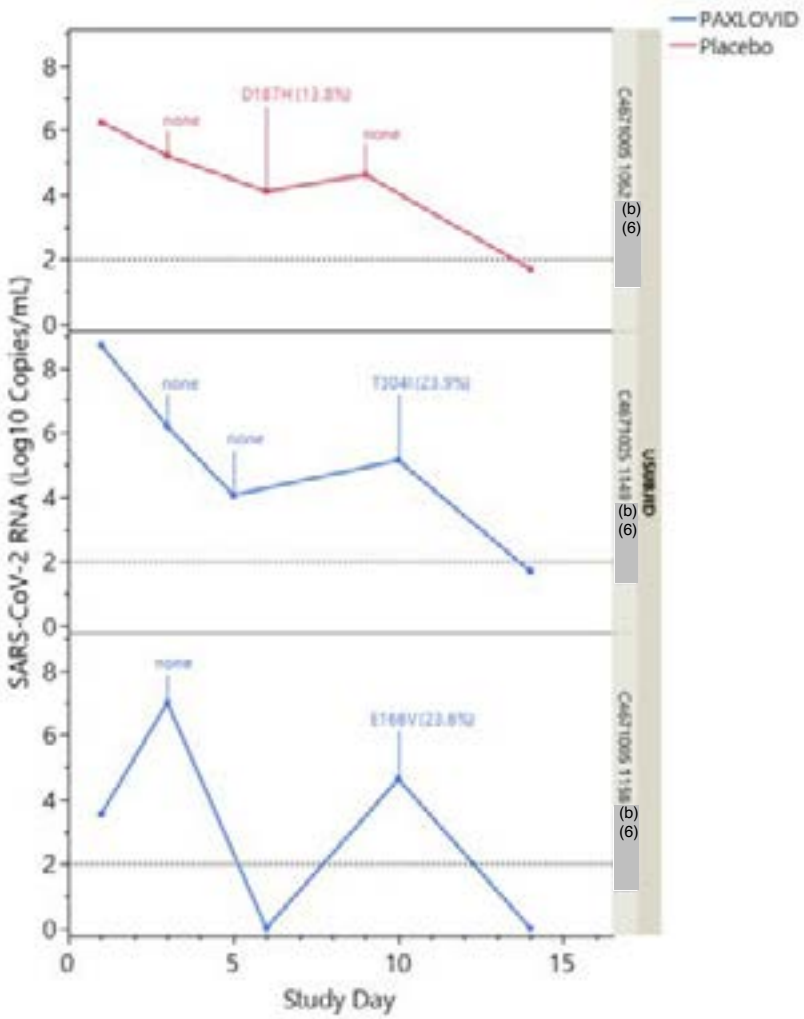
Figure 80. EPIC-HR: Viral RNA Levels in Subjects With Baseline Immunosuppression Risk



Source: FDA analysis of ADMC and ADSL datasets.
Note: Dashed line indicates assay LLOQ.
Note: Lines in the foreground indicate subjects with baseline immunosuppression risk. Results for all other subjects are in the background.
Abbreviations: LLOQ, lower limit of quantitation; log, logarithm; RNA, r bonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

With the exception of two PAXLOVID-treated subjects, post-treatment viral RNA rebound generally was not associated with the emergence of potential nirmatrelvir resistance-associated substitutions, defined as amino acid changes in M^{pro} at (1) a nirmatrelvir contact binding site residue (excluding positions V186 and Q189, discussed in Section 5), or (2) a position associated with resistance in cell culture. Of the 59 PAXLOVID treated subjects with viral RNA rebound and available viral sequence data, viruses from 2 (3%) subjects had a treatment-emergent substitution (TES) potentially associated with nirmatrelvir resistance, both around the time of viral RNA rebound on Day 10 (Figure 81). Virus from one placebo recipient (2% of 43 subjects with sequencing data) had an M^{pro} D187H TES, which occurred at a nirmatrelvir contact position but clearly would not have emerged due to nirmatrelvir drug pressure. Subject (b) (6) is the clearest case of post-treatment viral RNA rebound being associated with nirmatrelvir resistance, as the E166V substitution has been the clearest nirmatrelvir resistance-associated substitution observed to date based on the totality of nonclinical and clinical resistance data. The second PAXLOVID-treated subject ((b) (6)) had treatment-emergent M^{pro} T304I, which overlaps with the nsp5/nsp6 cleavage site and has also been associated with nirmatrelvir resistance in cell culture. Note that ~80% of the 103 subjects with post-treatment viral RNA rebound and viral sequencing data had sequence data available at a post-Day 5 timepoint.

Figure 81. EPIC-HR: Individual Subjects With Viral RNA Rebound and Detection of M^{pro} Treatment-Emergent Substitutions Potentially Associated With Nirmatrelvir Resistance (10% NGS Assay Sensitivity Cutoff)

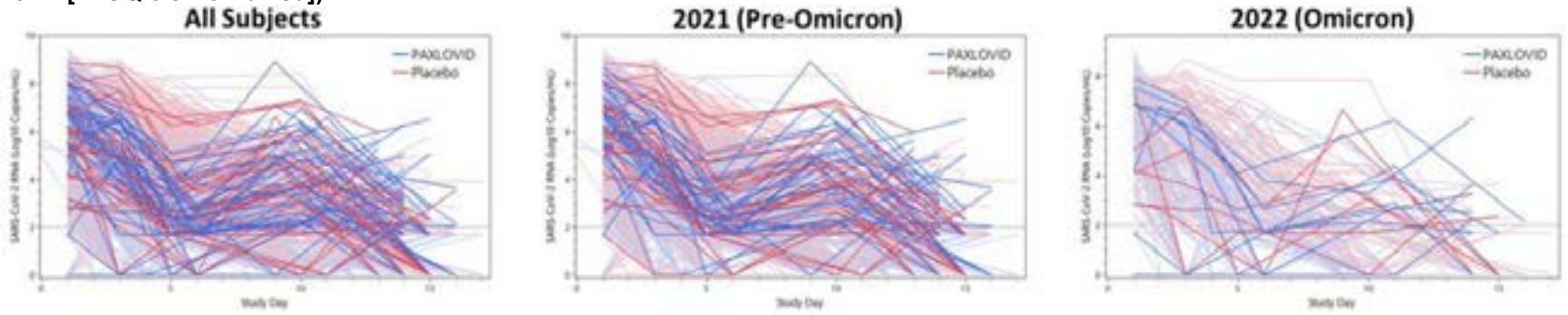


Source: FDA analysis of ADMC and ADSL datasets, and NGS analysis dataset.
Note: "None" indicates no treatment-emergent, resistance-associated substitutions were detected at the timepoint.
Note: Dashed lines indicate assay LLOQ.
Abbreviations: LLOQ, lower limit of quantitation; log, logarithm; M^{pro}, main protease; NGS, next-generation sequencing; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

EPIC-SR

Analyses of viral RNA levels for individual subjects in EPIC-SR with post-treatment viral RNA rebound again showed no obvious differences in the patterns or magnitude of viral RNA rebound between PAXLOVID and placebo recipients, either overall or within the 2021/Pre-Omicron or 2022/Omicron enrollment periods (Figure 82).

Figure 82. EPIC-SR: Viral RNA Levels Over Time for Individual Subjects Who Experienced Post-Treatment Viral RNA Rebound (Day 10/14 [LLOQ/0.5 Combined])



Source: FDA analysis of ADMC and ADSL datasets.
Note: Lines in the foreground indicate subjects with viral RNA rebound. Results for all other subjects are in the background.
Note: The dashed lines indicate the assay LLOQ.
Abbreviations: LLOQ, lower limit of quantitation; log, logarithm; RNA, r bonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Consistent with the results from EPIC-HR, PAXLOVID treatment ultimately did not result in a delay in viral RNA levels reaching <LLOQ in EPIC-SR. At all analysis visits, and in both the 2021/Pre-Omicron and 2022/Omicron periods, a similar or greater percentage of PAXLOVID recipients compared to placebo recipients had viral RNA <LLOQ (Table 187). Again, as in EPIC-HR, there is no indication that a positive SARS-CoV-2 RNA test result would be more likely for a PAXLOVID treated patient, compared to an untreated patient, at any single cross-sectional timepoint through Day 14 (i.e., 9 days post-treatment).

Table 187. EPIC-SR: Proportions of PAXLOVID or Placebo Recipients With Viral RNA <LLOQ at Each Analysis Visit

	All Subjects		2021 (Pre-Omicron)		2022 (Omicron)	
Visit	**PAXLOVID**	**Placebo**	**PAXLOVID**	**Placebo**	**PAXLOVID**	**Placebo**
Day 3	31.7% (199/628)	28.3% (174/614)	31.5% (164/520)	30.3% (154/509)	32.4% (35/108)	19.1% (20/105)
Day 5/EOT	50.6% (311/615)	39.8% (237/596)	49.3% (251/509)	40.4% (199/492)	56.6% (60/106)	36.5% (38/104)
Day 10	78.9% (471/597)	73.1% (431/590)	77.3% (382/494)	72.1% (352/488)	86.4% (89/103)	77.5% (79/102)
Day 14	89.7% (555/619)	86.5% (519/600)	89.2% (456/511)	85.7% (425/496)	91.7% (99/108)	90.4% (94/104)

Source: FDA analysis of ADMC and ADSL datasets.
Abbreviations: EOT, end of trial; LLOQ, lower limit of quantitation; RNA, ribonucleic acid

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On-Treatment Viral RNA Rebound (EPIC-HR)

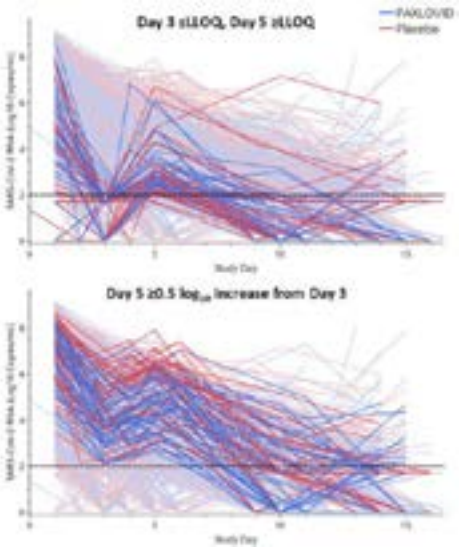
When conducting these analyses of viral RNA rebound it was observed that, while viral RNA levels in NP samples *on average* decline at a steady rate over time, and more rapidly among PAXLOVID recipients compared to placebo recipients, RNA levels from individual subjects can be highly variable and do not always follow a simple or consistent pattern, regardless of treatment. Transient increases in viral RNA levels within individuals may reflect natural variability in virus production in the upper respiratory compartment, periods of increased immune-mediated shedding of virus or viral components, or variability in technical sampling via topical swab, and not necessarily a clinically meaningful change in viral replication or viral burden due to removal of antiviral drug pressure.

To illustrate this point, viral RNA "rebound" (i.e., decrease followed by increase in RNA level) based on the same analysis parameters described above was frequently observed in EPIC-HR *during* treatment between Day 3 and Day 5 in both PAXLOVID and placebo recipients, and at a rate that was even greater than the rates of viral RNA rebound observed post-treatment (Figure 83). Given that viral RNA "rebound" observed during PAXLOVID treatment cannot be attributed to the cessation of PAXLOVID drug pressure, one should also not assume that an observation of post-treatment viral rebound must be caused by a sub-optimal treatment duration and the removal of PAXLOVID drug pressure, reflecting a post-treatment "relapse" of the viral infection. It may just as likely reflect natural variability in viral shedding or technical variability in viral sampling in the upper respiratory tract, which would be consistent with the similar rates of viral RNA rebound observed following treatment with either PAXLOVID or placebo in the EPIC-HR and EPIC-SR trials.

Figure 83. EPIC-HR: Observations of On-Treatment Viral RNA "Rebound" Between Day 3 and Day 5

	PAXLOVID	Placebo
On-treatment Viral RNA "Rebound"*	11.3% (77/680)	12.5% (74/594)
Post-treatment (D10/D14) Viral RNA Rebound, Day 5 Responders	8.1% (69/849)	6.5% (50/772)

*Day 3 Viral RNA Response (<LLOQ or ≥1 $\log_{10}$ copies/mL from BL to Day 3) AND
- Day 3 ≤LLOQ, followed by Day 5 ≥LLOQ, OR
- Day 3 ≥LLOQ, followed by Day 5 ≥0.5 $\log_{10}$ increase from Day 3



Source: FDA analysis of ADMC and ADSL datasets.
Abbreviations: D, day; LLOQ, lower limit of quantitation; log, logarithm; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

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18.2. Analyses of Cell Culture Infectious Virus in EPIC-HR

Late in the review cycle, the Applicant provided a final report on SARS-CoV-2 cell culture infectivity results from the EPIC-HR trial (Pfizer 2022b); no infectivity results were reported for EPIC-SR. A dataset with these results was subsequently submitted, but independent analyses of the dataset were not conducted.

Cell Culture Infectivity Assay Methods and Selection of Samples for Analysis

Viral infectivity assay methods were described in an earlier interim report (Pfizer 2022n). Briefly, NP/nasal swab samples were submitted for infectivity analysis if viral RNA levels were >2.0 $\log_{10}$ copies/mL. Two infectivity assays were conducted in parallel: a viral recovery assay and a viral titration (50% tissue culture infectious dose, $TCID_{50}$) immunoassay. In the viral recovery assay, samples were diluted (1:4, 1:10, 1:100 and 1:1,000) and plated onto Vero-TMPRSS2 cells. Infections were carried out for 5 days and wells positive for virus infectivity were identified by scoring for cytopathic effect (CPE). The viral titration immunoassay was also performed using Vero-TMPRSS2 cells. Samples were serially diluted and plated onto cells, and after 40 to 46 hours of incubation, the cell monolayer was fixed and assessed for the presence of SARS-CoV-2 antigen (specific antigen not specified) by an *in situ* enzyme linked immunosorbent assay (ELISA). Wells identified as positive for viral antigen were used to calculate viral titers (expressed as $TCID_{50}$/mL) of NP/nasal samples using the Spearman-Karber equation. The LLOQ of the viral titration assay was reported as 1.83 $\log_{10}$ $TCID_{50}$/mL.

Specific subjects/samples selected for infectivity analyses included the following:

1. Subjects who experienced treatment failure, defined as those who reached the primary endpoint event of COVID-19 related hospitalization or death from any cause through Day 28
2. Subjects who experienced Applicant-defined "transient viral load rebound (tVLR) or non-transient viral load rebound (ntVLR)" (note: we would refer to these as measures of "viral RNA shedding rebound"):
   - Transient viral load rebound (tVLR): Day 10 viral RNA ≥3.0 $\log_{10}$ copies/mL AND ≥0.5 $\log_{10}$ copies/mL relative to Day 5, AND Day 14 viral RNA <0.5 $\log_{10}$ copies/mL change relative to Day 5 or <3 $\log_{10}$ copies/mL (i.e., viral RNA rebound to ≥3.0 $\log_{10}$ copies/mL on Day 10 that does not persist through Day 14).
   - Non-transient viral load rebound (ntVLR): If Day 14 data are available, Day 14 viral RNA ≥3.0 $\log_{10}$ copies/mL and ≥0.5 $\log_{10}$ copies/mL relative to Day 5; if Day 14 data are not available, Day 10 viral RNA ≥3.0 $\log_{10}$ copies/mL AND ≥0.5 $\log_{10}$ copies/mL relative to Day 5. (i.e., viral RNA rebound to ≥3.0 $\log_{10}$ copies/mL through Day 14, or through Day 10 if Day 14 data are not available).
3. Subjects who experienced Applicant-defined "sustained viral load non-response (sNR-VL)," defined as having at least 2 viral RNA measurements at the Day 5, Day 10, and Day 14 visits, with all available results ≥4 $\log_{10}$ copies/mL
4. Randomly selected Day 3 and Day 5 samples with viral RNA measurements from 142 PAXLOVID-treated subjects and 142 placebo-treated subjects with baseline viral RNA levels ≥5 $\log_{10}$ copies/mL

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Note that the Applicant's definitions of tVLR and ntVLR would not capture all subjects who met the more sensitive FDA Day 10/14 (LLOQ/0.5) definition of viral RNA rebound, although they would capture those with higher viral RNA levels (≥3 $\log_{10}$ copies/mL at Day 10 or Day 14) in whom positive infectivity is more likely to be detected. Also note that only analysis (4) from the list above excluded subjects from EPIC-HR sites 1274 and 1470 due to data reliability issues. The inclusion of these sites in the infectivity samples from subjects who experienced viral RNA rebound does not change any conclusions from these analyses, as only 3 subjects from these sites (all PAXLOVID-treated) experienced viral RNA rebound; none of these subjects had positive infectivity results by either assay on Day 10 or Day 14.

Infectivity Assay Results for Subjects With Viral RNA Rebound

Based on the Applicant's definitions, and using the denominators previously reported (Pfizer 2022n), tVLR was observed in 4.1% (40/977) and 2.5% (24/964) of PAXLOVID and placebo recipients, respectively; ntVLR was observed in 2.3% (22/977) and 1.5% (14/964) of PAXLOVID and placebo recipients, respectively; and combined tVLR or ntVLR were observed in 6.3% (62/977) and 3.9% (38/964) of PAXLOVID and placebo recipients, respectively.

Table 188 summarizes available qualitative (viral recovery) and quantitative (viral titration) cell culture infectivity results for subjects who met the combined tVLR or ntVLR definitions of viral RNA rebound. Among subjects with Applicant-defined viral RNA rebound, positive cell culture infectivity results at Day 10 or Day 14 were observed in 11.3% (7/62) of PAXLOVID-treated subjects and 5.3% (2/38) of placebo-treated subjects.

Table 188. EPIC-HR: Cell Culture Infectivity Results by Viral Recovery Assay for Subjects Who Met the Applicant's Definitions of "Transient Viral Load Rebound" or "Non-Transient Viral Load Rebound"

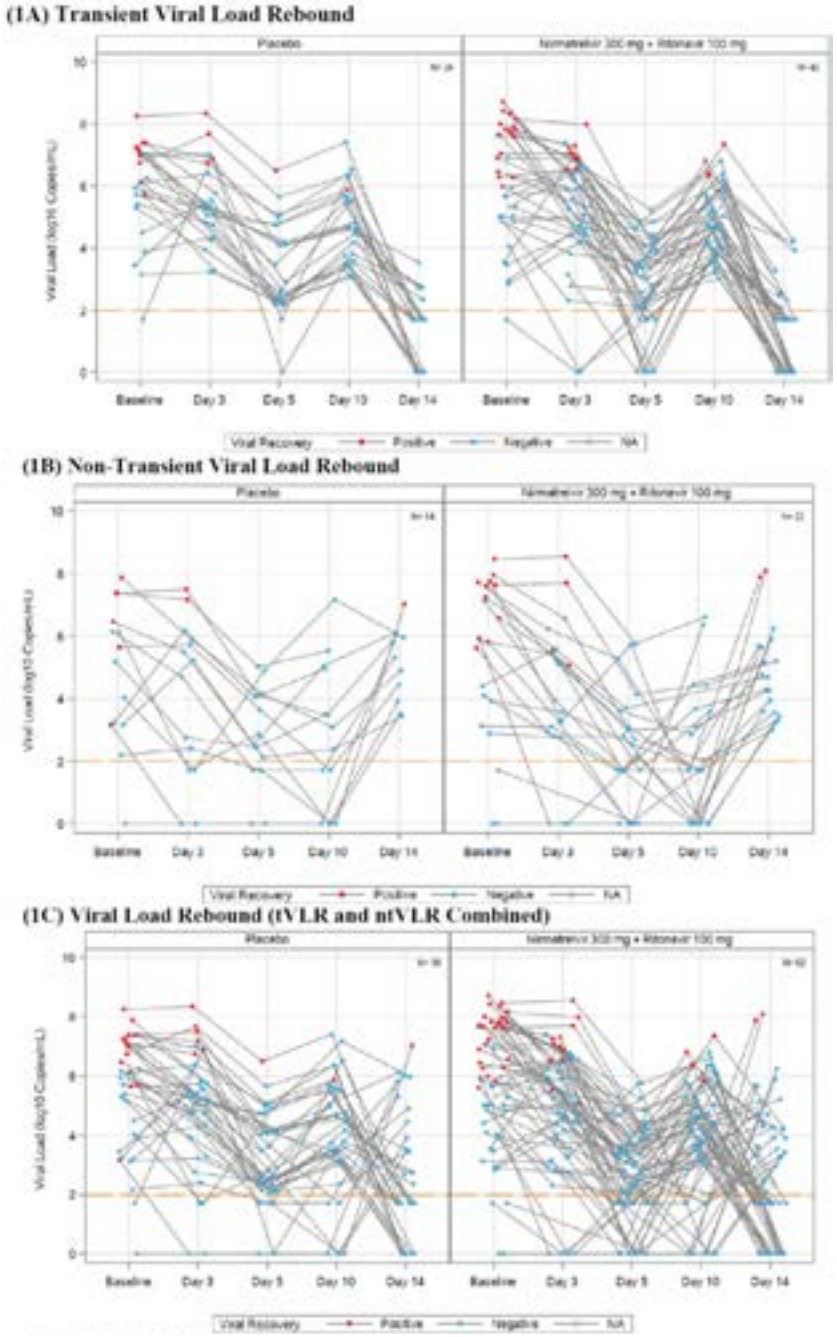
		Nirmatrelvir 300 mg + Ritonavir 100 mg (N=62)				
		log10(TCID50)				
VISIT	Positive Infectious Status by Viral Recovery	Mean (95% CI)	n	Median	SD	Min - Max
Baseline	29/57 (50.9%)	2.23 (2.01,2.45)	56	2	0.82	(1.53,5.17)
Day 3	13/61 (21.3%)	1.90 (1.77,2.04)	61	1.53	0.54	(1.53,3.50)
Day 5	0/62 (0.0%)	1.62 (1.57,1.67)	61	1.53	0.19	(1.53,2.17)
Day 10	5/61 (8.2%)	1.75 (1.65,1.86)	61	1.53	0.42	(1.53,3.17)
Day 14	2/59 (3.4%)	1.63 (1.57,1.68)	58	1.53	0.22	(1.53,2.50)

		Placebo (N=38)				
		log10(TCID50)				
VISIT	Positive Infectious Status by Viral Recovery	Mean (95% CI)	n	Median	SD	Min - Max
Baseline	17/38 (44.7%)	1.93 (1.74,2.11)	37	1.83	0.55	(1.53,3.83)
Day 3	6/37 (16.2%)	1.85 (1.67,2.03)	37	1.53	0.55	(1.53,3.50)
Day 5	1/38 (2.6%)	1.70 (1.60,1.80)	38	1.53	0.30	(1.53,2.83)
Day 10	1/38 (2.6%)	1.82 (1.68,1.95)	38	1.53	0.41	(1.53,2.83)
Day 14	1/35 (2.9%)	1.69 (1.57,1.82)	35	1.53	0.37	(1.53,3.17)

Source: EPIC-HR final infectivity assay report
Abbreviations: CI, confidence interval; log, logarithm; Max, maximum; Min, minimum; N, number of subjects in the viral subgroup within each treatment arm; n, number of subjects with a value in the analysis category for that given visit; SD, standard deviation; TCID50, median tissue culture infectious dose

Figure 84 shows the relationship between infectivity results and viral RNA levels. Positive infectivity results by the viral recovery assay were observed only for samples with high viral RNA levels of ≥5 $\log_{10}$ copies/mL, with the exception of a single baseline isolate that tested positive for infectivity but had a relatively lower viral RNA level of ~3 $\log_{10}$ copies/mL.

Figure 84. Viral RNA Levels for Subjects Who Experienced Applicant-Defined Viral RNA Rebound, and Association With Viral Cell Culture Infectivity by Viral Recovery Assay



Source: EPIC-HR final infectivity assay report.
Note: Samples taking using non-validated swabs have been excluded from this analysis.
Note: The gold line LLOQ of RT-PCR assay of SARS-CoV-2 (2 $\log_{10}$ copies/mL).
Abbreviations: LLOQ; lower limit of quantitation; log, logarithm; NA, not applicable; ntVLR, nontransient viral load rebound; RNA, r bonucleic acid; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; tVLR, transient viral load rebound

Quantitative infectivity results for the Day 10 and Day 14 samples based on the viral titration assay showed similar and low virus concentrations (generally ≤3 $\log_{10}$ $TCID_{50}$ units/mL) among PAXLOVID and placebo recipients with viral RNA rebound (Figure 85). Of note, several more Day 10 and Day 14 samples from both PAXLOVID and placebo recipients had qualitatively

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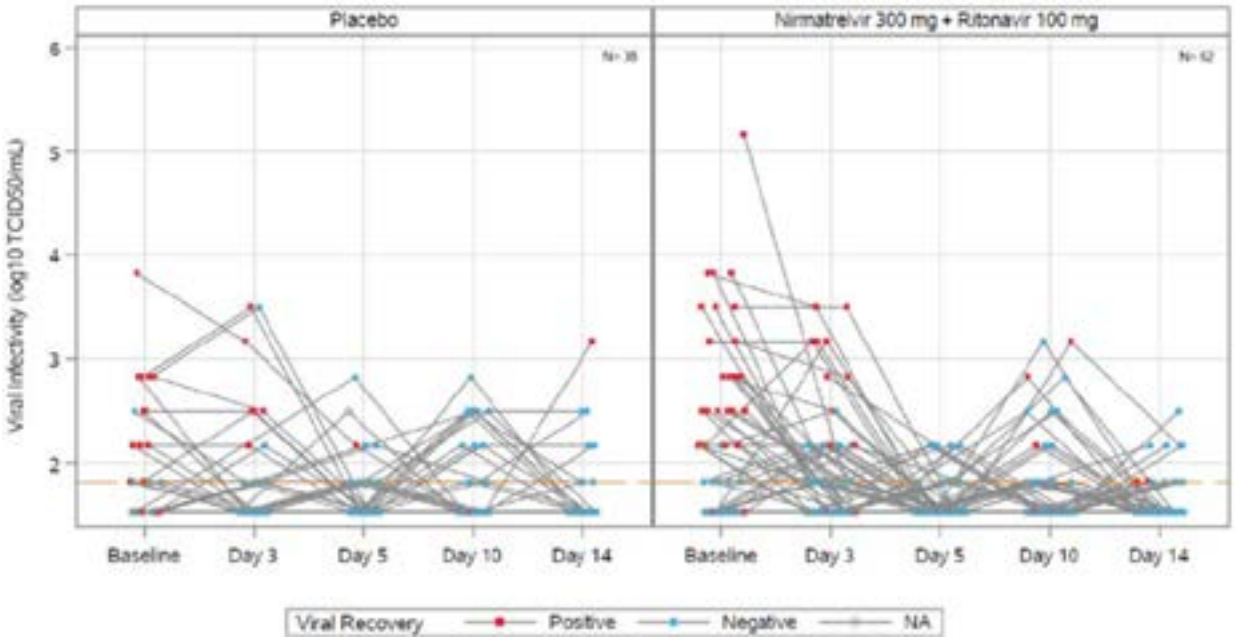
positive infectivity results (based on ≥LLOQ) based on the viral titration assay compared to the viral recovery assay, indicating the viral titration assay is more sensitive than the virus recovery assay at detecting the presence of cell culture infectious virus.

Figure 85. Quantitative (Viral Titration Assay) Results for Subjects Who Experienced Applicant-Defined Viral RNA Rebound (tVLR and ntVLR Combined).



Source: EPIC-HR final infectivity assay report.
Note: Qualitative results by viral recovery assay are also indicated in red (positive) and blue (negative).
Note: Samples taking using non-validated swabs have been excluded from this analysis.
Note: The gold line LLOQ of $TCID_{50}$ assay (1.83 log_{10} $TCID_{50}$/mL).
Abbreviations: LLOQ; lower limit of quantitation; log, logarithm; NA, not applicable; ntVLR, nontransient viral load rebound; RNA, ribonucleic acid; $TCID_{50}$, median tissue culture infectious dose; tVLR, transient viral load rebound

Considering either the viral recovery assay or the viral titration assay, among those who experienced Applicant-defined viral RNA rebound, qualitatively positive test results for virus infectivity for Day 10 or Day 14 samples were observed for 29% (18/62) and 39% (15/38) of PAXLOVID and placebo recipients, respectively (Table 189).

Table 189. Qualitative Cell Culture Infectivity Results Based on Viral Recovery Assay or Viral Titration Assay for Subjects Who Met the Applicant's Definitions of "Transient Viral Load Rebound" or "Non-Transient Viral Load Rebound".

	Nirmatrelvir + Ritonavir (N=62)			Placebo (N=38)		
Analysis Visit	Positive by Viral Recovery	Positive by TCID50	Positive by either Viral Recovery or TCID50	Positive by Viral Recovery	Positive by TCID50	Positive by either Viral Recovery or TCID50
Day 10	5/61 (8%)	10/61 (16%)	12/61 (20%)	1/38 (3%)	11/38 (29%)	12/38 (32%)
Day 14	2/59 (3%)	5/59 (8%)	7/59 (12%)	1/35 (3%)	5/35 (14%)	5/35 (14%)
Day 10 or Day 14	7/62 (11%)	14/62 (23%)	18/62 (29%)	2/38 (5%)	14/38 (37%)	15/38 (39%)

Source: December 23, 2022 Applicant response document.
Note: All VL measurements are in log_{10} copies/mL.
Note: tVLR is defined as meeting both D10VL change from D5VL >=0.5 and D10VL >=3, and D14VL change from D5VL <0.5 or D14VL <3.
Note: ntVLR is defined as meeting one or more of the following: (1) If D14VL is available: D14VL change from D5VL >=0.5 and D14VL >=3; (2) If D14VL is not available: D10VL change from D5VL >=0.5 and D10VL >=3.
Note: Infectivity data from all subjects who experienced either tVLR or ntVLR was included.
Note: Positive by $TCID_{50}$ is defined as $log_{10}(TCID_{50})$ > LLOQ.
Abbreviations: D, day; RNA; r bonucleic acid; LLOQ; lower limit of quantitation; log, logarithm; N, total number of subjects; ntVLR, nontransient viral load; $TCID_{50}$, median tissue culture infectious dose; tVLR, transient viral load rebound; VL, viral load

In analyses of "sustained viral load non-responders (sNR-VL)," defined as those having at least 2 viral RNA measurements at the Day 5, Day 10, and Day 14 visits, with all available results ≥4 log_{10} copies/mL, there were 12 PAXLOVID treated subjects and 19 placebo subjects who met this definition. Viral infectivity qualitative results by viral recovery assay for these subjects are summarized in Table 190. PAXLOVID-treated subjects tended to have lower rates of positive infectivity at on-treatment timepoints, although similarly low infectivity rates were observed between PAXLOVID and placebo "viral load non-responders" for Days 10 and 14. Not surprisingly, quantitative $TCID_{50}$ levels trended lower among PAXLOVID-treated subjects for Day 3 and Day 5 samples.

Table 190. Infectivity Results for Subjects With "Sustained Viral Load Non-Response"

		Nirmatrelvir 300 mg + Ritonavir 100 mg (N=12)				
		log10(TCID50)				
VISIT	Positive Infectious Status by Viral Recovery	Mean (95% CI)	n	Median	SD	Min - Max
Baseline	8/12 (66.7%)	2.62 (2.13,3.10)	12	2.665	0.76	(1.53,3.50)
Day 3	5/12 (41.7%)	2.29 (1.79,2.79)	12	2	0.79	(1.53,3.50)
Day 5	1/10 (10.0%)	1.65 (1.54,1.76)	10	1.53	0.15	(1.53,1.83)
Day 10	3/12 (25.0%)	1.82 (1.48,2.17)	11	1.53	0.52	(1.53,3.17)
Day 14	0/9 (0.0%)	1.71 (1.47,2.02)	9	1.53	0.36	(1.53,2.50)

		Placebo (N=19)				
		log10(TCID50)				
VISIT	Positive Infectious Status by Viral Recovery	Mean (95% CI)	n	Median	SD	Min - Max
Baseline	12/17 (70.6%)	2.78 (2.39,3.16)	17	2.63	0.75	(1.53,4.17)
Day 3	15/19 (78.9%)	2.84 (2.39,3.28)	19	2.5	0.92	(1.53,4.50)
Day 5	11/10 (57.9%)	2.13 (1.82,2.44)	19	2.17	0.64	(1.53,3.50)
Day 10	4/18 (22.2%)	1.83 (1.63,2.02)	18	1.68	0.39	(1.53,2.83)
Day 14	1/13 (7.7%)	1.82 (1.62,2.02)	13	1.83	0.33	(1.53,2.50)

Source: EPIC-HR final infectivity assay report.
Note: VL measurements are in log_{10} copies/mL
Note: sNR-VL is defined as meeting both: at least 2 VL measurements from D5, D10, and D14 visits, and VL ≥4 from all available D5/D10/D14 visits.
Abbreviations: CI, confidence interval; D, day; RNA; ribonucleic acid; log, logarithm; Max, maximum; Min, minimum; N, number of subjects in the viral subgroup within each treatment arm; n, number of subjects with a value in the analysis category for that given visit; SD, standard deviation; sNR-VL, sustained viral load nonresponder; $TCID_{50}$, median tissue culture infectious dose

Among subjects who experienced treatment failure, defined as those who reached the primary endpoint event of COVID-19 related hospitalization or death for any cause through Day 28, rates of positive infectivity trended lower for PAXLOVID-treated subjects (Table 191), although the numbers of subjects for comparison with placebo-treated subjects are small due to the substantially lower rate of hospitalization or death among PAXLOVID recipients.

Table 191. Infectivity Results for Subjects With Treatment Failure

		Nirmatrelvir 300 mg + Ritonavir 100 mg (N=10)				
		log10(TCID50)				
VISIT	Positive Infectious Status by Viral Recovery	Mean (95% CI)	n	Median	SD	Min - Max
Baseline	6/10 (60.0%)	2.18 (1.61,2.76)	10	1.85	0.80	(1.53,3.50)
Day 3	1/7 (14.3%)	1.57 (1.47,1.68)	7	1.53	0.11	(1.53,1.83)
Day 5	0/7 (0.0%)	1.66 (1.51,1.81)	7	1.53	0.16	(1.53,1.83)
Day 10	0/6 (0.0%)	1.53 (NE,NE)	5	1.53	0.00	(1.53,1.53)
Day 14	0/5 (0.0%)	1.53 (NE,NE)	5	1.53	0.00	(1.53,1.53)

		Placebo (N=68)				
		log10(TCID50)				
VISIT	Positive Infectious Status by Viral Recovery	Mean (95% CI)	n	Median	SD	Min - Max
Baseline	38/64 (59.4%)	2.27 (2.09,2.45)	64	2.17	0.72	(1.53,4.17)
Day 3	26/53 (49.1%)	2.18 (1.97,2.39)	53	1.83	0.76	(1.53,4.50)
Day 5	11/40 (27.5%)	1.88 (1.71,2.06)	40	1.53	0.55	(1.53,3.50)
Day 10	3/29 (10.3%)	1.77 (1.63,1.91)	29	1.53	0.37	(1.53,2.83)
Day 14	1/33 (3.0%)	1.58 (1.52,1.64)	33	1.53	0.16	(1.53,2.17)

Source: EPIC-HR final infectivity assay report.
Note: Treatment failure is defined as COVID-19-related hospitalization or death from any cause through D28.
Abbreviations: CI, confidence interval; D, day; RNA; ribonucleic acid; log, logarithm; Max, maximum; Min, minimum; N, number of subjects in the viral subgroup within each treatment arm; n, number of subjects with a value in the analysis category for that given visit; SD, standard deviation; sNR VL, sustained viral load nonresponder; TCID50, median tissue culture infectious dose

In the analysis of samples from randomly selected PAXLOVID recipients (n = 142) and placebo recipients (n = 142) with baseline viral RNA ≥5 $\log_{10}$ copies/mL, PAXLOVID led to a more rapid decline in cell culture infectious virus without evidence of prolonged virus shedding in the post-treatment period compared to placebo-treated subjects (Table 192). Approximately half of the subjects had positive cell culture infectivity results detected in baseline samples based on the viral titration assay. Of these subjects, those treated with PAXLOVID were more likely to have negative infectivity results on Day 3 and Day 5, while >95% of both PAXLOVID and placebo subjects had negative infectivity results on Day 10 and Day 14.

Table 192. Summary of Negative Cell Culture Infectivity Results Based on Viral Titration ($TCID_{50}$) Assay

Visit	Nirmatrelvir 300 mg + Ritonavir 100 mg (N=75)	Placebo(N=74)	Odds Ratio	95% CI	P-Value
Day 3	56/75 (74.7%)	38/74 (51.4%)	2.79	(1.40,5.58)	0.0018
Day 5	73/75 (97.3%)	58/74 (78.4%)	10.07	(2.22,45.57)	0.0003
Day 10	68/71 (95.8%)	60/63 (95.2%)	1.13	(0.22,5.83)	0.3152
Day 14	69/70 (98.6%)	66/68 (97.1%)	2.09	(0.19,23.61)	0.3721

Participants enrolled at sites 1274 and 1470 (including those switched to 1276) are excluded.

Source: EPIC-HR final infectivity assay report.
Note: Results are shown only for those with positive infectivity results at baseline.
Note: Participants enrolled at Sites 1274 and 1470 (including those switched to 1276) are excluded.
Abbreviations: CI, confidence interval; N, total number of subjects; TCID50, median tissue culture infectious dose

Infectivity assessments were also conducted for 3 PAXLOVID-treated subjects in whom the M^{pro} E166V substitution was detected. As noted in Section 18.3.2, this was the clearest resistance pathway observed in EPIC-HR. For two of the subjects, samples with E166V (≥90% frequency in both) tested negative for cell culture infectivity by both the virus recovery and viral titration

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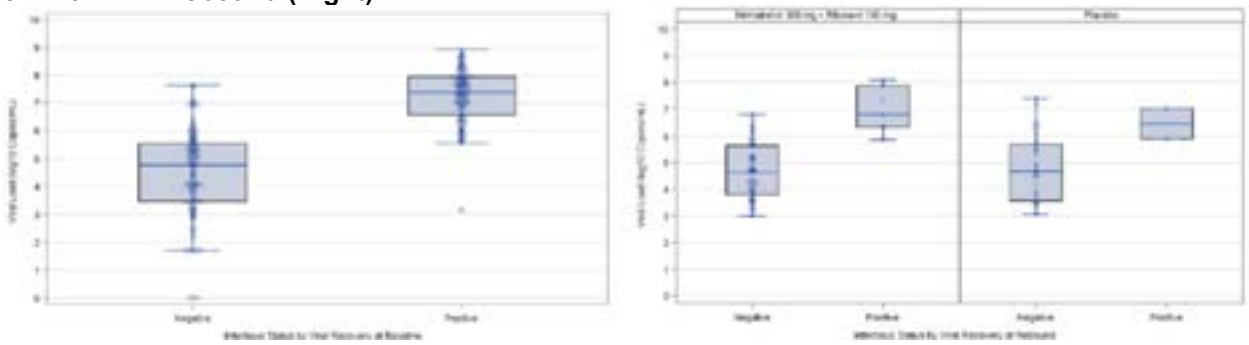
assays. For the third subject (SUBJID (b) (6)), E166V was detected at a 24% frequency, and the sample tested negative for virus recovery, but was positive in the viral titration assay. Given that E166V was not predominant in the viral population, it is unknown if it was represented in the cell culture infectious virus detected in this sample. Note that this subject also experienced post-treatment viral RNA rebound. Although it is challenging to draw broad conclusions given the mixed viral population and single subject observation, this raises at least the theoretical concern that in rare cases of viral rebound following PAXLOVID treatment, the virus population could be transmissible and include nirmatrelvir-resistant virus.

Of note, for the second PAXLOVID-treated subject with viral RNA rebound associated with emergence of an M^{pro} substitution potentially associated with nirmatrelvir resistance (Subject (b) (6), T304I [24%]), the Day 10 sample from this subject similarly tested negative by viral recovery but positive in the viral titration assay (FDA analysis of ADMCINF dataset).

As noted above, positive viral recovery results were usually obtained only from samples with high viral RNA levels ≥5 $\log_{10}$ copies/mL. This was observed both for baseline samples and for samples at Day 10 or 14 for those who experienced viral RNA rebound (Figure 86).

Figure 86. Boxplot of Viral RNA Levels Relative to Detection of Cell Culture Infectious Virus by Viral Recovery Assay for Samples Collected at Baseline (Left) and Samples Collected at the Time of Viral RNA Rebound (Right)



Source: EPIC-HR final infectivity assay report.
Note: Samples taken using non-validated swabs have been excluded from these analyses.
Abbreviations: log, logarithm; RNA, ribonucleic acid

Given that a viral RNA level of ≥5 $\log_{10}$ copies/mL in NP samples may indicate a greater likelihood of detection of cell culture infectious virus, an independent analysis of viral RNA results was conducted to assess the frequencies of PAXLOVID- and placebo-treated subjects with viral RNA ≥5 $\log_{10}$ copies/mL at different treatment visits. The results are shown in Table 193. Consistent with analyses of viral RNA results <LLOQ and the frequency of detection of cell culture infectious virus across all study visits, subjects treated with PAXLOVID were less likely to have viral RNA ≥5 $\log_{10}$ copies/mL at all study visits through Day 14, again confirming that PAXLOVID treatment was not associated with prolonged viral RNA shedding in NP samples, irrespective of viral RNA rebound. Furthermore, among those who experienced post-treatment viral RNA rebound, there was no apparent difference in the proportions of PAXLOVID and placebo recipients whose viral RNA rebounded to a level ≥5 $\log_{10}$ copies/mL on Day 10 or Day 14, further illustrating that the magnitude of viral RNA rebound was similar between PAXLOVID and placebo recipients.

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Table 193. Frequencies of Subjects With Viral RNA ≥5 log10 Copies/mL at Each Study Visit

All Subjects		
Visit	Paxlovid (n=1035)	Placebo (n=1048)
Day 3	29.1% (282/970)	38.9% (381/980)
Day 5/EOT	10.3% (96/936)	23.9% (225/942)
Day 10	3.7% (34/922)	5.3% (48/903)
Day 14	1.0% (9/942)	1.5% (14/948)
Subjects With Viral RNA Rebound*		
Visit	Paxlovid (n=77)	Placebo (n=53)
Day 10	25.0% (19/76)	23.1% (12/52)
Day 14	9.5% (7/74)	12.2% (6/49)
Day 10 or Day 14	33.8% (26/77)	30.2% (16/53)

Source: FDA analysis of ADMC and ADSL datasets.
* Day 10/14 LLOQ/0.5 Combined Definition.
Abbreviations: LLOQ, lower limit of quantitation; log, logarithm; n, number of subjects in sample

In summary, positive cell culture infectivity results from Day 10 or Day 14 samples were observed for a subset of subjects who experienced post-treatment viral RNA rebound, regardless of whether they were treated with PAXLOVID or placebo. In an analysis of samples from randomly selected PAXLOVID or placebo recipients with baseline viral RNA ≥5 $\log_{10}$ copies/mL, PAXLOVID led to a more rapid decline in cell culture infectious virus without evidence of prolonged virus shedding in the post-treatment period compared to placebo-treated subjects. For 2 PAXLOVID-treated subjects with post-treatment viral RNA rebound associated with emergence of the M^{pro} E166V or T304I substitutions, cell culture infectious virus was detected in the post-treatment rebound sample, indicating that in rare cases of viral rebound following PAXLOVID treatment the virus population could be transmissible and include nirmatrelvir-resistant virus (note: the precise relationship between SARS-CoV-2 cell culture infectivity and transmissibility is unclear).

18.3. Drug Resistance Analyses for EPIC-HR and EPIC-SR

18.3.1. Viral Sequencing Analysis Methods

NP samples were analyzed at the [redacted] (b) (4) using a "tiling amplicon panel" next-generation sequencing (NGS) method based on the Illumina platform (for details see: [redacted] (b) (4) The sequencing covers the whole SARS-CoV-2 genome. Samples were required to have SARS-CoV-2 RNA levels >500 copies/mL (>2.7 $\log_{10}$ copies/mL) for analysis. Sequences were mapped against the SARS-CoV-2 Wuhan-Hu-1 reference sequence (NCBI 045512.2). Amino acid substitutions detected at a ≥1% frequency were reported. Independent FDA analyses were conducted starting from the Applicant's analysis-ready datasets, and additional independent analyses were conducted using the raw NGS fastq data.

Due to evidence of a large number of sequencing artifacts observed at low amino acid frequencies, initial analyses of treatment-emergent substitutions (TES) conducted by FDA and

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by the Applicant, including for prior EUA submissions, used a 5% amino acid frequency cutoff for detection versus non-detection of amino acid substitutions. However, during the NDA review (and also noted in prior EUA reviews) it was observed that there were still numerous amino acid changes in the ~5 to 10% frequency range in both PAXLOVID- and placebo-treated subjects, including many changes that likely represent sequencing artifacts such as frameshifts and premature stop codons. Even after censoring frameshifts and stop codons, using a 5% frequency cutoff there were 811 M^{pro} or M^{pro} cleavage site TES detected in 45% (258/573) of subjects who received placebo, which is an unexpectedly high number of changes in a conserved protein for virus populations that are not under M^{pro} inhibitor selective pressure. Increasing the frequency cutoff from 5% to 10% eliminated 70% of these detected TES, consistent with a high rate of sequencing artifacts reported in the 5-10% frequency range.

As further evidence of a potentially high rate of amino acid sequencing artifacts at frequencies <10%, in the full table of reported amino acid substitutions throughout the SARS-CoV-2 genome using the original ≥1% cutoff, 42% (370,131/874,579) of amino acid changes were frameshifts or stop codons. Of these changes, 86% were reported in the ≥1% to <5% frequency range, and another 10% were reported in the ≥5% to <10% frequency range. Using a less sensitive 10% frequency cutoff eliminates 96% of reported frameshifts and stop codons, and presumably most sequencing artifacts of any type. Therefore, because we were concerned that a substantial proportion of TES detected only at the 5 to 10% level could reflect sequencing artifacts and underemphasize real changes occurring in the viral population, we revised our sensitivity cutoff for sequencing analyses to 10% during the review.

Independent FDA analyses of the SARS-CoV-2 sequencing data focused on the full M^{pro} amino acid coding sequence and M^{pro} cleavage sites. Table 194 summarizes the M^{pro} cleavage sites that were analyzed and their positions in the SARS-CoV-2 polyproteins (pp) pp1a and pp1ab.

Table 194. M^{pro} Cleavage Sites Analyzed for PAXLOVID Treatment-Emergent Changes

Cleavage Site	pp1a/pp1ab Proteins Cleaved	AA Cleavage Sites	pp1ab AA Positions
M^{pro} (nsp5) CS#1	nsp4/nsp5	SAVLQ↓SGFRK	3259-3268
M^{pro} (nsp5) CS#2	nsp5/nsp6	GVTFQ↓SAVKR	3565-3574
M^{pro} (nsp5) CS#3	nsp6/nsp7	VATVQ↓SKMSD	3855-3864
M^{pro} (nsp5) CS#4	nsp7/nsp8	RATLQ↓AIASE	3938-3947
M^{pro} (nsp5) CS#5	nsp8/nsp9	AVKLQ↓NNELS	4136-4145
M^{pro} (nsp5) CS#6	nsp9/nsp10	TVRLQ↓AGNAT	4249-4258
M^{pro} (nsp5) CS#7	nsp10/nsp11-12	EPMLQ↓SADAQ	4388-4397
M^{pro} (nsp5) CS#8	nsp12/nsp13	HTVLQ↓AVGAC	5320-5329
M^{pro} (nsp5) CS#9	nsp13/nsp14	VATLQ↓AENVT	5921-5930
M^{pro} (nsp5) CS#10	nsp14/nsp15	FTRLQ↓SLENV	6448-6457
M^{pro} (nsp5) CS#11	nsp15/nsp16	YPKLQ↓SSQAW	6794-6803

Source: Adapted from (Pfizer 2022a).
Abbreviations: AA, amino acid; CS, cleavage site; Mpro, main protease; nsp, nonstructural protein; pp, polyprotein

18.3.2. EPIC-HR: SARS-CoV-2 Variants and Resistance Analyses

As expected based on the timing of subject enrollment in EPIC-HR, clades/lineages representative of the SARS-CoV-2 Delta variant were predominant among subjects with available viral sequencing and variant assignment results, representing ~99% of detected variants

(Table 195). Of the 78 subjects who reached the hospitalization/death endpoint, 77 (99%) were infected with a Delta variant.

Table 195. SARS-CoV-2 Clades/Variants Detected in EPIC-HR

Nextstrain Clade/ WHO Variant	Paxlovid (n=764)	Placebo (n=757)	All Subjects (n=1521)
Any Delta Variant	752 (98%)	750 (99%)	1502 (99%)
21J/Delta	601 (79%)	622 (82%)	1223 (80%)
21I/Delta	120 (16%)	112 (15%)	232 (15%)
21A/Delta	31 (4%)	16 (2%)	47 (3%)
20J/Gamma,V3	3 (<1%)	3 (<1%)	6 (<1%)
21G/Lambda	3 (<1%)	0 (0%)	3 (<1%)
20C	1 (<1%)	2 (<1%)	3 (<1%)
20I/Alpha,V1	2 (<1%)	0 (0%)	2 (<1%)
21H/Mu	2 (<1%)	0 (0%)	2 (<1%)
20G	1 (<1%)	1 (<1%)	2 (<1%)
20A	0 (0%)	1 (0%)	1 (<1%)

Source: FDA analysis of NGS analysis dataset.
Abbreviations: n, number of subjects in sample; NGS, next-generation sequencing; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization

Three different algorithms/approaches were used to identify PAXLOVID TES in EPIC-HR:

- Unbiased analysis ("TE"): Amino acid substitutions that emerged at the same M^{pro} or M^{pro} cleavage site residue in ≥3 PAXLOVID-treated subjects (any change at same position), and at a ≥2-fold greater frequency than in placebo-treated subjects, considering all available timepoints from subjects with baseline and at least one post-baseline result. Note that the Applicant's similar algorithm for identifying TES initially did not consider Day 3 results, which resulted in some substitutions identified in the FDA analyses but not reported by the Applicant.
- Any treatment-emergent amino acid changes at any of the following NIR M^{pro} contact residues (within 5 Å) ("CR"): H41, M49, Y54, F140, L141, N142, G143, S144, C145, H163, H164, M165, E166, L167, P168, H172, V186, D187, R188, Q189, T190, A191, Q192.
- Any treatment-emergent amino acid changes at any M^{pro} residues associated with NIR phenotypic resistance in cell culture (Section 20.3, partially overlaps with contact residues) ("Ph"): T21, L50, P108, T135, F140, S144, C160, E166, L167, T169, H172, A173, V186, R188, A191, A193, P252, S301, T304.

Results from these analyses are summarized in Table 196.

Table 196. PAXLOVID Treatment-Emergent Amino Acid Substitutions Observed in EPIC-HR

AA Position and Substitution(s)	Reporting Criteria[1]	# PAX-Tx Subjects (n=539 w/ data)	# PBO-Tx Subjects (n=552 w/ data)	AA Frequency in PAX-Tx Subjects[2]	Hosp. or Death Endpt (PAX-Tx Subjects)	NIR Fold-Change (AA)[3]
M^{pro} Amino Acid Substitutions						
G11C/S/V	TE	3 (1 each)	1 (C)	0.10-0.16	N	nd
T111I	TE	3	1	0.11-0.14	N	nd
P132H/L/S	TE	5 (2H,1L,2S)	0	0.18-0.35	N	0.5-1.1[(c)] (H) 0.6-1.1[(b)] (H/L/S)
C145F/R/Y	CR	1 (F/R/Y in same subject)	0	0.41 (F/R/Y pooled)	N	nd
C160R	Ph	1	0	0.15	N	nd
E166V	TE, CR, Ph	3	0	0.24-0.94	N	25-288[(c)]
P168S	CR	1	0	0.12	N	0.6[(b)]
A173T	Ph	1	0	0.20	N	0.9-2.3[(c)] (V) <1.8[(b)] (T)-16[(b)] (V)
V186G	CR, Ph	22	15	0.10-0.24	N	1.4[(b)]
R188M	CR, Ph	1	0	0.13	N	1.0[(b)]
Q189K	CR	5	5	0.14-0.32	N	0.2[(c)] <1.6[(b)]
T190I	CR	1	1	0.29 (0.33 in PBO)	N	0.7[(b)]
A193P	Ph	1	0	0.13	N	0.9[(b)]
A260S/T/V	TE	7 (1S,4T,2V)	1 (V)	0.11-0.21	Yes=1, N=6	0.6[(b)] (V)
T304I	Ph	1	0	0.24	N	2.1-5.5[(c)] 1.0[(b)]
Any	TE, CR or Ph	53 (10%)	28 (5%)			
Any	CR or Ph	37 (7%)	25 (5%)			
M^{pro} Cleavage Site Amino Acid Substitutions						
CS#2 A3571V	TE	3	1	1 (all >0.99)	N	nd
CS#8 A5328P/S	TE	4 (3S,1P)	0	0.10-0.34	N	nd

Source: FDA analysis of NGS analysis dataset.

[1] Substitutions detected in PAXLOVID-treated subjects meeting one or more of the following criteria:

- TE: treatment-emergent in ≥3 PAXLOVID-treated subjects (i.e., ≥0.5% of subjects) at the same amino acid position in M^{pro} or M^{pro} cleavage site, AND ≥2-fold more frequently in PAXLOVID-treated subjects relative to placebo-treated subjects
- CR: emerged in ≥1 PAXLOVID-treated subject at a nirmatrelvir contact residue in M^{pro} (w/in 5 Å); 'Any' calculations included substitutions only detected in Placebo-treated subjects.
- Ph: emerged in ≥1 PAXLOVID-treated subject at a residue in M^{pro} associated with NIR phenotypic resistance in cell culture (i.e., emerged in selection studies and/or shown to confer reduced NIR activity in cell culture); 'Any' calculations included substitutions only detected in Placebo-treated subjects)

[2] Amino acid frequency ≥10% considered for detection.

[3] Based on EC_{50} value in cell culture assay:

- [(c)] or IC_{50} value in biochemical assay
- [(b)]. nd, no data

Abbreviations: AA, amino acid; C, cysteine; CS, cleavage site; EC_{50}, half-maximal effective concentration; Endpt, endpoint; F, phenylalanine; H, histidine; Hosp, hospitalization; IC_{50}, half-maximal inhibitory concentration; L, leucine; M^{pro}, main protease; N, no; n, number of subjects in sample; nd, no data; NGS, next-generation sequencing; NIR, nirmatrelvir; P, proline; PAX, paxlovid; PBO, placebo; R, arginine; S, serine; T, threonine; Tx, treated; V, valine; w/, with; Y, tyrosine

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Key observations from these analyses include the following:

- Overall, the detection of PAXLOVID treatment-emergent viral populations potentially resistant to nirmatrelvir was uncommon. Considering nirmatrelvir contact residues ("CR" positions) and positions shown to be associated with phenotypic resistance in cell culture ("Ph" positions), 37 (7%) PAXLOVID recipients and 25 (5%) placebo recipients had a TES detected at one of these positions, indicating a generally modest signal of potential resistance emergence associated with PAXLOVID treatment. Considering the full list of M^{pro} substitutions noted in Table 196, including TES observed at positions of unknown significance, at least one of the noted M^{pro} amino acid substitutions was detected in 53 (10%) PAXLOVID recipients, of whom 50 (94%) had only a single M^{pro} TES detected (including mixtures at the same position) while 3 other PAXLOVID recipients had 2 different M^{pro} substitutions detected, with no shared combinations between the 3 subjects.
- Considering all of the TES noted in these analyses, the primary endpoint of hospitalization or death was observed in only 1 PAXLOVID-treated subject (SUBJID (b) (6); hospitalization) with one of these substitutions detected, M^{pro} A260T (A260 substitutions discussed further below).
- M^{pro} E166V was the clearest nirmatrelvir resistance-associated TES observed. Although treatment-emergent E166V was detected only in 3 (0.6%) PAXLOVID treated subjects, in 2 of the subjects the substitution was detected in ≥90% of sequence reads at this position on Day 5. It also did not emerge in any placebo recipients. As summarized in Section 20, M^{pro} E166 is located in the nirmatrelvir binding site, and a variety of substitutions at this position have been shown by the Applicant and other independent researchers to be associated with resistance to nirmatrelvir in cell culture and biochemical assays. In recombinant SARS-CoV-2 viruses, the M^{pro} E166V substitution conferred 25 to 288-fold higher nirmatrelvir EC_{50} values (Zhou et al. 2022b; Iketani et al. 2023).
- M^{pro} V186G, which is in the nirmatrelvir binding site (no direct interaction), was a commonly detected TES in both PAXLOVID and placebo treated subjects. This may represent a common sequencing artifact in the Applicant's analysis, as it was frequently detected in both treatment arms and only one PAXLOVID-treated subject was found to have a TES at this position (V186L) in independent FDA analyses of the raw NGS data (using a 10% frequency threshold, see Section 18.3.4). Furthermore, V186G had no impact on nirmatrelvir activity in a biochemical assay. Thus, the totality of data indicate that V186G was not a clear nirmatrelvir resistance-associated substitution in EPIC-HR.
- Like M^{pro} V186G, Q189K is in the nirmatrelvir binding site (no direct interaction) and was detected in numerous subjects in baseline and post-baseline samples, with no clear signal of treatment emergence associated with PAXLOVID over placebo. Position Q189 is highly conserved in publicly available SARS-CoV-2 sequence data, and previous analyses found a high likelihood of sequence artifacts reported at this position (as indicated by low coverage and bias in the read direction balance). Furthermore, independent FDA analyses of the raw NGS data did not identify Q189K in any PAXLOVID or placebo treated subjects at any visit (using a 10% frequency threshold, see Section 18.3.4). The Applicant had previously reported that Q189K confers reduced nirmatrelvir activity in a biochemical assay; however, it was subsequently found that the reduction observed was an artifact of the negative impact of the substitution on M^{pro} catalytic efficiency. Also, Q189K engineered into SARS-CoV-2 did

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not reduce nirmatrelvir activity in cell culture. Therefore, the totality of data indicate Q189K was not a clear nirmatrelvir resistance-associated substitution in EPIC-HR.

- The M^{pro} T304I substitution emerged in one PAXLOVID-treated subject. T304 is located near the C-terminus of M^{pro} and overlaps the P3 position of the nsp5/nsp6 cleavage site. In cell culture assays, the presence of T304I in SARS-CoV-2 was associated with a 2.1 to 5.5-fold increase in nirmatrelvir EC_{50} values, while it had no impact on nirmatrelvir activity in biochemical assays when engineered into recombinant SARS-CoV-2 M^{pro} enzyme. These findings raise the possibility that any contribution of T304I to nirmatrelvir resistance is related to its impact on the nsp5/nsp6 cleavage site (see also Section 20).
- PAXLOVID TES were infrequently observed at other M^{pro} nirmatrelvir contact positions or other positions associated with nirmatrelvir resistance in nonclinical studies, including C145F/R/Y (n = 1), P168S (n = 1), A173T (n = 1), R188M (n = 1), T190I (n = 1; also detected in 1 placebo recipient), and A193P (n = 1). The significance of treatment-emergent C145F/R/Y and its role in nirmatrelvir resistance is unclear as C145 is a critical catalytic residue in the M^{pro} active site and amino acid changes at this position rendered the enzyme inactive in biochemical assays.
- Substitutions at M^{pro} position A260 (A260S/T/V), which is outside of the nirmatrelvir binding site and not known to be a nirmatrelvir resistance-associated position, appeared to be enriched in PAXLOVID recipients (n = 7) compared to placebo recipients (n = 1). Only A260T emerged in one PAXLOVID treated subject in independent FDA analyses of the raw NGS data using a 10% frequency threshold (see Section 18.3.4). The A260S, T or V substitutions did not reduce nirmatrelvir activity in a biochemical assay. Of note, in EPIC-SR, A260P/V emerged in 4 placebo recipients and 0 PAXLOVID recipients. Thus, A260 substitutions are considered unlikely to be associated with nirmatrelvir resistance.
- Substitutions P132H/L/S emerged in 5 PAXLOVID-treated subjects and 0 placebo-treated subjects. The P132H substitution is notable as it emerged in 2 subjects ([(b) (6)]) and this represents the only consensus M^{pro} amino acid polymorphism in SARS-CoV-2 Omicron lineages relative to previous lineages, and thus would raise concerns that PAXLOVID has reduced activity against SARS-CoV-2 Omicron lineages. However, a closer examination of the sequencing data indicates the detection of P132H in these subjects is likely due to laboratory contamination or some other technical artifact. In both subjects the substitution was detected only in Day 3 samples but not in Baseline or Day 5 samples, and in both Day 3 samples several additional Omicron signature amino acid changes were detected in Spike and other viral proteins. Further investigation by the Applicant found 17 other cases of low-level detection (<10% frequency) of P132H, all in single samples from different subjects. Of the 19 samples with P132H detected, 17 (including the Day 3 samples from subjects [(b) (6)]) were analyzed on the same date [(b) (6)]) after the emergence of the Omicron variant (Applicant's response to September 16, 2022, information request (Pfizer 2022o)). Three other PAXLOVID-treated subjects had treatment-emergent P132L (n = 1) or P132S (n = 2). None of these amino acid changes at position P132 (H, L or S) have been shown to affect nirmatrelvir activity in biochemical or cell-based assays, so the relevance of any P132 TES is unclear. In addition, using X-ray crystallography, the Applicant has demonstrated that P132H is located distal (~16 Å) to the NIR binding pocket and does not significantly affect the conformation of the binding pocket or the binding of nirmatrelvir to the enzyme (Greasley et al. 2022). See Section 18.3.4 for additional

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independent analyses of this position from the raw NGS data. Note that no P132 TES were observed in EPIC-SR.

- M^{pro} G11C/S/V or T111I were detected as TES at low amino acid frequencies (≤16% in all cases) across 6 PAXLOVID-treated subjects. These positions are outside of the nirmatrelvir binding site and are not known to be associated with nirmatrelvir resistance. In EPIC-SR, no PAXLOVID recipients had a T111 TES, and 1 PAXLOVID versus 3 placebo recipients had a G11A/R/V TES. Thus, G11 and T111 substitutions are considered unlikely to be associated with nirmatrelvir resistance. The Applicant will be requested to phenotypically characterize the impact of G11V (observed in 2 PAXLOVID recipients across EPIC-HR and EPIC-SR) on nirmatrelvir activity as a post-marketing requirement.
- A small number of M^{pro} cleavage site (CS) substitutions appeared to emerge preferentially in PAXLOVID-treated subjects, including CS#2 (nsp5/nsp6) A3571V and CS#8 (nsp12/nsp13) A5328P/S. Of note, CS#8 (nsp12/nsp13) A5328S/V was also observed as a PAXLOVID TES in EPIC-SR. As shown in Table 197, there were no clear patterns of association between these M^{pro} cleavage site TES and M^{pro} TES. In independent FDA analyses of the raw NGS data (Section 18.3.4), the A3571V TES was identified in 3 PAXLOVID-treated subjects and 2 placebo-treated subjects, and thus was not considered enriched in the PAXLOVID arm. In contrast, the A5328P/S TES was not identified (using a 10% frequency threshold) in any subjects. However, two other potential PAXLOVID M^{pro} cleavage site TES were identified. To our knowledge, other than the M^{pro} T304I substitution, which overlaps the nsp5/nsp6 cleavage site as discussed above, no phenotypic data have been reported regarding the impact of amino acid changes in any M^{pro} cleavage site on SARS-CoV-2 susceptibility to nirmatrelvir. Of note, A3571V is one of the most common naturally occurring polymorphisms in M^{pro} cleavage sites (Section 18.4).

Table 197. Subjects With PAXLOVID Treatment-Emergent Amino Acid Substitutions at M^{pro} Cleavage Sites (CS#2 A3571V, CS#8 A5328P/S), and Other Detected Treatment-Emergent M^{pro} Substitutions

USUBJID	Arm	Tx-Emergent Substitution(s) (AA frequency)	Tx-Emergent M^{pro} Substitution(s) (AA frequency)
(b) (6)	Placebo	CS#2 A3571V (>0.99)	V73I (0.10)
	PAXLOVID	CS#2 A3571V (>0.99)	None
	PAXLOVID	CS#2 A3571V (>0.99)	None
	PAXLOVID	CS#2 A3571V (>0.99)	None
	PAXLOVID	CS#8 A5328S (0.10)	L30F (0.11)
	PAXLOVID	CS#8 A5328S (0.19)	None
	PAXLOVID	CS#8 A5328P (0.13)	V186G (0.16)
	PAXLOVID	CS#8 A5328S (0.34)	None

Source: FDA analysis of NGS analysis dataset.
Abbreviations: AA, amino acid; CS, cleavage site; M^{pro}, main protease; NGS, next-generation sequencing; Tx, treatment; USUBJID; unique subject identified

Detailed baseline resistance analyses could not be conducted due the conserved nature of the M^{pro} amino acid sequence and the low frequency of subjects with amino acid polymorphisms detected at M^{pro} positions potentially associated with nirmatrelvir resistance. Only 10 (1.4%) PAXLOVID-treated subjects had an amino acid polymorphism detected at a potential nirmatrelvir resistance-associated position in M^{pro} (Figure 87). Viral RNA levels over time in

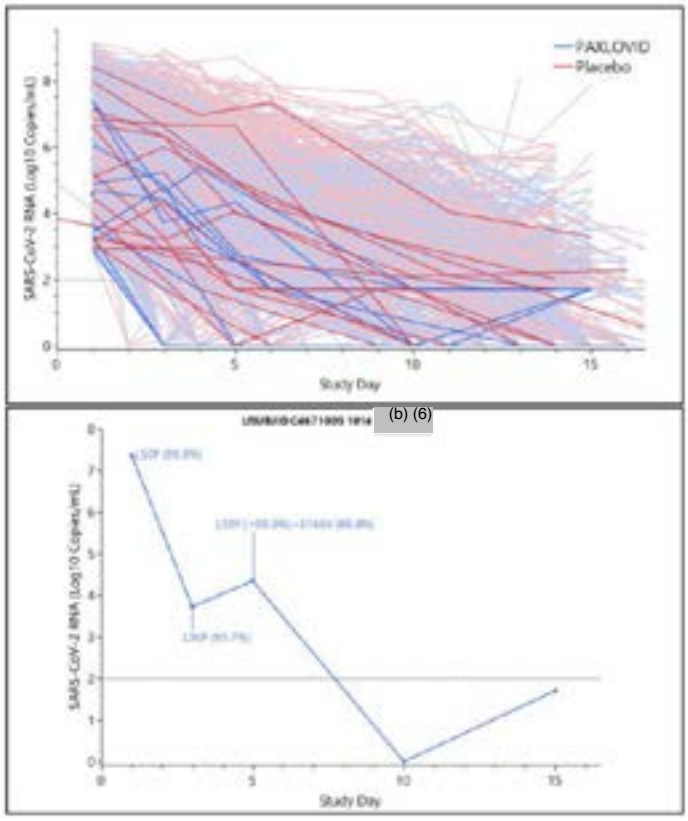
these subjects were generally consistent with other subjects, and none of the subjects reached the primary endpoint of hospitalization or death.

Although the baseline resistance analyses were limited by the small number of subjects infected with viruses with M^{pro} polymorphisms, there was one notable example of a subject (SUBJID (b) (6)) with a predominant (~99.9% frequency) M^{pro} L50F polymorphism. The subject had a treatment-emergent M^{pro} E166V (~90% frequency) substitution detected in the Day 5 visit sample, which was associated with a ~0.6 $\log_{10}$ copies/mL increase in viral RNA level during treatment between Day 3 and Day 5/End-of-treatment (Figure 87). As noted above, E166V was a clear treatment-emergent nirmatrelvir RAS. In a biochemical assay, L50F alone did not reduce nirmatrelvir activity, but the combination of L50F + E166V was associated with high level nirmatrelvir resistance (4,500-fold increase in K_i value). Furthermore, both Iketani et al and Zhou et al. reported that recombinant viruses with L50F + E166V had enhanced replication capacity compared to those with only the E166V substitution, indicating L50F may serve as a compensatory fitness substitution for viruses with E166V (Zhou et al. 2022b; Iketani et al. 2023). Although observed in only one participant in EPIC-HR, this observation provides a clear example of how a specific baseline M^{pro} polymorphism could contribute to nirmatrelvir resistance.

Figure 87. EPIC-HR: Frequency of Detection of M^{pro} Polymorphisms and Their Association With Viral RNA Responses

Baseline M^{pro} Polymorphism*	PAXLOVID	Placebo
L50F	1	2
P108L	1	1
P108S	1	3
E166K	0	1
T169P	1	0
Q189K	2	6
T190I	1	0
A191V	0	1
Q192L	1	0
A193V	2	1
T190P, A191V, Q192R	0	1
Any	1.4% (10/719)	2.3% (16/694)

*Based on 10% frequency cutoff, considering any M^{pro} change at (1) contact binding site residue, or (2) position associated with resistance in cell culture



Source: FDA analysis of ADMC and NGS analysis datasets.
Note: In the top figure panel, lines in the foreground represent individual subjects with one of the noted M^{pro} baseline polymorphisms detected, and lines in the background represent all other subjects.
Note: Dashed lines indicate the assay LLOQ.
Abbreviations: LLOQ, lower limit of quantitation; log, logarithm; M^{pro}, main protease; NGS, next-generation sequencing; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SUBJID, unique subject identifier

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18.3.3. EPIC-SR: SARS-CoV-2 Variants and Resistance Analyses

The EPIC-SR analyses summarized below were conducted using the NGS analysis dataset submitted on December 21, 2022, during the review cycle.

Of the 1288 subjects enrolled in EPIC-SR (after site censoring), SARS-CoV-2 variant assignments were available from 1006 (78%) subjects. Variant results separated by enrollment period are summarized in Table 198. SARS-CoV-2 Delta variants were predominant in the 2021 enrollment period, while 100% of variants were identified with an Omicron variant (96%) or Omicron-containing recombinant (4%) in the 2022 enrollment period. Among those with Omicron variant infections (n = 188, excluding recombinants), the most common PANGO lineages identified were BA.2 (38%), BA.2.9 (22%), and BA.2.12.1 (10%).

Table 198. SARS-CoV-2 Variants Detected in EPIC-SR

		2021 Enrollment Period			2022 Enrollment Period		
WHO Variant	Nextstrain Clade	Paxlovid (n=418)	Placebo (n=393)	All Subjects (n=811)	Paxlovid (n=98)	Placebo (n=97)	All Subjects (n=195)
Delta	21A	11 (3%)	21 (5%)	32 (4%)	0	0	0
	21I	45 (11%)	43 (11%)	88 (11%)	0	0	0
	21J	356 (85%)	320 (81%)	676 (83%)	0	0	0
	All Delta	412 (99%)	384 (98%)	796 (98%)	0	0	0
Omicron	21K	0	0	0	3 (3%)	4 (4%)	7 (4%)
	21L	0	0	0	69 (70%)	63 (65%)	132 (68%)
	22A	0	0	0	8 (8%)	7 (7%)	15 (8%)
	22B	0	0	0	5 (5%)	8 (8%)	13 (7%)
	22C	0	0	0	10 (10%)	11 (11%)	21 (11%)
	All Omicron	0	0	0	95 (97%)	93 (96%)	188 (96%)
Gamma	20J	5 (1%)	5 (1%)	10 (1%)	0	0	0
Lambda	21G	1 (<1%)	1 (<1%)	2 (<1%)	0	0	0
Mu	21H	0	3 (<1%)	3 (<1%)	0	0	0
Recombinant		0	0	0	3 (3%)	4 (4%)	7 (4%)*

Source: FDA analysis of ADSL and NGS analysis datasets (updated/final NGS dataset submitted December 21, 2022).
* Omicron recombinants XZ (n=6) or XE (n=1).
Abbreviations: n, number of subjects in sample; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization

Resistance analyses were conducted for EPIC-SR following a similar analysis approach as conducted for EPIC-HR.

A total of 784 subjects (n = 382 PAXLOVID, n = 402 Placebo) had baseline and post-baseline viral sequencing data available. This includes 140 subjects with an Omicron variant infection (n = 64 PAXLOVID, n = 76 Placebo). As for EPIC-HR, a 10% frequency cutoff was used to identify amino acid changes relative to reference. Also, a similar algorithm was used to identify treatment-emergent amino acid changes associated with PAXLOVID treatment:

- Unbiased analysis: Amino acid substitutions that emerged at the same M^{pro} or M^{pro} cleavage site residue in ≥3 PAXLOVID-treated subjects (≥0.8% of subjects), and at a ≥2-fold greater frequency than in Placebo-treated subjects, considering all available timepoints from subjects with baseline and at least one post-baseline result.

- Any treatment-emergent amino acid changes at any of the following NIR M^{pro} contact residues (within 5 Å) ("CR"): H41, M49, Y54, F140, L141, N142, G143, S144, C145, H163, H164, M165, E166, L167, P168, H172, V186, D187, R188, Q189, T190, A191, Q192
- Any treatment-emergent amino acid changes at any M^{pro} residues associated with NIR phenotypic resistance in cell culture (Section 20.3, partially overlaps with contact residues) ("Ph"): T21, L50, P108, T135, F140, S144, C160, E166, L167, T169, H172, A173, V186, R188, A191, A193, P252, S301, T304

Results from these analyses are summarized in Table 199.

Table 199. PAXLOVID Treatment-Emergent Amino Acid Substitutions Observed in EPIC-SR

AA Position and Substitution(s)	Reporting Criteria[1]	# PAX-Tx Subjects (n=382 w/ data)	# PBO-Tx Subjects (n=402 w/ data)	AA Frequency in PAX-Tx Subjects[2]	Hosp. or Death Endpt (PAX-Tx Subjects)	NIR Fold-Change (AA)[3]
M^{pro} Amino Acid Substitutions						
L50F	Ph	1	0	0.11	N	1.5[(c)] 0.2[(b)]
T98I/R	TE	3 (2I,1R)	0	0.12-0.15	N	nd
P108S	Ph	1	0	0.10	N	2.9[(b)]
H172del	CR/Ph	1	0	0.13	N	nd (del), 250[(b)] (Y)
Q189K	CR	7	11	0.10-0.54	N	0.2[(c)] <1.6[(b)]
S301L	Ph	1	0	0.11	N	nd (L), 0.2[(b)] (P)
Any	TE, CR or Ph	12 (3%)	11 (3%)			
Any	CR or Ph	10 (3%)	11 (3%)			
M^{pro} Cleavage Site Amino Acid Substitutions						
CS#8 A5328S/V	TE	4 (2S,2V)	0	0.10-0.37	N	nd

Source: FDA analysis of NGS analysis dataset.

[1] Substitutions detected in PAXLOVID-treated subjects meeting one or more of the following criteria:

- TE: treatment-emergent in ≥3 PAXLOVID-treated subjects (i.e., ≥0.8% of subjects) at the same amino acid position in M^{pro} or M^{pro} cleavage site, AND ≥2-fold more frequently in PAXLOVID-treated subjects relative to placebo-treated subjects.
- CR: emerged in ≥1 PAXLOVID-treated subject at a nirmatrelvir contact residue in M^{pro} (w/in 5 Å); 'Any' calculations included substitutions only detected in Placebo-treated subjects.
- Ph: emerged in ≥1 PAXLOVID-treated subject at a residue in M^{pro} associated with NIR phenotypic resistance in cell culture (i.e., emerged in selection studies and/or shown to confer reduced NIR activity in cell culture); 'Any' calculations included substitutions only detected in Placebo-treated subjects).

[2] Amino acid frequency ≥10% considered for detection.

[3] Based on EC_{50} value in cell culture assay:

- [(c)] or IC_{50} value in biochemical assay
- [(b)]. nd, no data

Abbreviations: AA, amino acid; C, cysteine; CS, cleavage site; del, deletion; EC_{50}, half-maximal effective concentration; Endpt, endpoint; F, phenylalanine; H, histidine; I, isoleucine; Hosp, hospitalization; IC_{50}, half-maximal inh bitory concentration; L, leucine; M^{pro}, main protease; N, no; n, number of subjects in sample; nd, no data; NGS, next-generation sequencing; NIR, nirmatrelvir; P, proline; PAX, paxlovid; R, arginine; S, serine; Tx, treated; w/, with; Y, tyrosine

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Key observations from these analyses include the following:

- Overall, as in EPIC-HR, the detection of PAXLOVID treatment-emergent viral populations potentially resistant to nirmatrelvir was uncommon. Considering nirmatrelvir contact residues ("CR" positions) and positions shown to be associated with phenotypic resistance in cell culture ("Ph" positions), 10 (3%) of PAXLOVID recipients and 11 (3%) of placebo recipients had a TES detected at one of these positions, indicating no clear signal of potential resistance emergence associated with PAXLOVID treatment.
- Other noted TES in M^{pro} generally occurred in small numbers of PAXLOVID recipients and at low amino acid frequencies, with the exception of Q189K which was not associated with PAXLOVID treatment (also observed and noted as potentially common sequence artifact in EPIC-HR).
- The M^{pro} H172del TES was observed in 1 PAXLOVID recipient. Although observed only in a single subject (and not in EPIC-HR), this change is notable as another substitution at this position (H172Y) conferred a 250-fold reduction in nirmatrelvir activity in a biochemical assay, and the deletion in theory would be more difficult to generate spontaneously during viral replication. The change was observed in Day 14 sequences at a 13% frequency, but not in Day 1, 3, 5, or 10 sequences from the subject. Independent FDA analyses of the raw fastq data from this subject confirmed the detection of H172del (7.2% frequency by FDA analysis) in the Day 14 sequences but not the other sequences. The change was created by the deletion of 3 nucleotides (ATG) spanning the codons for H172 and A173 (H172-A173del, insP), and sequences from Day 14 were clearly of lower quality relative to the other sequences as reflected by larger numbers of changes throughout the M^{pro} coding sequence, including several frameshifts and stop codons. Thus, it is unclear if H172del truly emerged or if its detection reflects a sequencing artifact.
- M^{pro} S301L emerged in 1 PAXLOVID-treated subject at a 0.11 frequency. An S301P substitution emerged in a cell culture drug resistance selection study but this change did not reduce NIR activity in a biochemical assay. This position overlaps with the P6 position of the nsp5/nsp6 cleavage site located at the C-terminus of M^{pro}.
- In contrast with the results from EPIC-HR, no PAXLOVID TES were observed at M^{pro} positions T111, P132, or A260. Interestingly, A260P/V TES were observed in 4 placebo recipients. Also, 3 placebo recipients and 1 PAXLOVID recipient had a TES at position G11 (A/R/V).
- The M^{pro} CS#8 (nsp12/nsp13) substitution A5328S/V emerged in 4 PAXLOVID recipients and 0 placebo recipients. No other M^{pro} or M^{pro} cleavage site TES were detected in these subjects. Of note, A5328P/S was identified as a potential PAXLOVID TES in EPIC-HR (depending on specific analysis). Additional phenotypic characterizations of this cleavage site position are warranted to assess a potential role in nirmatrelvir resistance.
- Of the PAXLOVID TES indicated above, only the M^{pro} cleavage site TES A5328V was observed in 1 subject who enrolled in the 2022/Omicron period; all other TES noted for PAXLOVID recipients were observed among subjects who enrolled in the 2021/Pre-Omicron period.
- No subjects with any of the noted M^{pro} or M^{pro} cleavage site TES experienced the endpoint of hospitalization or death, consistent with the low number of such events overall in the trial.

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Overall, these results from EPIC-SR are consistent with those from EPIC-HR in that PAXLOVID TES potentially associated with nirmatrelvir resistance were infrequently observed.

18.3.4. EPIC-HR: Independent FDA Analyses of Raw NGS Data

Methods

The Applicant's NGS data from EPIC-HR were independently analyzed using the High-Performance Integrated Virtual Environment (HIVE) (Simonyan and Mazumder 2014). HIVE contains specific tools that allow the reviewer to batch rename files to meet nomenclature rules for the analysis pipeline, to assess the quality of sequence files, to align sequence reads to a reference sequence and identify variants, and to convert variant call files into amino acid frequency tables. The workflow in HIVE was as follows: 1) sequence reads were imported and mapped to the reference sequence using the Hexagon aligner tool, 2) variants were called at the amino acid level using the Heptagon profiling tool, and 3) amino acid frequency tables were generated using the Viral Mutation Comparator tool. Each step of the analysis process is described in more detail below.

Preparing Fastq Files and Reference Sequences

Data files were submitted to the FDA on a portable hard drive, which included fastq file pairs for every sample that was sequenced. The fastq files were uploaded into HIVE and assessed for quality control by analyzing the following parameters: the overall proportion of each nucleotide (G/C/A/T), the average quality of each nucleotide, average sequence length, average sequence quality, and the count and average quality of each nucleotide by read position. For analysis of M^{pro} substitutions, the SARS-CoV-2 Wuhan-Hu-1 M^{pro} sequence was uploaded as the reference sequence for mapping (NCBI 045512.2). For analysis of M^{pro} cleavage sites, the SARS-CoV-2 Wuhan-Hu-1 pp1ab sequence was uploaded as the reference sequence for mapping.

Mapping Reads to the Reference Sequences

Sequence reads were mapped to the appropriate reference sequence using the Hexagon aligner tool in HIVE. Default analysis parameters were applied, including local alignment, match benefit: 5, mismatch penalty: -4, mismatch continuation penalty: -6, gap continuation cost: -4, gap opening cost: -12, minimum match of 40 nucleotides, and 15% mismatches allowed. The output files were assessed to determine the proportions of mapped reads, the lengths of aligned segments, and sequencing coverage for each sample.

Generating Amino Acid Frequency Tables

Next, variants were called using the HIVE Heptagon Sequence Profiler tool (Simonyan et al. 2017). Default analysis parameters were applied. Variant call tables were converted into amino acid frequency tables using the HIVE Viral Mutation Comparator tool, with a substitution frequency threshold of 1%. Synonymous mutations were excluded. The amino acid frequency table contains information for each position and each sample for which variation from the reference was detected. The frequency table contains the following columns: unique subject identifier (USUBJID), visit (VISIT), the amino acid position within the protein of interest

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(AAPOS), the amino acid found in the reference sequence (AAREF), the amino acid substitution (AASUB), the frequency at which the variant was detected (AAFREQ), the coverage at the nucleotide level for the variant (VCOV), and the total coverage at the nucleotide position (TCOV). Two additional columns were manually added to the table based on information from the Applicant's datasets: actual treatment (TRT01A) and a flag for hospitalization/death through Day 28 (HPDTHFL).

Analyzing Amino Acid Frequency Tables

Amino acid frequency tables from HIVE were analyzed using custom Python scripts and various analysis criteria, which are described in the results sections below. Most analyses were focused on baseline polymorphisms and TES that were detected at a frequency ≥10%, due to the high frequency of probable sequencing artifacts (as indicated by M^{pro} premature stop codons) below this threshold. The 10% threshold excluded ~96% of M^{pro} premature stop codons with a frequency >1%.

Results

Characterization of Dataset

After excluding censored subjects, the Applicant provided sequencing data for 3,573 samples from 1,526 subjects. Overall, M^{pro} amino acid substitution frequency results were obtained for 3,563 (99.7%) samples, including 1,714 samples from PAXLOVID-treated subjects, 1,843 samples from placebo-treated subjects, and 6 samples from untreated subjects (Table 200). Results from at least one sample were obtained for 1,525 (99.9%) subjects, including 763 PAXLOVID-treated subjects, 757 placebo-treated subjects, and 5 untreated subjects (Table 201). Results from baseline and at least one post-baseline sample were obtained for 537/763 (70.4%) of PAXLOVID-treated subjects and 550/757 (72.7%) of placebo-treated subjects. Results from untreated subjects were excluded from further analyses.

Table 200. Samples With M^{pro} Amino Acid Substitution Frequency Results

Treatment	# Baseline/ Day 1 Samples	# Day 3 Samples	# Day 5 Samples	# Day 10 Samples	# Day 14 Samples	Total
PAXLOVID	718	497	358	107	34	1,714
Placebo	693	539	429	133	49	1,843
Untreated	5	0	1	0	0	6
Total	1,416	1,036	788	240	83	3,563

Source: FDA analysis of raw NGS fastq data.
Abbreviations: M^{pro}, main protease; NGS, next-generation sequencing

Table 201. Subjects With Baseline and/or Post-Baseline M^{pro} Amino Acid Substitution Frequency Results

Treatment	# Subjects	# Subjects With Baseline Sample	# Subjects With ≥1 Post-Baseline Sample	# Subjects With Baseline and ≥1 Post-Baseline Sample
PAXLOVID	763	717	583	537
Placebo	757	693	614	550
Untreated	5	5	1	1
Total	1,525	1,415	1,198	1,088

Source: FDA analysis of raw NGS fastq data.
Abbreviations: M^{pro}, main protease; NGS, next-generation sequencing

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Identification of Baseline M^{pro} Polymorphisms at Positions of Interest

Baseline M^{pro} amino acid polymorphisms with frequencies ≥10% were analyzed at 34 residues that are considered positions of interest (Table 202), including 23 residues that directly contact or are located in close proximity (<5 Å) of NIR and 11 additional residues that have been associated with NIR resistance in cell culture. Baseline polymorphisms were identified at 12/34 positions of interest. The M^{pro} Y54S and N142D polymorphisms are considered likely to be sequencing artifacts, as they were identified in many subjects in both arms, usually had low frequencies, and occurred at residues that are highly conserved (>99.99%) in the GISAID sequence database. Excluding Y54S and N142D, baseline polymorphisms at positions of interest were identified in 9/717 (1.3%) of PAXLOVID-treated subjects and 14/693 (2.0%) of placebo-treated subjects. Baseline polymorphisms at these positions were not significantly associated with hospitalization or death in either treatment arm.

Table 202. Baseline M^{pro} Amino Acid Polymorphisms at 34 Positions of Interest

M^{pro} Residue	AA Substitution	# PAX-Tx Subjects (n=717 w/ data)	# PBO-Tx Subjects (n=693 w/ data)	AA Freq (PAX-Tx, Placebo-Tx)	Hosp. or Death Endpt (PAX-Tx, Placebo-Tx)	NIR EC_{50} Fold-Change
T21	N/A	0	0	N/A	N/A	N/A
H41	N/A	0	0	N/A	N/A	N/A
M49	N/A	0	0	N/A	N/A	N/A
L50	L50F	1	2	0.68, 0.21-0.84	No, No	1.4-4.2
Y54	Y54S	711	688	0.10-0.74, 0.10-0.73	Yes (10/711), Yes (60/688)	ND
P108	P108L/S	2	4	0.10-0.13, 0.37-0.82	No, No	ND
T135	N/A	0	0	N/A	N/A	N/A
F140	N/A	0	0	N/A	N/A	N/A
L141	N/A	0	0	N/A	N/A	N/A
N142	N142D	57	65	0.10-0.72, 0.10-0.76	No, Yes (4/65)	ND
G143	N/A	0	0	N/A	N/A	N/A
S144	N/A	0	0	N/A	N/A	N/A
C145	N/A	0	0	N/A	N/A	N/A
C160	N/A	0	0	N/A	N/A	N/A
H163	N/A	0	0	N/A	N/A	N/A
H164	N/A	0	0	N/A	N/A	N/A
M165	N/A	0	0	N/A	N/A	N/A
E166	E166K	0	1	N/A, 0.1	N/A, No	ND
L167	N/A	0	0	N/A	N/A	ND
P168	N/A	0	0	N/A	N/A	N/A
T169	T169P	1	0	1.0, N/A	No, N/A	ND
H172	N/A	0	0	N/A	N/A	N/A
A173	N/A	0	0	N/A	N/A	N/A
V186	N/A	0	0	N/A	N/A	N/A
D187	D187S	1	1	0.32, 0.16	No, No	ND
R188	R188I	1	1	0.32, 0.16	No, No	ND
Q189	N/A	0	0	N/A	N/A	N/A
T190	T190I	1	0	0.30, N/A	No, N/A	ND
A191	A191V	0	1	N/A, 0.39	N/A, No	ND
Q192	Q192K	1	0	0.10, N/A	No, N/A	ND
A193	A193E/V	2	5	1.0, 0.1-1.0	No, Yes (1/5)	ND

M^{pro} Residue	AA Substitution	# PAX-Tx Subjects (n=717 w/ data)	# PBO-Tx Subjects (n=693 w/ data)	AA Freq (PAX-Tx, Placebo-Tx)	Hosp. or Death Endpt (PAX-Tx, Placebo-Tx)	NIR EC_{50} Fold-Change
P252	N/A	0	0	N/A	N/A	N/A
S301	N/A	0	0	N/A	N/A	N/A
T304	N/A	0	0	N/A	N/A	N/A

Source: FDA analysis of raw NGS fastq data.
Note: Grey shading indicates positions at which baseline polymorphisms were not observed in any subjects.
Abbreviations: AA, amino acid; EC_{50}, half maximal effective concentration; Endpt, endpoint; Freq, frequency; Hosp, hospitalization; M^{pro}, main protease; n, number of subjects; N/A, not applicable; ND, no data; NGS, next-generation sequencing; NIR, nirmatrelvir; Pax, Paxlovid; PBO, placebo; Tx, treated

Identification of M^{pro} Treatment-Emergent Substitutions (TES) Associated With PAXLOVID

Next, M^{pro} TES were identified, which were defined as substitutions that had a frequency <10% at baseline and a frequency ≥10% in at least one post-baseline sample from the same subject. Subsequently, TES associated with PAXLOVID treatment were identified, which were defined as TES that emerged in at least three more PAXLOVID-treated subjects than placebo-treated subjects. This analysis was performed using two methods. In method #1, different substitutions at the same position (e.g., G23D and G23S) were considered independently. In method #2, all substitutions at the same position were grouped together. The same results were obtained regardless of whether premature stop codons were included or excluded from the analysis. With method #1, two M^{pro} TES were identified: G23S and E166V (Table 203). With method #2, 4 M^{pro} TES were identified: G23D/S/V, C85R/Y, E166V, and T199I/P/S (Table 204). The E166V TES is considered likely to be a resistance-associated substitution (RAS), as it was observed only in the PAXLOVID arm, occurred at high frequencies (26 to 94%), and has been associated with NIR resistance in cell culture (Zhou et al. 2022b; Iketani et al. 2023). It is unclear whether the other TES represent RAS, as they were usually observed in both arms (except C85R/Y), often had low frequencies, and did not occur at positions that contact NIR, are located in close proximity of NIR, or have been associated with NIR resistance in cell culture. These M^{pro} TES were not significantly associated with hospitalization or death. The E166V TES was also identified by FDA analysis of the Applicant's amino acid frequency table.

Table 203. M^{pro} TES Enriched in PAXLOVID-Treated Subjects (Method #1)

AA Substitution	# PAX-Tx Subjects (n=537 w/ data)	# Placebo-Tx Subjects (n=550 w/ data)	AA Freq (PAX-Tx, Placebo-Tx)	Hosp. or Death Endpt? (PAX-Tx, Placebo-Tx)	Position of Interest?	NIR EC_{50} Fold-Change
G23S	18	10	0.10-0.12, 0.10-0.13	No, Yes (1/10)	No	ND
E166V	3	0	0.26-0.94, N/A	No, N/A	Yes	25-288

Source: FDA analysis of raw NGS fastq data.
Abbreviations: AA, amino acid; EC_{50}, half maximal effective concentration; Endpt, endpoint; Freq, frequency; Hosp, hospitalization; M^{pro}, main protease; n, number of subjects; N/A, not applicable; ND, no data; NGS, next generation sequencing; NIR, nirmatrelvir; Pax, Paxlovid; TES, treatment-emergent substitution; Tx, treated

Table 204. M^{pro} TES Enriched in PAXLOVID-Treated Subjects (Method #2)

AA Substitution	# PAX-Tx Subjects (n=537 w/ data)	# Placebo-Tx Subjects (n=550 w/ data)	AA Freq (PAX-Tx, Placebo-Tx)	Hosp. or Death Endpt? (PAX-Tx, Placebo-Tx)	Position of Interest?	NIR EC_{50} Fold-Change
G23D/S/V	23	17	0.10-0.12, 0.10-0.16	No, Yes (2/17)	No	ND
C85R/Y	3	0	0.11-0.14, N/A	No, N/A	No	ND

AA Substitution	# PAX-Tx Subjects (n=537 w/ data)	# Placebo-Tx Subjects (n=550 w/ data)	AA Freq (PAX-Tx, Placebo-Tx)	Hosp. or Death Endpt? (PAX-Tx, Placebo-Tx)	Position of Interest?	NIR EC_{50} Fold-Change
E166V	3	0	0.26-0.94, N/A	No, N/A	Yes	25-288
T199I/P/S	5	2	0.10-0.39, 0.12-0.16	Yes (1/5), No	No	ND

Source: FDA analysis of raw NGS fastq data.
Abbreviations: AA, amino acid; EC_{50}, half maximal effective concentration; Endpt, endpoint; Freq, frequency; Hosp, hospitalization; M^{pro}, main protease; n, number of subjects; N/A, not applicable; ND, no data; NGS, next generation sequencing; NIR, nirmatrelvir; Pax, Paxlovid; TES, treatment-emergent substitution; Tx, treated

Identification of M^{pro} TES at Positions of Interest

Next, M^{pro} TES (defined as described above) were analyzed at 34 residues that are considered positions of interest (Table 205), including 23 residues that directly contact or are located in close proximity (<5 Å) of NIR and 11 additional residues that have been associated with NIR resistance in cell culture. This analysis included all TES at positions of interest, regardless of whether they were enriched in the PAXLOVID arm. M^{pro} TES were identified at 17/34 positions of interest. The M^{pro} Y54S and N142D TES are considered likely to be sequencing artifacts, as they were identified in many subjects at baseline in both arms (Table 202), usually had low frequencies, and occurred at residues that are highly conserved (>99.99%) in the GISAID sequence database. Excluding Y54S and N142D, TES at positions of interest were identified in 12/537 (2.2%) of PAXLOVID-treated subjects and 5/550 (0.9%) of placebo-treated subjects. As described above, the E166V TES is considered likely to be a RAS. It is unclear whether any of the other TES represent RAS, as they were not clearly associated with PAXLOVID treatment and often occurred at low frequencies. The T21I and T304I substitutions have been associated with NIR resistance in cell culture. The TES in the PAXLOVID arm were not significantly associated with hospitalization or death. The C145F, C160R, E166V, A173T, and T304I TES were also identified by FDA analysis of the Applicant's amino acid frequency table (Section 18.3.2 and Table 196).

Table 205. M^{pro} TES at 34 Positions of Interest

M^{pro} Residue	AA Substitution	# PAX-Tx Subjects (n=537 w/data)	# PBO-Tx Subjects (n=550 w/data)	AA Freq (PAX-Tx, Placebo-Tx)	Hosp. or Death Endpt (PAX-Tx, Placebo-Tx)	NIR EC_{50} Fold-Change
T21	T21I	1	0	0.11, N/A	No, N/A	1.1-4.6
H41	N/A	0	0	N/A	N/A	N/A
M49	N/A	0	0	N/A	N/A	N/A
L50	N/A	0	0	N/A	N/A	N/A
Y54	Y54S	0	3	N/A, 0.12-0.63	N/A, Yes (2/3)	ND
P108	N/A	0	0	N/A	N/A	N/A
T135	N/A	0	0	N/A	N/A	N/A
F140	N/A	0	0	N/A	N/A	N/A
L141	N/A	0	0	N/A	N/A	N/A
N142	N142D	37	60	0.10-0.20, 0.10-0.36	No, Yes (5/60)	ND
G143	N/A	0	0	N/A	N/A	N/A
S144	N/A	0	0	N/A	N/A	N/A
C145	C145F/H	1	0	0.10-0.17, N/A	No, N/A	ND
C160	C160R/[a]	2	0	0.15-0.32, N/A	No, N/A	ND
H163	N/A	0	0	N/A	N/A	N/A
H164	N/A	0	0	N/A	N/A	N/A

M^{pro} Residue	AA Substitution	# PAX-Tx Subjects (n=537 w/data)	# PBO-Tx Subjects (n=550 w/data)	AA Freq (PAX-Tx, Placebo-Tx)	Hosp. or Death Endpt (PAX-Tx, Placebo-Tx)	NIR EC_{50} Fold-Change
M165	N/A	0	0	N/A	N/A	N/A
E166	E166V	3	0	0.26-0.94, N/A	No, N/A	25-288
L167	N/A	0	0	N/A	N/A	N/A
P168	N/A	0	0	N/A	N/A	N/A
T169	T169S	0	1	N/A, 0.13	N/A, No	ND
H172	N/A	0	0	N/A	N/A	N/A
A173	A173N/T	2	1	0.13-0.20, 0.11	No, No	ND
V186	V186L	1[b]	1	0.11, 0.16	No, No	ND
D187	D187Y	1[b]	0	0.11, N/A	No, N/A	ND
R188	R188K	1[b]	0	0.11, N/A	No, N/A	ND
Q189	N/A	0	0	N/A	N/A	N/A
T190	T190P	1[b]	0	0.11, N/A	No, N/A	ND
A191	A191P	1[b]	0	0.11, N/A	No, N/A	ND
Q192	Q192[a]	1	0	0.33, N/A	No, N/A	ND
A193	A193V	0	1	N/A, 0.20	N/A, No	ND
P252	P252H	0	1	N/A, 0.10	N/A, No	ND
S301	N/A	0	0	N/A	N/A	N/A
T304	T304I	1	0	0.24, N/A	No, N/A	2.1-5.5

Source: FDA analysis of raw NGS fastq data.
Note: Grey shading indicates positions at which TES were not observed in any subjects.
[a] Stop codon
[b] same subject
Abbreviations: AA, amino acid; EC_{50}, half maximal effective concentration; Endpt, endpoint; Freq, frequency; Hosp, hospitalization; n, number of subjects N/A, not applicable; ND, no data; NGS, next generation sequencing; NIR, nirmatrelvir; Pax, Paxlovid; PBO, placebo; TES, treatment-emergent substitution; Tx, treated

Identification of M^{pro} Cleavage Site TES Associated With PAXLOVID

Next, M^{pro} cleavage site TES associated with PAXLOVID treatment were identified, defined as in section C. This analysis was performed using two methods. In method #1, different substitutions at the same position were considered independently, and in method #2, all substitutions at the same position were grouped together. With method #1, one M^{pro} cleavage site TES was identified: K6796T (pp1ab numbering), which is located in the P3 position of the nsp15/nsp16 cleavage site (Table 206). With method #2, one other M^{pro} cleavage site TES was identified: M3862I/K, which is located in the P3′ position of the nsp6/nsp7 cleavage site. It is unclear whether these TES represent RAS, as they were observed in both arms, often had low frequencies, and have not been associated with NIR resistance in cell culture. These TES were not associated with hospitalization or death.

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Table 206. M^{pro} Cleavage Site (CS) TES Enriched in PAXLOVID-Treated Subjects

Method	AA Substitution	CS, Position	# PAX-Tx Subjects (n=528 w/ data)	#PBO-Tx Subjects (n=544 w/ data)	AA Freq (PAX-Tx, Placebo-Tx)	Hosp. or Death Endpt (PAX-Tx, Placebo-Tx)	NIR EC_{50} Fold-Change
#1	K6796T	nsp15/nsp16, P3	6	2	0.10-0.29, 0.10-0.18	No, No	ND
#2	M3862I/K	nsp6/nsp7, P3′	5	2	0.10-0.12, 0.10-0.11	No, No	ND

Source: FDA analysis of raw NGS fastq data.
Abbreviations: AA, amino acid; CS, cleavage site; EC_{50}, half maximal effective concentration; Endpt, endpoint; Freq, frequency; Hosp, hospitalization; n, number of subjects; N/A, not applicable; ND, no data; NG, next-generation sequencing; nsp, nonstructured protein; NIR, nirmatrelvir; PAX, Paxlovid; PBO, placebo; TES, treatment-emergent substitution; Tx, treated

Additional Analysis of M^{pro} E166V Substitutions

Additional analysis was performed to further characterize the M^{pro} E166V substitution, which was considered likely to be a RAS. As described in section C, the E166V TES was identified in 3 PAXLOVID-treated subjects and 0 placebo-treated subjects. None of these subjects experienced hospitalization or death. For subject (b) (6), sequencing results were available from samples collected on Days 1, 3, and 5. The E166V substitution was detected with a frequency of 90% on Day 5 but was not detected on Days 1 or 3 (frequency <1%). The M^{pro} L50F polymorphism was also detected in this subject on Day 1 (68%), Day 3 (82%), and Day 5 (85%). For subject (b) (6), sequencing results were available from samples collected on Days 1, 3, and 10. The E166V substitution was detected with a frequency of 26% on Day 10 but was not detected on Days 1 or 3. For subject (b) (6), sequencing results were available from samples collected on Days 1, 3, and 5. The E166V substitution was detected with a frequency of 94% on Day 5 but was not detected on Days 1 or 3.

Additional analyses were performed to determine whether the M^{pro} E166V substitution was detected at a frequency ≥1% in any additional subjects. The E166V substitution was only identified in 1 additional subject, who was treated with PAXLOVID. This subject did not experience hospitalization or death. For this subject, sequencing results were available from samples collected on Days 1, 3, 5, 10, and 14. The E166V substitution was only detected on Day 5, with a frequency of 2%. The E166V substitution was not detected in samples from any other subjects, including post-baseline samples from subjects who were missing baseline samples. Thus, overall, the E166V substitution was detected in 4/537 (0.7%) of PAXLOVID-treated subjects with baseline and post-baseline samples and 4/583 (0.7%) of PAXLOVID-treated subjects with at least one post-baseline sample.

Additional Analysis of M^{pro} P132H/L/S Substitutions

In FDA analysis of the Applicant's amino acid frequency table (Section 18.3.2 and Table 196), the M^{pro} P132H/L/S TES was identified in 5 PAXLOVID-treated subjects and 0 placebo-treated subjects. However, as described in Section 18.3.2, the two instances of P132H appeared to be due to contamination with Omicron sequences, based on detection of other Omicron-specific changes. After excluding P132H, the M^{pro} P132L/S TES was identified in 3 PAXLOVID-treated subjects (at frequencies of 19 to 35%) and 0 placebo-treated subjects. In FDA analysis of the Applicant's raw NGS data, the M^{pro} P132T TES was identified (with a 10% frequency cutoff) in 1 PAXLOVID-treated subject and 0 placebo-treated subjects. Thus, the M^{pro} P132T TES was not considered enriched in the PAXLOVID arm and was not included in Table 203 and Table 204.

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Further analysis revealed that the P132L/S/T TES were detected by the FDA in the same 3 PAXLOVID-treated subjects identified by the Applicant, but at lower frequencies (5-12%) that were below the 10% cutoff in 2/3 subjects (Table 207). When FDA analysis of the Applicant's raw NGS data was repeated with a 5% frequency cutoff, the P132L/S/T TES were detected in 4 PAXLOVID-treated subjects and 0 placebo-treated subjects. With an even lower 1% frequency cutoff, the P132A/L/S/T TES were detected in 9 PAXLOVID-treated subjects and 8 placebo-treated subjects. The M^{pro} P132H/L/S substitutions did not affect nirmatrelvir activity in biochemical and/or cell culture assays.

Table 207. Analysis of 3 PAXLOVID-Treated Subjects With M^{pro} P132L/S TES

SUBJID	Applicant's Analysis	FDA Analysis
(b) (6)	P132S detected on Day 5 (35%) but not Days 1 or 10 (<1%)	P132S detected on Day 5 (5%) but not Days 1 or 10 (<1%)
	P132S detected on Day 10 (26%) but not Day 1 (<1%)	P132T detected on Day 10 (12%) but not Day 1 (<1%)
	P132L detected on Day 5 (19%) but not Days 1 or 3 (<1%)	P132L detected on Day 5 (5%) but not Days 1 or 3 (<1%)

Source: FDA analysis of raw NGS fastq data.
Abbreviations: NGS, next-generation sequencing; SUBJID, subject identifier; TES, treatment-emergent substitution

Additional Analysis of M^{pro} V186G Substitutions

In FDA analysis of the Applicant's amino acid frequency table (Section 18.3.2 and Table 196), the M^{pro} V186G TES was identified in 22 PAXLOVID-treated subjects (average frequency: 15%, range: 10-24%) and 15 placebo-treated subjects (average frequency: 15%, range: 10-22%). In FDA analysis of the Applicant's raw NGS data, the M^{pro} V186L TES was identified (with a 10% frequency cutoff) in 1 PAXLOVID-treated subject (frequency: 11%) and 1 placebo-treated subject (frequency: 16%). However, the V186G TES was not observed in any subjects. Further analysis revealed that the V186G TES was detected by the FDA in 20/22 PAXLOVID-treated subjects, but at lower frequencies (average frequency: 4%, range: 1-8%) that were below the 10% cutoff in all subjects. When FDA analysis of the Applicant's raw NGS data was repeated with a 5% frequency cutoff, the V186G TES was detected in 7 PAXLOVID-treated subjects and 6 placebo-treated subjects. With an even lower 1% frequency cutoff, the V186G TES was detected in 29 PAXLOVID-treated subjects and 20 placebo-treated subjects. The M^{pro} V186G substitution did not affect nirmatrelvir activity in a biochemical assay.

Additional Analysis of M^{pro} Q189K Substitutions

In FDA analysis of the Applicant's amino acid frequency table (Section 18.3.2 and Table 196), the M^{pro} Q189K TES was identified in 5 PAXLOVID-treated subjects (at frequencies of 14 to 32%) and 5 placebo-treated subjects (at frequencies of 11 to 31%). In FDA analysis of the Applicant's raw NGS data, the M^{pro} Q189K TES was not identified (with a 10% frequency cutoff) in any subjects. Further analysis revealed that the Q189K TES was detected by the FDA in all 10 subjects, but at lower frequencies (2-6%) that were below the 10% cutoff in all subjects. When FDA analysis of the Applicant's raw NGS data was repeated with a 5% frequency cutoff, the Q189K TES was detected in 2 PAXLOVID-treated subjects and 1 placebo-treated subjects. With an even lower 1% frequency cutoff, the Q189K TES was detected in 47 PAXLOVID-treated subjects and 33 placebo-treated subjects. The M^{pro} Q189K substitution did not affect nirmatrelvir activity in cell culture.

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Additional Analysis of M^{pro} A260S/T/V Substitutions

In FDA analysis of the Applicant's amino acid frequency table (Section 18.3.2 and Table 196), the M^{pro} A260S/T/V TES was identified in 7 PAXLOVID-treated subjects (at frequencies of 11 to 21%) and 1 placebo-treated subject (frequency: 11%). In FDA analysis of the Applicant's raw NGS data, the M^{pro} A260T TES was identified (with a 10% frequency cutoff) in 1 PAXLOVID-treated subject (frequency: 11%) and 0 placebo-treated subjects. Further analysis revealed that the A260S/T/V TES was detected by the FDA in all 8 subjects, but at lower frequencies (1 to 11%) that were below the 10% cutoff in 7/8 subjects. When FDA analysis of the Applicant's raw NGS data was repeated with a 5% frequency cutoff, A260 TES were detected in 5 PAXLOVID-treated subjects and 2 placebo-treated subjects. With an even lower 1% frequency cutoff, A260 TES were detected in 17 PAXLOVID-treated subjects and 12 placebo-treated subjects. The M^{pro} A260S/T/V substitutions did not affect nirmatrelvir activity in a biochemical assay.

Additional Analysis of pp1ab A3571V Substitutions

In FDA analysis of the Applicant's amino acid frequency table (Section 18.3.2 and Table 196), the pp1ab A3571V TES was identified in 3 PAXLOVID-treated subjects (at frequencies >99%) and 1 placebo-treated subject (at a frequency >99%). In FDA analysis of the Applicant's raw NGS data, the A3571V TES was identified (with a 10% frequency cutoff) in 3 PAXLOVID-treated subjects (at frequencies of 89-96%, same subjects identified by the Applicant) and 2 placebo-treated subjects (at frequencies of 27 to 98%, same subject identified by the Applicant and one additional subject). Thus, the A3571V TES was not considered enriched in the PAXLOVID arm and was not included in Table 206. Also note that A3571V is one of the most common naturally occurring M^{pro} cleavage site polymorphisms (Section 18.4).

Additional Analysis of pp1ab A5328P/S Substitutions

In FDA analysis of the Applicant's amino acid frequency table (Section 18.3.2 and Table 196), the pp1ab A5328P/S TES was identified in 4 PAXLOVID-treated subjects (at frequencies of 10 to 34%) and 0 placebo-treated subjects. In FDA analysis of the Applicant's raw NGS data, the A5328P/S TES was not identified (with a 10% frequency cutoff) in any subjects. Further analysis revealed that the A5328P/S TES was detected by the FDA in all 4 subjects, but at lower frequencies (1-7%) that were below the 10% cutoff in all subjects. When FDA analysis of the Applicant's raw NGS data was repeated with a 5% frequency cutoff, the A5328S TES was detected in 1 PAXLOVID-treated subject and 0 placebo-treated subjects. With an even lower 1% frequency cutoff, A5328 TES were detected in 5 PAXLOVID-treated subjects and 2 placebo-treated subjects.

Analysis of Ten Additional Samples in CLC Genomics Workbench

M^{pro} amino acid substitution frequency results were not obtained in HIVE for 10/3,573 (0.3%) samples, including 4 samples from PAXLOVID-treated subjects and 6 samples from placebo-treated subjects. Upon further review, the sequencing results from these ten samples appeared to be of low quality. Specifically, a large portion of the reads appeared to result from non-specific PCR products (e.g., primer dimers). These ten samples were analyzed using a separate bioinformatics pipeline in CLC Genomics Workbench (Qiagen 2023). M^{pro} and M^{pro} cleavage

site substitutions (≥10% frequency) were not detected in any of the 4 samples from PAXLOVID-treated subjects, in agreement with the Applicant's results for these samples.

Conclusions From Independent FDA Analyses of Raw NGS Data

- The M^{pro} E166V TES was confirmed in 3 PAXLOVID-treated subjects. Using a lower frequency cutoff (1%), the M^{pro} E166V TES was identified in 1 additional PAXLOVID-treated subject. In one instance, the E166V substitution co-occurred with an M^{pro} L50F baseline polymorphism. Both the L50F and E166V substitutions have been associated with NIR resistance in cell culture and should be considered RAS. None of these subjects experienced hospitalization or death.
- Several additional M^{pro} TES were identified in PAXLOVID-treated subjects, including T21I, G23D/S/V, C85R/Y, C145F/H, C160R, A173N/T, V186L, D187Y, R188K, T190P, A191P, T199I/P/S, and T304I. In addition, two M^{pro} cleavage site TES were identified in PAXLOVID-treated subjects: M3862I/K and K6796T. It is currently unclear whether any of these TES represent RAS, as they were often identified in both arms and/or at low frequencies. In addition, when the criteria for identifying M^{pro} or M^{pro} cleavage site TES were simply reversed (to identify TES that occurred more frequently in placebo-treated subjects than in PAXLOVID-treated subjects), more M^{pro} and M^{pro} cleavage site TES were found to be enriched in placebo-treated subjects than in PAXLOVID-treated subjects. This finding indicates that some of the TES enriched in PAXLOVID-treated subjects may not be associated with PAXLOVID resistance. However, the T21I and T304I substitutions were associated with NIR resistance in cell culture and should be considered potential RAS.
- In cases of disagreement between the Applicant's frequency table and the FDA's frequency table (e.g., for the M^{pro} P132L/S, V186G, Q189K, A260S/T/V and M^{pro} cleavage site A3571V and A5328P/S TES), most of the differences in results were attributed to substitution frequencies that were above the frequency threshold (10%) in the Applicant's table (~10-30%) but below the threshold in the FDA's table (~1 to 10%). It is currently unclear whether any of these TES represent RAS, as they were often identified in both arms and/or had low frequencies that were not clearly distinguishable from background errors.
- In PAXLOVID-treated subjects, there did not appear to be a significant association between hospitalization or death and baseline M^{pro} polymorphisms at positions of interest, M^{pro} TES associated with PAXLOVID treatment, M^{pro} TES at positions of interest, or M^{pro} cleavage site TES associated with PAXLOVID treatment. Thus, the clinical significance of these substitutions remains unclear.

18.3.5. Updated/Pooled EPIC-HR and EPIC-SR Resistance Analyses

Late in the review cycle the Applicant submitted updated resistance analysis study reports and datasets for the EPIC-HR and EPIC-SR trials. These updated data did not change the overall conclusions from the resistance analyses summarized above. However, in the context of labeling discussions, it was determined that a pooled analysis of the latest available data from the EPIC-HR and EPIC-SR trials would be conducted, and the results of this analysis would be described in Section 12.4 of the prescribing information. As in the analyses described above for the

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individual trials, a 10% sensitivity cutoff was used to identify viral M^{pro} or M^{pro} cleavage site amino acid substitutions in each sample. Also consistent with the analyses for the individual trials, the pooled analysis focused on amino acid substitutions that emerged at the same M^{pro} or M^{pro} cleavage site residue in ≥3 PAXLOVID-treated subjects (any change at same position), and at a ≥2-fold greater frequency than in Placebo-treated subjects, across the EPIC-HR and EPIC-SR trials. This algorithm was ultimately used to determine which specific substitutions to describe in the prescribing information.

After censoring subjects from study sites with data anomalies or data reliability concerns, as well as subjects whose "Baseline/Day 1" visit samples were obtained more than 1 hour after the start of study drug dosing (discussed in (Pfizer 2023e)), the pooled analysis was conducted for a total of 907 PAXLOVID recipients and 942 placebo recipients with available baseline and post-baseline sequence analysis data. The following PAXLOVID treatment-emergent substitutions were identified in this analysis:

- M^{pro} substitutions: T98I/R/del (n=4 PAXLOVID [1 EPIC-HR, 3 EPIC-SR], n=0 placebo), E166V (n=3 PAXLOVID [all EPIC-HR], n=0 placebo), and W207L/R/del (n=4 PAXLOVID [2 EPIC-HR, 2 EPIC-SR], n=0 placebo).
- M^{pro} cleavage site substitutions: A5328S/V (n = 7 PAXLOVID [3 EPIC-HR, 4 EPIC-SR], n=1 placebo [EPIC-HR, A5328T]) and S6799A/P/Y (n = 4 PAXLOVID [3 EPIC-HR, 1 EPIC-SR], n = 1 placebo [EPIC-SR, S6799F]).

As discussed above, M^{pro} E166V was the clearest nirmatrelvir resistance-associated TES observed in these analyses. The clinical relevance and potential impact of the other substitutions on nirmatrelvir activity are unclear. Besides M^{pro} E166V, phenotype data are only available for M^{pro} W207L, which did not reduce nirmatrelvir activity in a biochemical assay. Therefore, a post-marketing requirement will be issued for the Applicant to conduct phenotypic analyses of the other noted TES. In addition, while M^{pro} G11V was not identified as a PAXLOVID TES based on this algorithm, any change at this position (C/S/V) was observed in 3 PAXLOVID recipients in EPIC-HR and 1 PAXLOVID recipient (and 3 placebo recipients) in EPIC-SR; only G11V was observed in 2 PAXLOVID recipients. Therefore, the post-marketing requirement will include phenotypic analysis of G11V.

18.4. SARS-CoV-2 Genomic Database Surveillance (Through November 30, 2022)

As a condition for Emergency Use Authorization, the Applicant has been required to provide the FDA with monthly surveillance reports to monitor for circulating and emerging SARS-CoV-2 variants with amino acid polymorphisms in M^{pro} or M^{pro} cleavage sites. Note that the Applicant will be required to conduct similar surveillance activities post-approval (see Section 24.1). These reports also contain listings of all amino acid polymorphisms in M^{pro} or M^{pro} cleavage sites (P5 to P5′ positions), their cumulative counts and frequencies, and their counts and frequencies for each of the three previous months. The latest versions of these reports have been cross-referenced to the NDA and cover sequences deposited in the GISAID EpiCov sequence database through November 30, 2022, and thus contains cumulative polymorphism counts and frequencies, as well as counts and frequencies for sequences deposited in August, September, October, or November 2022. Only complete genome sequences with high coverage were

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included in the analysis, resulting in a total of 12,664,696 sequences deposited globally since the beginning of the pandemic. Note that analyses of these sequences are affected by disparities in sequencing coverage across geographic regions and countries.

M^{pro} and M^{pro} Cleavage Site Polymorphisms With Frequencies ≥0.1%

In the Applicant's reports, only 16 M^{pro} amino acid polymorphisms had a cumulative or ≥1 monthly frequency of ≥0.1% (1/1,000) in the GISAID database: G15S, T21I, L30I, T45N, A70T, L75F, K88R, L89F, K90R, V104I, P108S, P132H, T169S, F223L, H246Y, and A260V (Table 208). Some of these polymorphisms are known to be associated with particular SARS-CoV-2 variants, e.g., G15S with Lambda, K90R with Beta, and P132H with Omicron sub-variants. Only the L30I,T169S, and F223L polymorphisms had ≥1 monthly frequency increase of ≥3-fold from August 2022 to November 2022. The L30I polymorphism is primarily associated with the Omicron BQ.1.3 sub-variant. Of these polymorphisms, only T21I and P108S have been associated with NIR resistance in cell culture (in combination with other M^{pro} substitutions, Section 20); in analyses of raw NGS data T21I and L30I each emerged at a low level in 1 PAXLOVID-treated subject in EPIC-HR. In biochemical assays, the M^{pro} G15S, T21I, A70T, L75F, K88R, L89F, K90R, P108S, P132H, T169S, and A260V substitutions did not affect NIR activity (Section 20), while the L30I, T45N, V104I, F223L, and H246Y substitutions have not been tested.

Table 208. SARS-CoV-2 M^{pro} Polymorphisms With Cumulative or Monthly Frequencies ≥0.1%

M^{pro} Polymorphism	Cumulative Freq.	8/2022 Freq.	9/2022 Freq.	10/2022 Freq.	11/2022 Freq.
P132H	45.5%	94.6%	93.8%	94.7%	88.1%
K90R	1.39%	0.55%	0.62%	0.70%	0.80%
L89F	1.15%	0.17%	0.14%	0.24%	0.28%
T169S	0.48%	0.07%	0.01%	0.18%	0.01%
P108S	0.22%	0.16%	0.12%	0.10%	0.23%
A260V	0.20%	0.04%	0.06%	0.06%	0.09%
G15S	0.18%	0.02%	0.03%	0.05%	0.04%
L75F	0.15%	0.21%	0.18%	0.18%	0.13%
K88R	0.15%	0.03%	0.05%	0.05%	0.05%
T21I	0.13%	0.10%	0.14%	0.15%	0.14%
H246Y	0.06%	0.15%	0.16%	0.15%	0.16%
T45N	0.03%	0.14%	0.16%	0.19%	0.30%
A70T	0.02%	0.11%	0.04%	0.05%	0.03%
F223L	0.02%	0.01%	0.02%	0.05%	0.26%
V104I	0.02%	0.02%	0.03%	0.05%	0.12%
L30I	0.01%	<0.01%	0.01%	0.10%	0.35%

Source: FDA analysis of 10/2022 and 11/2022 surveillance reports.
Abbreviations: Freq, frequency; M^{pro}, main protease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

In the Applicant's report, only 7 M^{pro} cleavage site polymorphisms had a cumulative or ≥1 monthly frequency of ≥0.1% (1/1,000) in the GISAID database: A3571V, R3574K, V3855I, T4249I, A5922S/V, and T5923I (Table 209). Only the R3574K and V3855I polymorphisms increased in frequency ≥3-fold from October 2022 to November 2022. Note that A3571V emerged in 3 PAXLOVID-treated subjects in EPIC-HR, but also in 1 or 2 placebo-treated subjects (depending on analysis). None of these changes have been associated with NIR resistance in cell culture, and their impact on NIR activity has not been determined.

Table 209. SARS-CoV-2 M^{pro} Cleavage Site Polymorphisms With Cumulative or Monthly Frequencies ≥0.1%

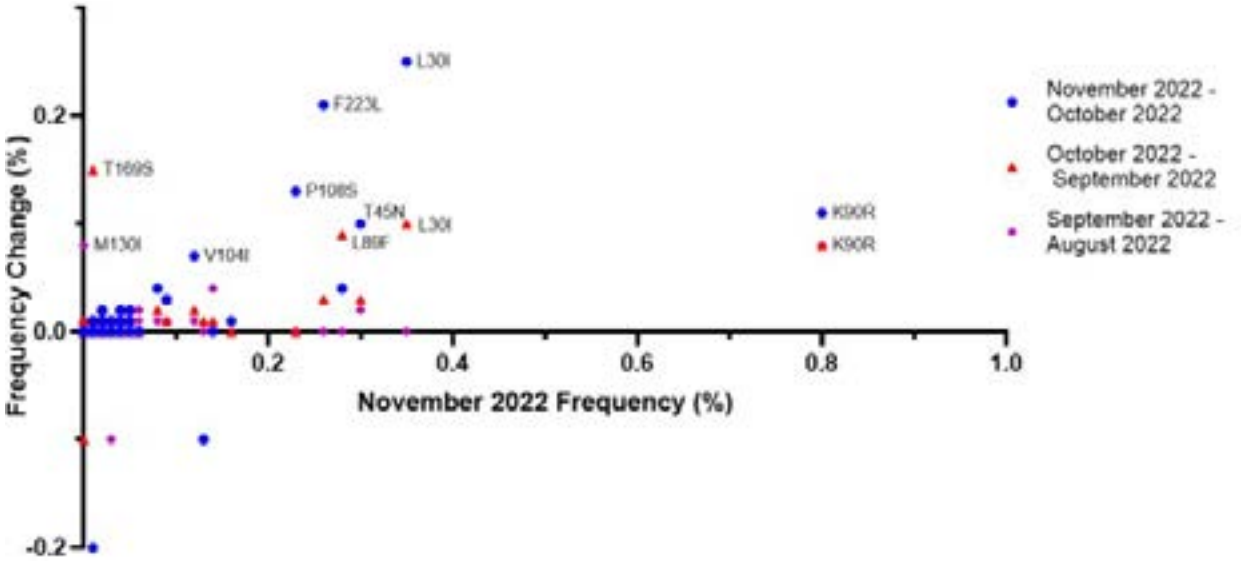
pp1ab Polymorphism	CS	CS Position	Cumulative Freq.	10/2022 Freq.	11/2022 Freq.
A3571V	nsp5/nsp6	P2′	0.50%	0.05%	0.08%
A5922S	nsp13/nsp14	P4	0.24%	0.02%	0.03%
T5923I	nsp13/nsp14	P3	0.13%	0.08%	0.09%
T4249I	nsp9/nsp10	P5	0.13%	0.12%	0.12%
A5922V	nsp13/nsp14	P4	0.10%	0.05%	0.07%
R3574K	nsp5/nsp6	P5′	0.03%	0.04%	0.16%
V3855I	nsp6/nsp7	P5	0.01%	0.07%	0.31%

Source: FDA analysis of 10/2022 and 11/2022 surveillance reports.
Abbreviations: CS, cleavage site; Freq, frequency; M^{pro}, main protease; nsp, nonstructural protein; P, position; pp, polyprotein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

M^{pro} and M^{pro} Cleavage Site Polymorphisms With Recent Increases in Frequencies

To identify emerging M^{pro} polymorphisms, the frequency of each M^{pro} polymorphism in November 2022 was plotted against the absolute change in polymorphism frequency from August 2022 through November 2022 (Figure 88). The M^{pro} polymorphisms with the greatest increases in absolute frequencies (at least 1 monthly increase of ≥0.05%) were L30I, T45N, L89F, K90R, V104I, P108S, M130I, P132H, T169S, and F223L. Of these polymorphisms, only P108S has been associated with NIR resistance in cell culture (in combination with other M^{pro} substitutions, Section 20). In biochemical assays, the M^{pro} L89F, K90R, P108S, P132H, and T169S substitutions did not affect NIR activity (Section 20), while the L30I, T45N, V104I, M130I, and F223L substitutions have not been tested.

Figure 88. Changes in SARS-CoV-2 M^{pro} Polymorphism Frequencies From August 2022 Through November 2022



Source: FDA analysis of 10/2022 and 11/2022 surveillance reports.
Note: The x-axis indicates the M^{pro} polymorphism frequency (%) in November 2022, while the y-axis indicates the absolute change in M^{pro} polymorphism frequency (%) between the indicated months. The M^{pro} P132H polymorphism is not shown.
Abbreviations: M^{pro}, main protease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

To identify emerging M^{pro} cleavage site polymorphisms, the frequency of each M^{pro} cleavage site polymorphism in November 2022 was compared to its cumulative frequency and frequency in

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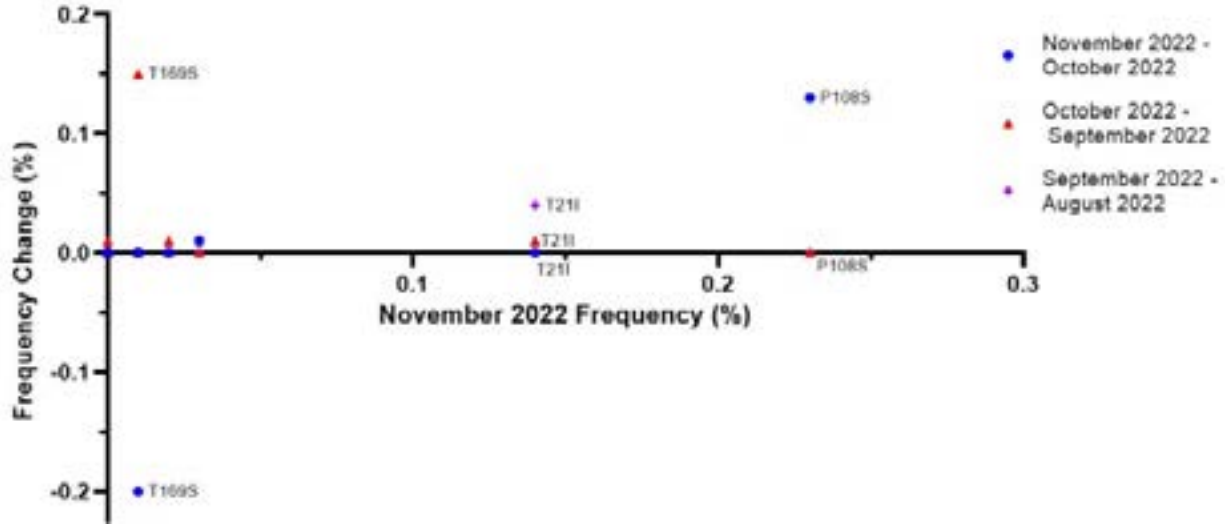
October 2022. Only two M^{pro} cleavage site polymorphisms had a frequency in November 2022 that was at least 0.05% greater than its cumulative frequency or frequency in October 2022: V3855I and R3574K (Table 209). These substitutions have not been associated with NIR resistance in cell culture, and their impact on NIR activity has not been determined.

M^{pro} Polymorphism Frequencies at 34 Positions of Interest

Lastly, M^{pro} polymorphism frequencies were analyzed at 34 residues that are considered positions of interest (Table 202), including 23 residues that directly contact or are located in close proximity (<5 Å) of NIR and 11 additional residues that have been associated with NIR resistance in cell culture. The most common polymorphisms at these positions in November 2022 sequences were T21I and P108S (Figure 89). The T21I polymorphism increased in frequency from August 2022 to September 2022, but subsequently did not change much in frequency. Conversely, the P108S polymorphism only increased in frequency from October 2022 to November 2022. The T169S polymorphism increased in frequency from September 2022 to October 2022 but subsequently decreased in frequency from October 2022 to November 2022. The T21I and P108S polymorphisms have both been associated with NIR resistance in cell culture (in combination with other substitutions) but did not affect NIR activity in a biochemical assay (Section 20). The E166V polymorphism was observed in only 9 of ~12.7 million sequences.

Figure 89. Changes in SARS-CoV-2 M^{pro} Polymorphism Frequencies at Positions of Interest From August 2022 Through November 2022



Source: FDA analysis of 10/2022 and 11/2022 surveillance reports.
Note: The x-axis indicates the M^{pro} polymorphism frequency (%) at 34 positions of interest in November 2022, while the y-axis indicates the absolute change in M^{pro} polymorphism frequency (%) between the indicated months.
Abbreviations: M^{pro}, main protease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

18.5. Investigation of Clinical Virology Data Anomalies

During the review we identified certain unusual patterns of viral RNA levels and viral sequencing results at selected study sites in EPIC-HR and EPIC-SR. In at least one of these sites

highly unusual patterns of symptom data collection were also observed in some of the same subjects with unusual viral RNA patterns. These observations triggered additional site inspections and in-depth investigation of all study data and sites from EPIC-HR and EPIC-SR.

18.5.1. Observations of Viral RNA and Sequencing Anomalies at Specific Study Sites

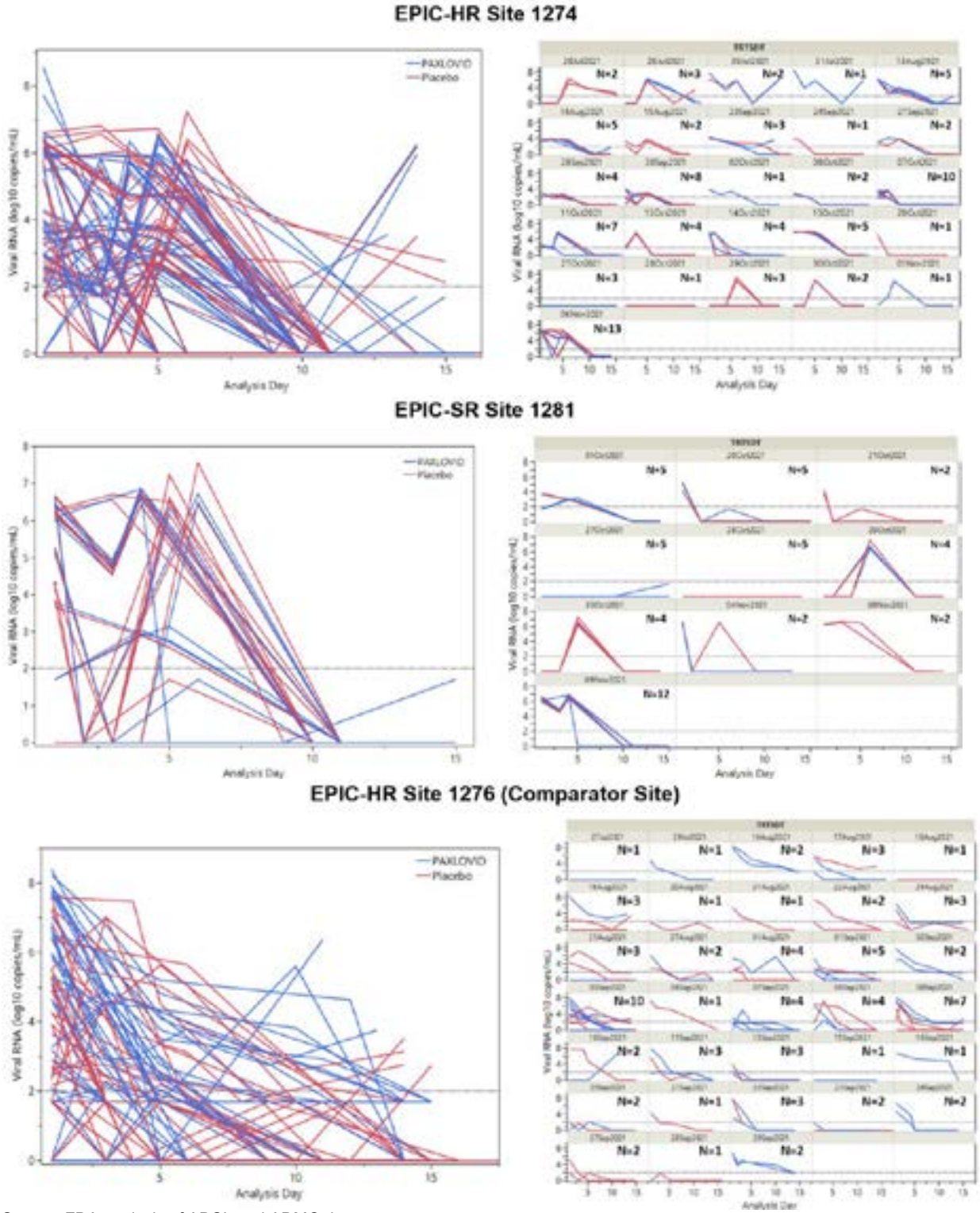
Unusual patterns of viral RNA levels in NP samples over time were observed among subjects at the following study sites:

- EPIC-HR: Site 1274 (Principal investigator [PI]: Gonzalez/Martinez, Cutler Bay, FL, USA; same location as EPIC-SR site 1281)
- EPIC-SR: Site 1281 (PI: Gonzalez/Martinez, Cutler Bay, FL, USA; same location as EPIC-HR site 1274), Site 1157 (PI: Medzhidiev, Sofia, Bulgaria), and Site 1197 (PI: Haytova, Vratsa, Bulgaria, 2022 enrollment period)

The unusual viral RNA patterns were characterized by a high degree of overlapping and often implausible trends in viral RNA shedding levels over time in different subjects at the same site, which in many cases were associated with similar timing of treatment initiation (Figure 90, Figure 91, Figure 92, and Figure 93, FDA analyses). For example, in EPIC-HR Site 1274, 4 different subjects who all started treatment on October 13, 2021, (2 received PAXLOVID, 2 received placebo) had a similar major spike in viral RNA levels between the Baseline and the Day 3 visits, and in all subjects viral RNA declined to undetected levels at all subsequent visits. As another example from EPIC-HR Site 1274, 5 subjects who started treatment on October 15, 2021, (3 received PAXLOVID, 2 received placebo) all had highly similar viral RNA levels which had a relatively delayed decline over time.

The overlapping viral RNA patterns within the Gonzalez/Martinez site (EPIC-HR Site 1274/EPIC-SR Site 1281) extended between both trials. For example, 12 different subjects across both trials who initiated treatment on October 29, 2021, or October 30, 2021, had highly similar patterns of viral RNA over time, with viral RNA levels of 6.2 to 7.6 $\log_{10}$ copies in the Day 5 visit window, which corresponded to actual analysis Days 5 or 6 (Figure 91). At all other study visits for all 12 subjects, including the Baseline visit, viral RNA levels were reported as target not detected. One additional subject who started treatment on October 29, 2021, had viral RNA target not detected at all study visits, and the subject was missing data for the Day 5 visit when the other 12 subjects had the characteristic spike in viral RNA. The viral RNA peak in the 12 subjects was staggered by 1 Analysis Day (i.e., day relative to start of treatment), although for all 12 subjects the viral RNA sampling actually occurred on the same exact date (November 3, 2021) within a ~4-hour window. These and other viral RNA patterns from this site are highly implausible and raise concerns about virology data quality or data integrity.

Figure 90. Viral RNA Levels in NP Swab Samples From Subjects Who Enrolled at EPIC-HR 1274/EPIC-SR 1281 Sites (PI: Martinez), or EPIC-HR Site 1276 (Comparator Site)



Source: FDA analysis of ADSL and ADMC datasets.
Note: Dashed lines indicate qRT-PCR assay LLOQ.
Abbreviations: LLOQ, lower limit of quantitation; log, logarithm; N, total number of subjects; qRT-PCR, real-time, quantitative, reverse transcription-polymerase chain reaction; RNA, ribonucleic acid; TRTSDT, treatment start date

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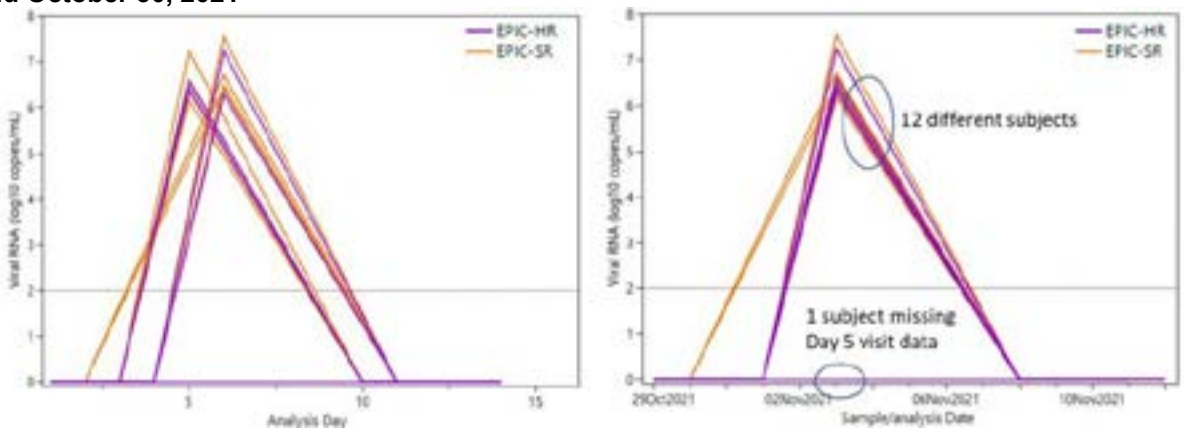
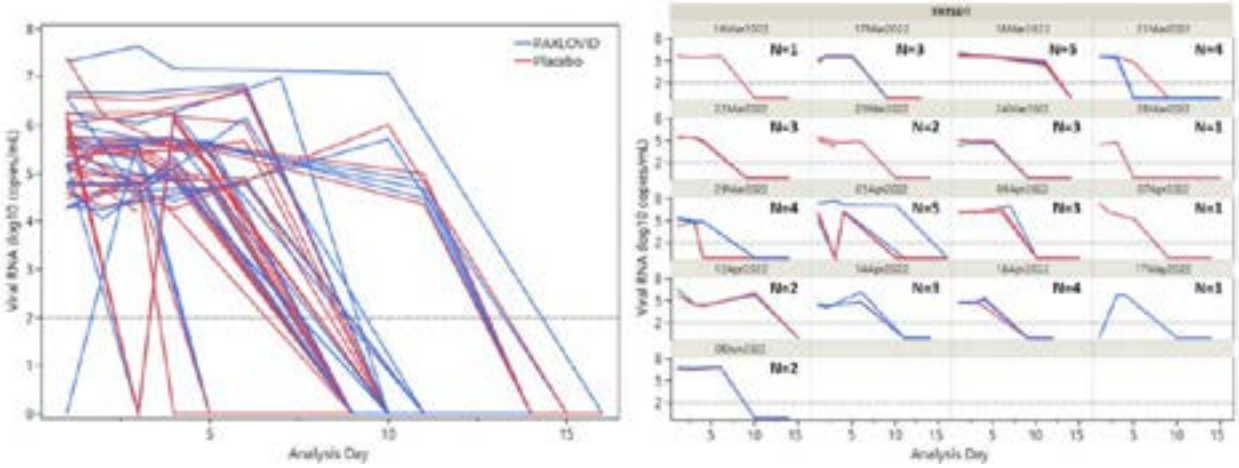
Figure 91. Viral RNA Levels in NP Swab Samples From Subjects Who Enrolled at EPIC-HR 1274/EPIC-SR 1281 Sites (PI: Gonzalez/Martinez) With Treatment Start Dates of October 29, 2021 and October 30, 2021



Source: FDA analysis of ADSL and ADMC datasets.
Note: Dashed lines indicate qRT-PCR assay LLOQ.
Abbreviations: LLOQ, lower limit of quantitation; log, logarithm; qRT-PCR, real-time, quantitative, reverse transcription-polymerase chain reaction; RNA, ribonucleic acid

Unusual patterns of overlapping viral RNA levels over time were also observed in EPIC-SR site 1157 (PI: Medzhidiev, Bulgaria) (Figure 92). As in EPIC-HR 1274/EPIC-SR 1281, the viral RNA patterns clustered largely by treatment start date.

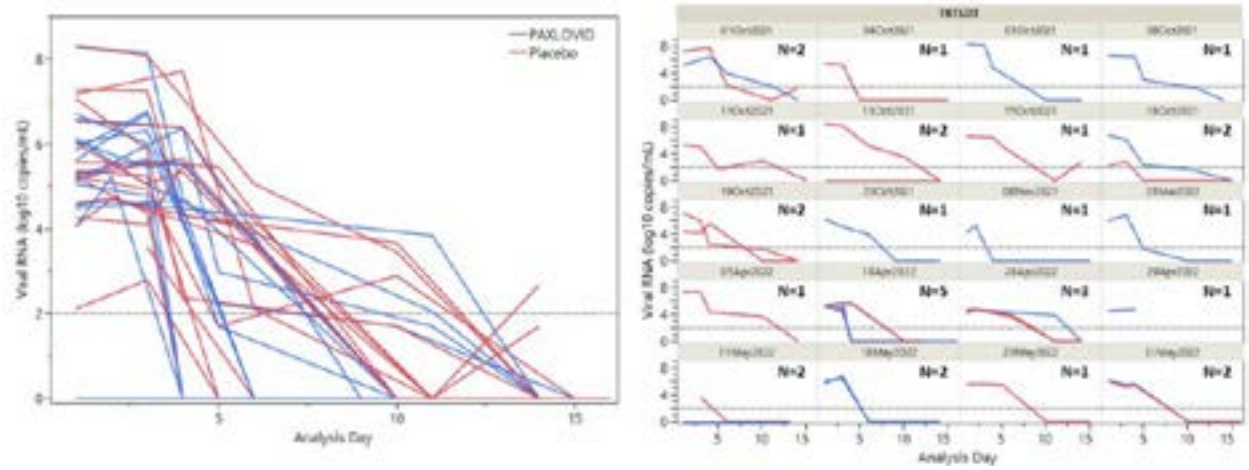
Figure 92. Viral RNA Levels in NP Swab Samples From Subjects Who Enrolled at EPIC-SR Site 1157 (PI: Medzhidiev)



Source: FDA analysis of ADSL and ADMC datasets.
Note: Dashed lines indicate qRT-PCR assay LLOQ.
Abbreviations: LLOQ, lower limit of quantitation; log, logarithm; qRT-PCR, real-time, quantitative, reverse transcription-polymerase chain reaction; RNA, ribonucleic acid

Unusual viral RNA patterns, again clustered by treatment start date, were also observed at a second EPIC-SR site in Bulgaria, site 1197 (PI: Haytova) (Figure 93). The overlapping viral RNA patterns at this site were not as striking as the other sites noted above and appeared to be restricted to the 2022 enrollment period (i.e., Omicron infections). Note that the same PI enrolled subjects in EPIC-HR as site 1193, and analyses of viral RNA levels from these subjects did not identify evidence of overlapping patterns of viral RNA over time, either overall or grouped by treatment start date (analyses not shown).

Figure 93. Viral RNA Levels in NP Swab Samples From Subjects Who Enrolled at EPIC-SR Site 1197 (PI: Haytova)



Source: FDA analysis of ADSL and ADMC datasets.
Notes: Dashed lines indicate qRT-PCR assay LLOQ.
Abbreviations: LLOQ, lower limit of quantitation; log, logarithm; N, total number of subjects; qRT-PCR, real-time, quantitative, reverse transcription-polymerase chain reaction; RNA, ribonucleic acid

The same viral RNA samples used for qRT-PCR analyses were also subjected to next generation sequencing analyses to support resistance analyses and identification of SARS-CoV-2 variants. Following the observations of overlapping viral RNA patterns noted above, extensive analyses of viral sequences were conducted by the Applicant and FDA to assess for unusual patterns of genetic clustering, which could indicate flawed or improper sample handling or processing. Independent FDA analyses were conducted using CLC genomics software. These analyses were conducted on consensus nucleotide sequences spanning the entire ~30 kb SARS-CoV-2 genome.

As shown in Figure 94, phylogenetic analyses of viral consensus nucleotide sequences conducted by the Applicant indicated extensive genetic clustering of numerous viral sequences from different subjects from the EPIC-HR 1274/EPIC-SR 1281 site, as well as from the EPIC-SR site 1157, with many sequences having minimal to nonexistent branch lengths indicating nearly or completely identical viral nucleotide sequences. This extent of viral genetic conservation across different subjects is implausible and strongly indicates flawed NP swab sample collection, handling, or processing from these sites.

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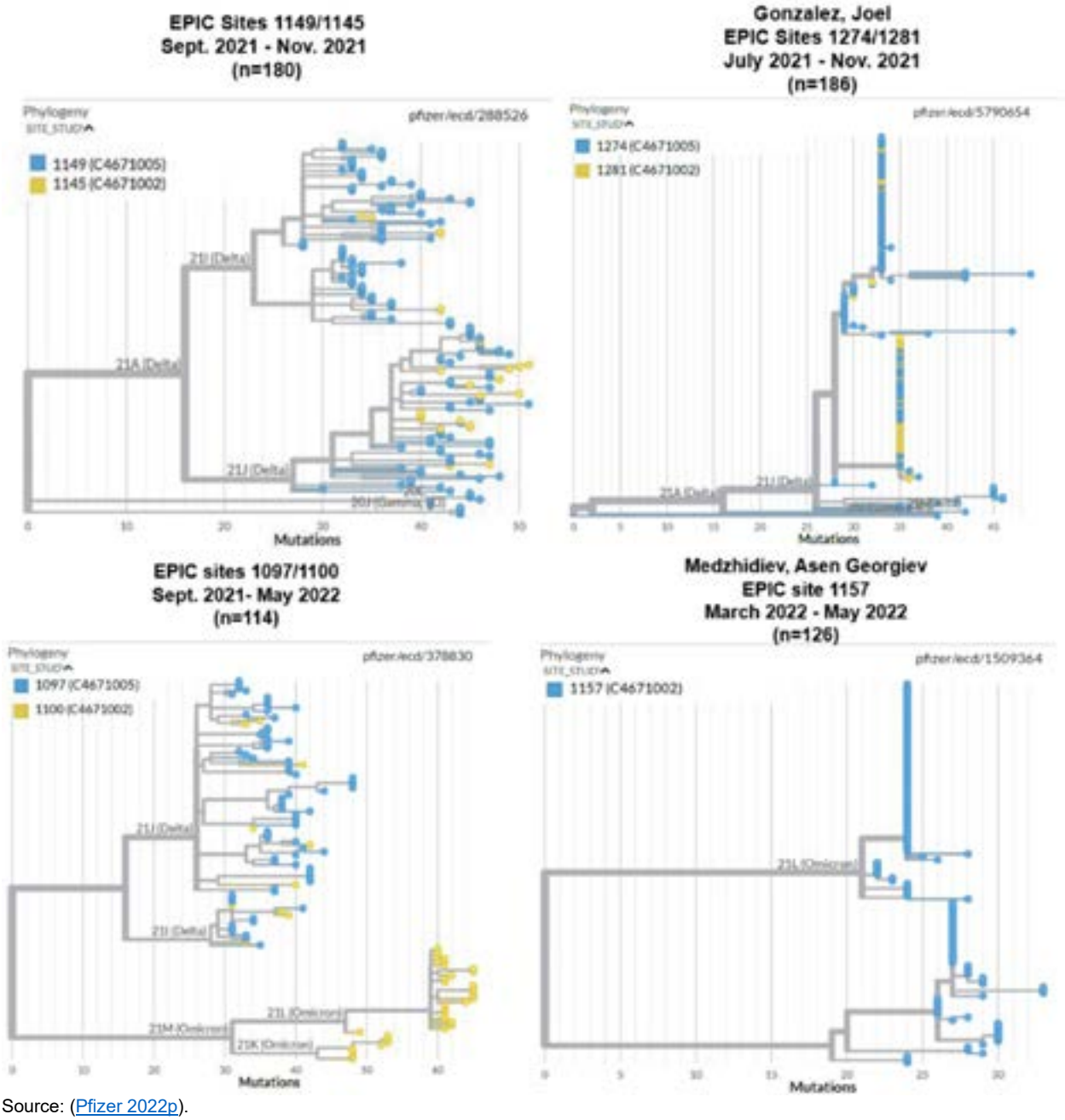
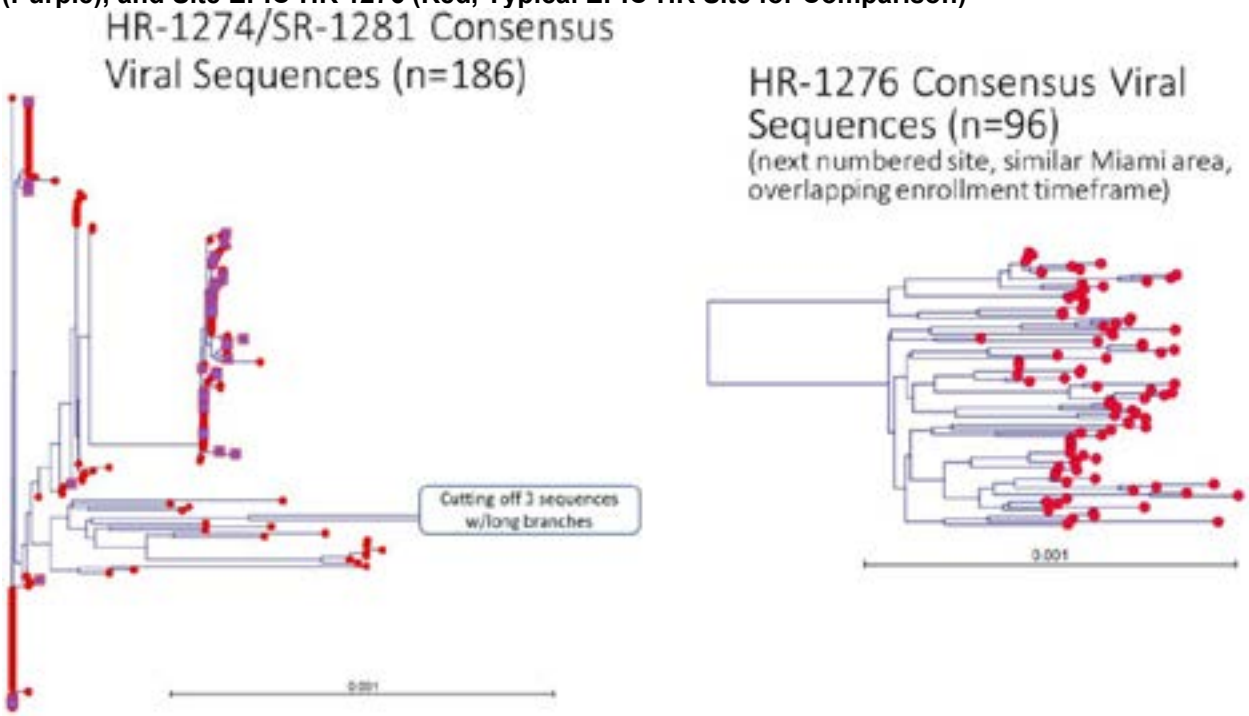
Figure 94. Nextstrain Phylogenetic Analysis of Viral Sequences From the EPIC-HR 1274/EPIC-SR 1281 site, EPIC-SR Site 1157, and Comparator Sites



Source: (Pfizer 2022p).
Abbreviations: n, number of subjects in sample

Independent FDA analyses confirmed the extensive clustering of viral sequences from different subjects from the EPIC-HR 1274/EPIC-SR 1281 site (Figure 95).

Figure 95. Phylogenetic Analysis of Viral Sequences From Site EPIC-HR 1274 (Red)/EPIC-SR 1281 (Purple), and Site EPIC-HR 1276 (Red, Typical EPIC-HR Site for Comparison)



Source: FDA analysis of viral fasta consensus sequences and ADSL dataset.
Abbreviations: n, number of subjects in sample; w/, with

Independent FDA analyses also confirmed extensive clustering of viral sequences from EPIC-SR site 1157 in Bulgaria (Figure 96). Clustering of viral sequences from site 1197 (also in Bulgaria) was not as clear as in site 1157, but for subjects who enrolled in the 2022 period (among whom anomalous viral RNA patterns were observed) there is some evidence of clustering of viral sequences with short or no branch lengths. Furthermore, combined phylogenetic analyses of viral sequences from EPIC-SR sites 1157 and 1197 revealed a cluster of closely matched sequences from both sites, including 2 site 1197 samples ((b) (6) Days 1/5) that were 100% identical with a large cluster of identical sequences from site 1157, and a third sample from 1197 ((b) (6) Day 1) being 100% identical to sequences from two other subjects from site 1157 (Day 3, (b) (6) Day 5). The fact that both sites are located in the same country could account for some genetic clustering of viral sequences, although this extent of genetic clustering between sites was not as apparent in phylogenetic analyses combining sequences from site 1197 with those from the other 21 EPIC-SR sites in Bulgaria (data not shown).

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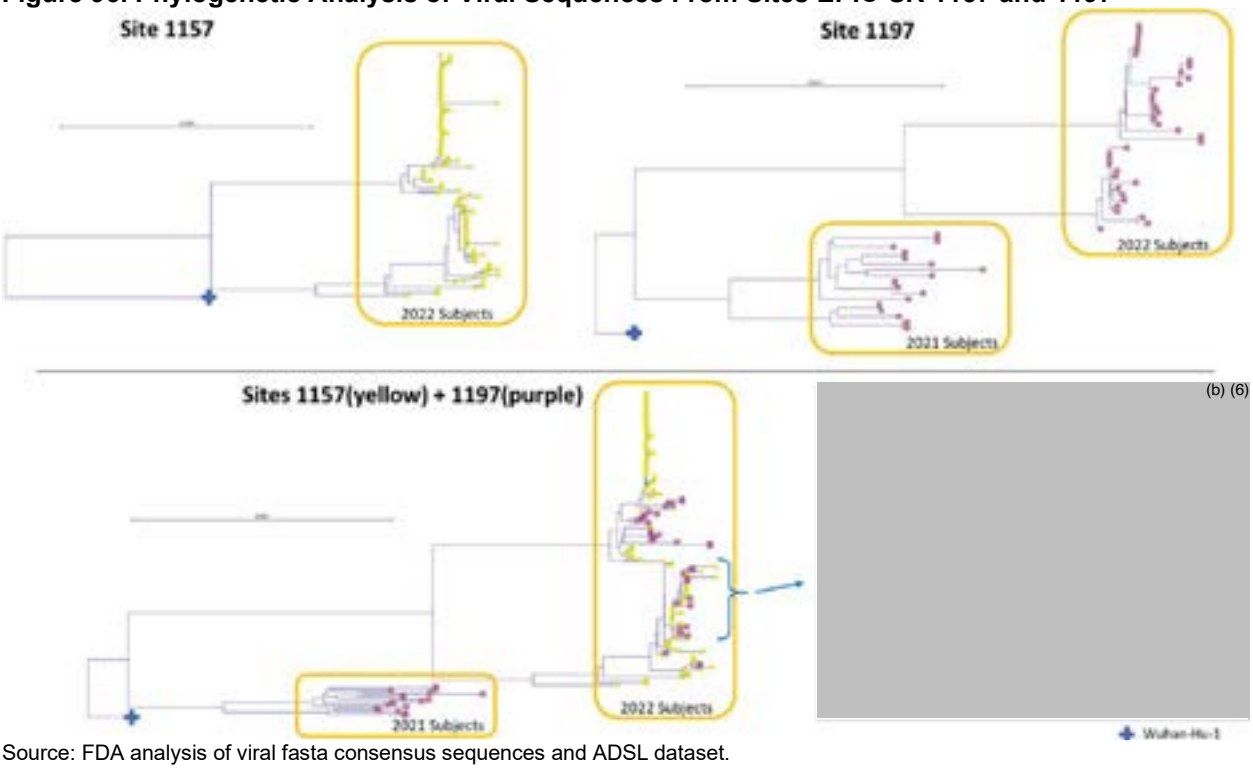
Figure 96. Phylogenetic Analysis of Viral Sequences From Sites EPIC-SR 1157 and 1197



Source: FDA analysis of viral fasta consensus sequences and ADSL dataset.

18.5.2. Expanded Investigations of All Study Sites for Viral RNA or Sequencing Anomalies

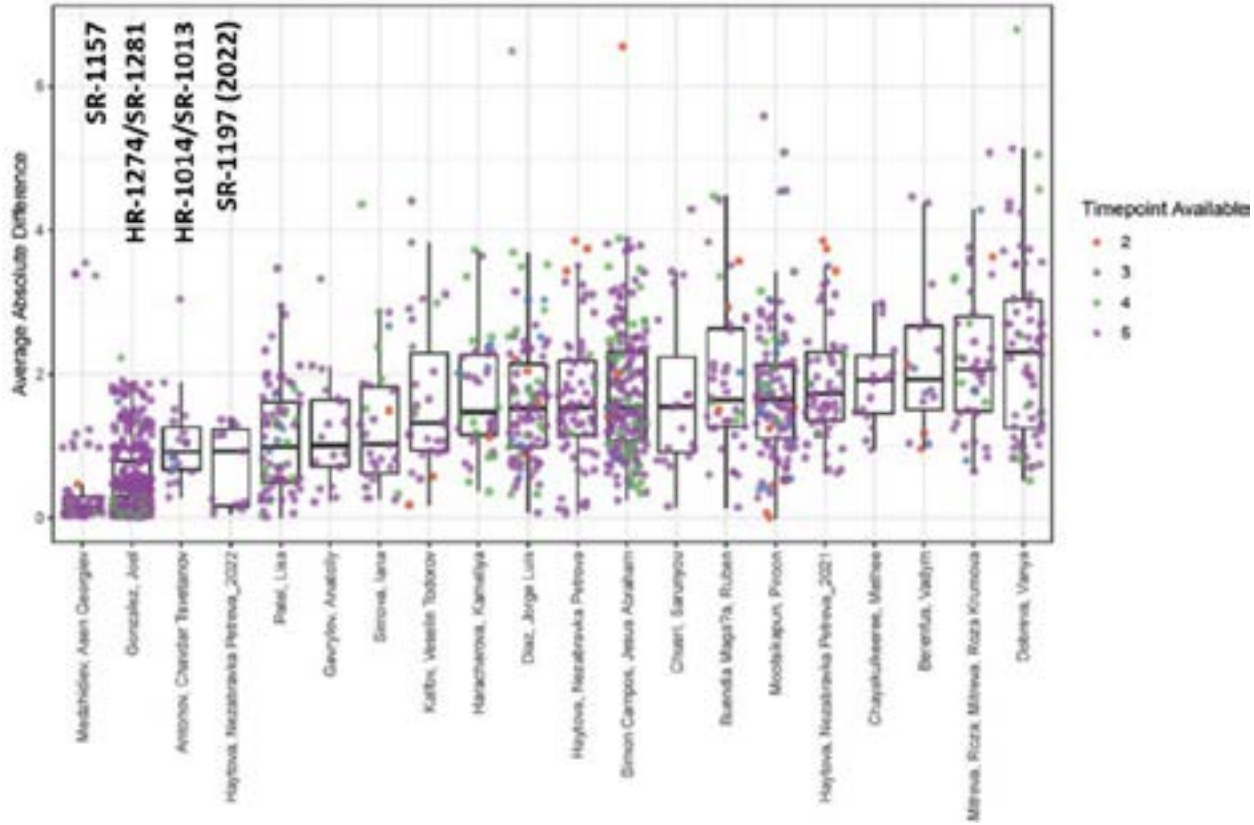
Numerous additional analyses were conducted by the Applicant and FDA to assess for viral RNA or sequencing anomalies across all study sites in EPIC-HR and EPIC-SR, and ultimately to ensure reliability of these data after censoring data from the concerning sites discussed above. Note that across different sites there was a wide range in the numbers of subjects with unquantifiable or undetected viral RNA at baseline or throughout the study period, which was at least partially associated with baseline serostatus (discussed below), and viral sequence data would only be available for samples with sufficient viral RNA. Therefore, these analyses for viral RNA or sequencing anomalies were necessarily biased towards sites with sufficient numbers of subjects with quantifiable viral RNA and available viral sequencing data.

In somewhat subjective analyses, viral RNA patterns within individual study sites with viral RNA data from ≥10 subjects were assessed visually by FDA for evidence of overlapping trends between subjects, both overall and also grouped by treatment start date, as described above. While some degree of overlapping viral RNA patterns between small numbers of subjects was observed and was expected by chance alone, no additional sites beyond those noted above had such clear patterns of overlapping viral RNA levels over time between different subjects, particularly between those with the same or similar treatment start dates.

In a more quantitative assessment, the Applicant conducted an analysis of "longitudinal viral RNA level profile similarity" between pairs of participants with the same treatment start date. These analyses considered sites across both EPIC-HR and EPIC-SR with ≥15 subjects, but the analyses excluded sites from India due to low average baseline viral RNA levels, as well as

participants with viral RNA levels <LLOQ across all study visits. As shown in Figure 97, and consistent with the viral RNA patterns noted above, EPIC-SR 1157 and EPIC-HR 1274/EPIC-SR 1281 were clear outliers based on the relatively low differences in log_{10} viral RNA levels between participants with the same treatment start date. The median difference shown for EPIC-SR 1197 (2022) was similar to multiple other sites, although there was a group of data points showing minimal differences in viral RNA levels between a subset of participants with the same treatment start date. Site EPIC-HR 1014/EPIC-SR 1013 had a relatively low median difference in this analysis, but the median was similar to multiple other sites, and no data points clustered near 0, indicating no two subjects with the same treatment start date had highly overlapping viral RNA patterns. Visual analysis of viral RNA results from this EPIC-HR 1014/EPIC SR-1013 indicated some similar viral RNA patterns between different subjects, but not to the same extent as the other sites, and not tightly associated with treatment start date. Overall, this analysis confirms the observations of overlapping viral RNA patterns noted above for sites EPIC-HR 1274/EPIC-SR 1281, EPIC-SR 1157 and EPIC-SR 1197 (2022 enrollment period), and no other sites with similar patterns were identified.

Figure 97. Applicant's Analysis of Average Absolute Difference in Log10 Viral RNA Level Across Timepoints Between Participants With the Same Treatment Start Day, Grouped by EPIC-HR and EPIC-SR Investigators

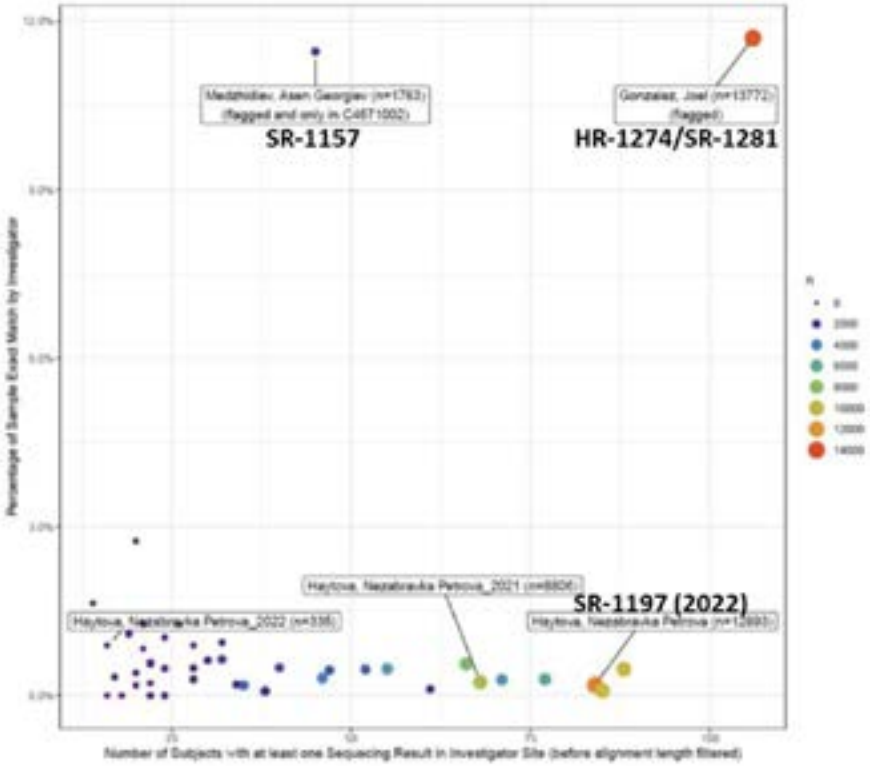


Source: (Pfizer 2022p) (modified to include site numbers).
Abbreviations: log, logarithm; RNA, ribonucleic acid

The Applicant conducted nucleotide basic local alignment search tool (BLASTN) analyses of full-length viral genome consensus nucleotide sequences to measure viral genome similarity between all pairs of samples from different participants within each investigator site (NCBI

2023). This analysis calculated the numbers of nucleotide mismatches between sequences across the full viral genome. Results from each site were summarized by the percentage of sample comparisons between different participants that yielded an exact match (mismatch count = 0). The rationale for this analysis was that different visit samples from the same participant might match exactly; however, samples from different participants should rarely match exactly at the nucleotide level, and thus a high number of matching sequences between different subjects would indicate contaminating sequences or otherwise implausible concordance of viral sequences due to mishandling of virology samples or another potential technical problem. The analysis was conducted for investigator sites (excluding sites from India, as described previously) with numbers of sample comparisons ≥300. As shown in Figure 98, EPIC-SR 1157 (Medzhidiev) and EPIC-HR 1274/EPIC-SR 1281 (Gonzalez/Martinez) were again clear outliers based on having relatively high numbers of samples between participants within these sites with exactly matching viral nucleotide sequences. No other sites, including EPIC-SR 1197 (2022, Haytova), were identified in this analysis for having an unusually high percentage of samples with exactly matching viral nucleotide sequences.

Figure 98. BLASTN Analysis of Consensus Full-Length Viral Nucleotide Sequences for Exact Matches of Sequences Between Different Subjects at the Same Site

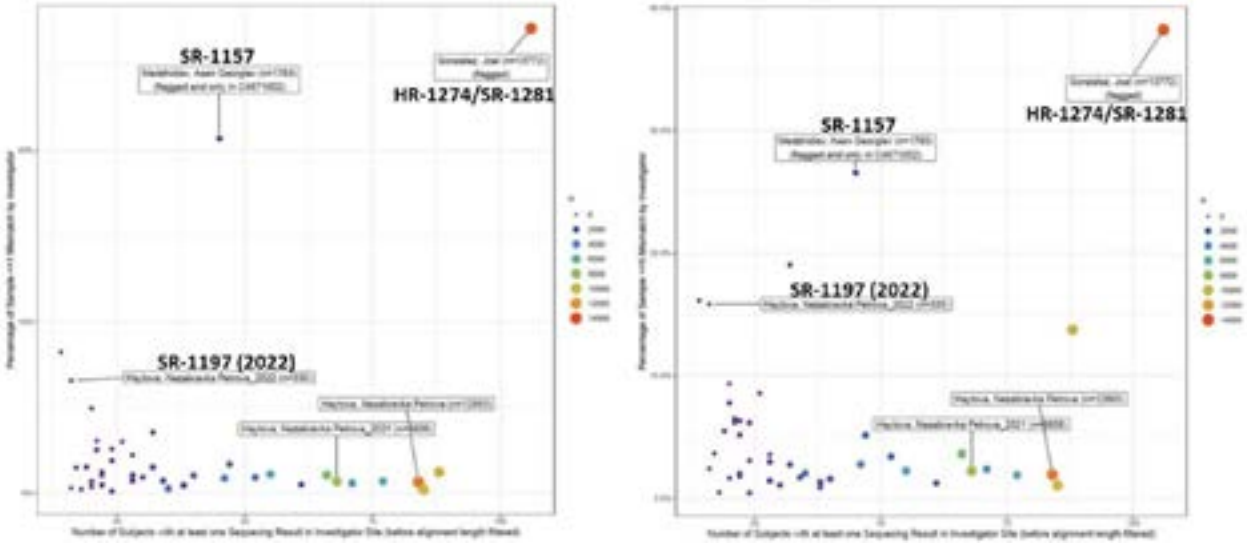


Source: (Pfizer 2022p) (modified to include site numbers).
Note: Shown are the percentages of samples with exact sequence matches between pairs of samples from different participants for sites with ≥300 sequence pairs.
Abbreviations: BLASTN, nucleotide basic local alignment search tool; n, number of paired sequence comparisons

Given the length of the viral genome (~30 kb) and the expectation that any SARS-CoV-2 clinical specimen would have a mixture of co-existing viral sequences, if the same exact specimen were processed and sequenced in two independent analyses it would not be surprising to observe a small number of nucleotide differences between the consensus viral nucleotide sequences

generated from the two replicates. Therefore, the requirement for exactly matching viral nucleotide sequences in the BLASTN analysis above could be too stringent to identify pairs of highly similar viral sequences from different subjects that might indicate technical mishandling of samples. To address this limitation, we requested that the Applicant repeat the BLASTN analysis identifying similar sequences based on different stringencies of sequence mismatches (≤1, ≤5 or ≤10 mismatches). As shown in Figure 99, when the analysis was repeated to identify sequences with ≤1 or ≤5 mismatches, the EPIC-SR 1157 (Medzhidiev) and EPIC-HR 1274/EPIC-SR 1281 (Gonzalez/Martinez) sites remained the outliers, while the data from SR-1197 (2022, Haytova) showed an increasing signal in the percentages of samples with highly similar viral sequences, consistent with the short branch lengths observed in the phylogenetic analyses from this site (summarized above). Nevertheless, the signal from SR-1197 (2022, Haytova) was not as obvious as those from EPIC-SR 1157 (Medzhidiev) and EPIC-HR 1274/EPIC-SR 1281 (Gonzalez/Martinez). The BLASTN analyses allowing for ≤10 mismatches were found to be insufficiently stringent as much larger percentages of samples across several sites were identified as having similar sequences, likely reflecting natural sequence similarities within local geographic regions.

Figure 99. BLASTN Analysis of Consensus Full-Length Viral Nucleotide Sequences to Identify Highly Similar Sequences Between Different Subjects at the Same Site

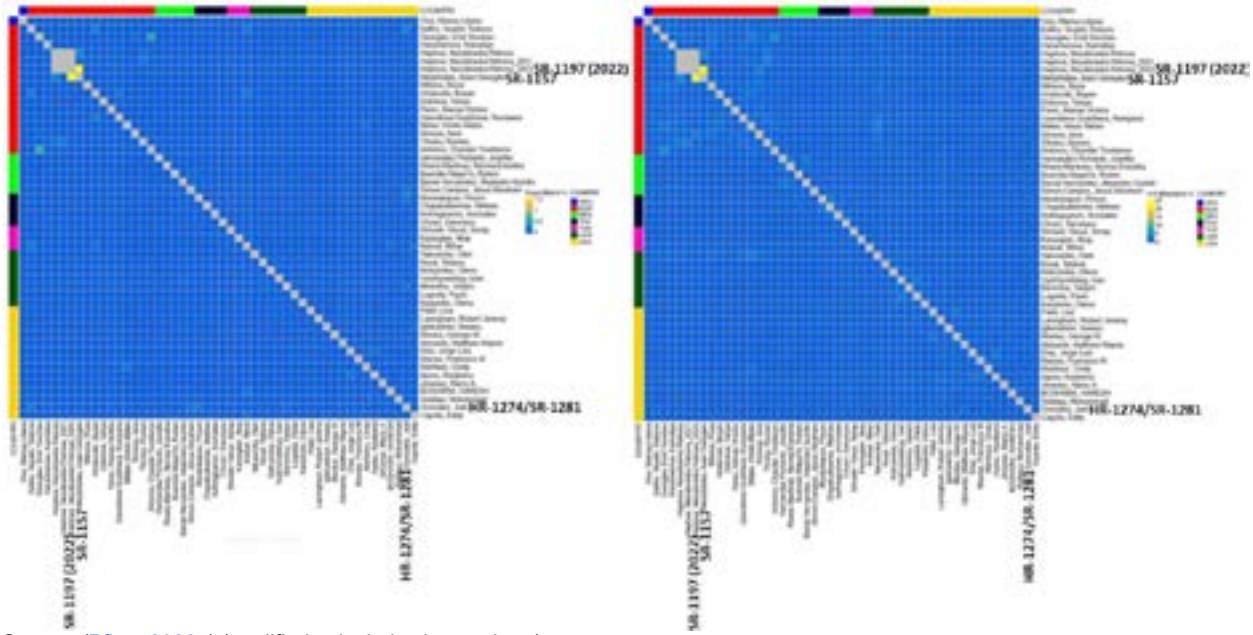


Source: (Pfizer 2022p) (modified to include site numbers).
Note: Shown are the percentages of samples with ≤1 (left) or ≤5 (right) mismatches between pairs of samples from different participants for sites with ≥300 sequence pairs.
Abbreviations: BLASTN, nucleotide basic local alignment search tool; n, number of nucleotide matches

The Applicant also conducted additional BLASTN analyses to identify instances of identical or nearly identical viral consensus nucleotide sequences between subjects from different investigator sites. These analyses were restricted to sites with at least 15 subjects with available sequencing results, and again different levels of allowed mismatches between sequences (0 [i.e., exact], ≤1, ≤5 and ≤10) were considered. Figure 100 shows heatmaps of results from the analyses of identical (0 mismatches) and nearly identical (≤5 mismatches) sequences between study sites, illustrating that EPIC-SR Sites 1157 (Medzhidiev) and 1197 (Haytova, 2022) were the only sites that showed a signal of similar sequences between subjects from different study sites. No other sites even within Bulgaria or any other country showed a similar degree of nearly

identical viral sequences between subjects from different sites. These results are consistent with the phylogenetic analyses summarized above that show clustering of viral nucleotide sequences between EPIC-SR Sites 1157 (Medzhidiev) and 1197 (Haytova, 2022).

Figure 100. BLASTN Analysis of Consensus Full-Length Viral Nucleotide Sequences to Identify Highly Similar Sequences Between Different Subjects at Different Study Sites



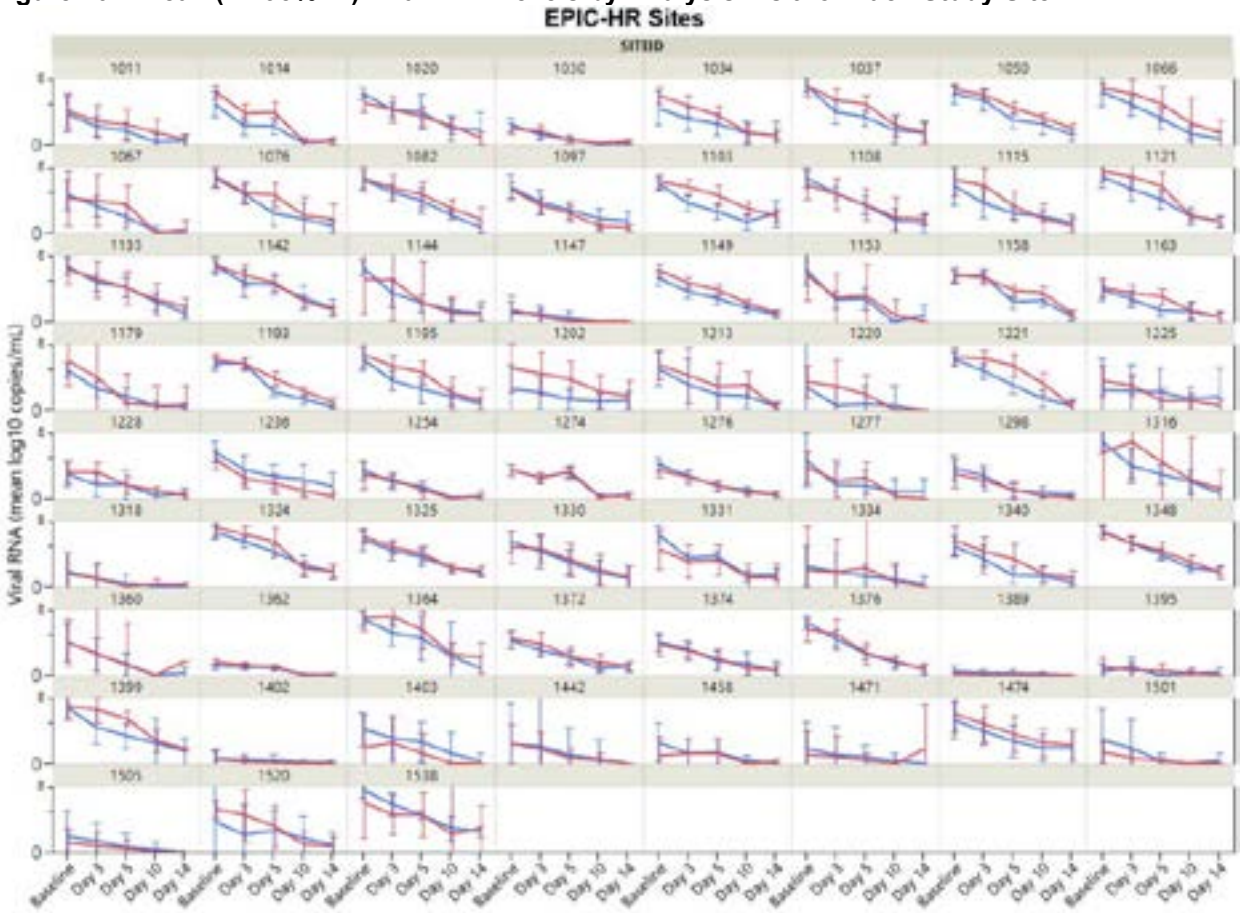
Source: (Pfizer 2022q) (modified to include site numbers).
Note: Shown are heatmaps illustrating the percentages of samples with exact sequences (left) or ≤5 mismatches (right) between samples from two different sites, restricted to investigators with ≥15 subjects.
Abbreviations: ARG, Argentina; BRG, Bulgaria; BLASTN, nucleotide basic local alignment search tool; MEX, Mexico; n, number of nucleotide matches; THA, Thailand; TUR, Turkey; UKR, Ukraine; USA, United States of America

Extensive additional phylogenetic analyses were conducted by both FDA and the Applicant (data not shown), and these analyses did not identify any unusual patterns of viral genetic clustering between sequences from different subjects either within or between study sites, beyond the observations summarized above.

18.5.3. Study Sites with High Frequencies of Undetected Viral RNA

As noted above, while conducting these analyses we found that across different study sites there was a wide range in the numbers of subjects with low or undetected viral RNA at baseline or throughout the study period. Figure 101 and Figure 102 show the mean viral RNA levels at each study visit for each study site with viral RNA data from ≥10 subjects.

Figure 101. Mean (+/- 95% CI) Viral RNA Levels by Analysis Visit for Each Study Site in EPIC-HR



Source: FDA analysis of ADMC and ADSL datasets.
Note: Blue: PAXLOVID-treated subjects. Red: Placebo-treated subjects.
Note: Viral RNA results of detected/<LLOQ were assigned a value of 1.7 $\log_{10}$ copies/mL, and results of undetected RNA were assigned a value of 0 copies/mL.
Note: Analysis includes sites with viral RNA data from ≥10 subjects.
Abbreviations: CI, confidence interval; LLOQ, lower limit of quantitation; log, logarithm; RNA, ribonucleic acid; SITEID, site identifier

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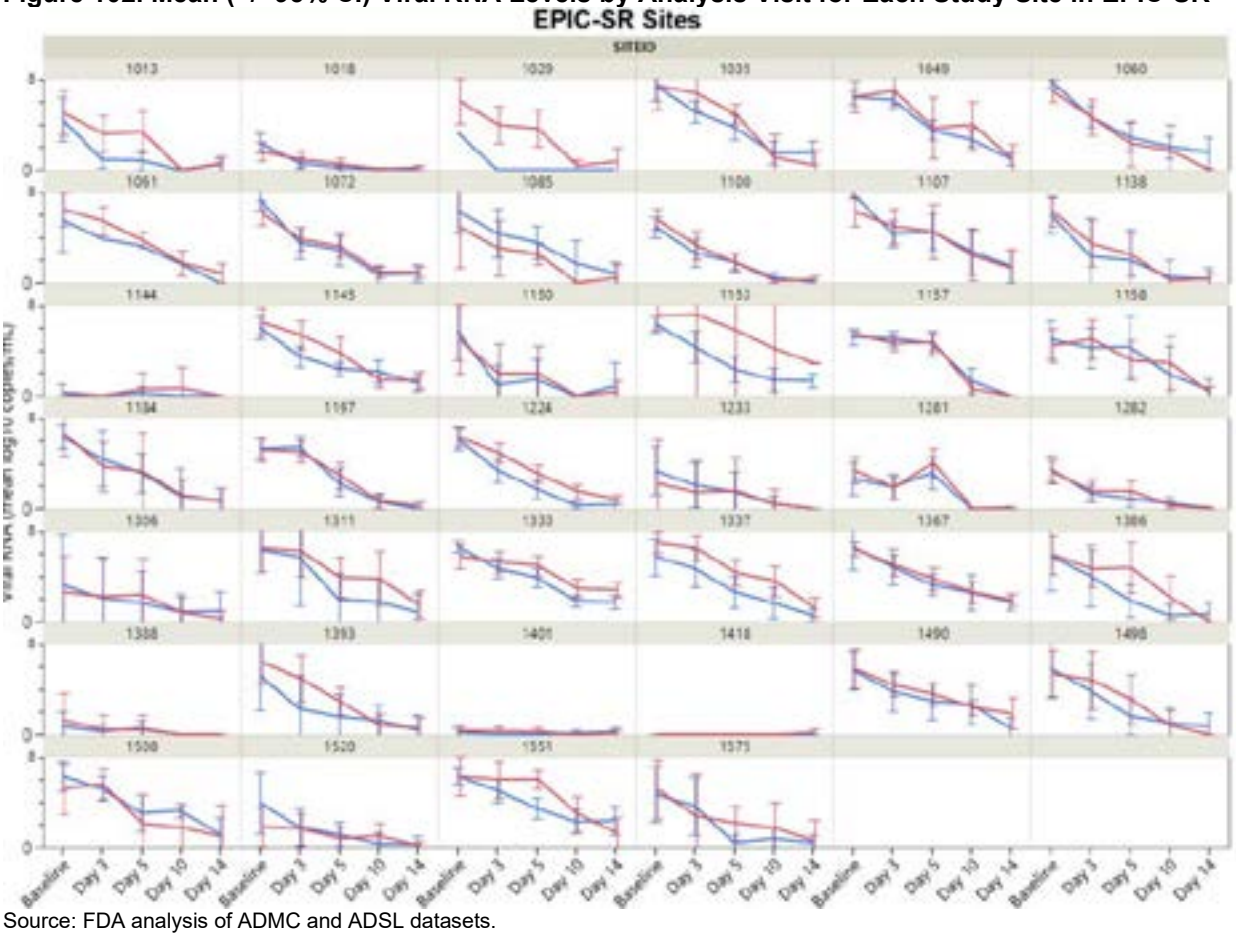
Figure 102. Mean (+/- 95% CI) Viral RNA Levels by Analysis Visit for Each Study Site in EPIC-SR



Source: FDA analysis of ADMC and ADSL datasets.
Note: Blue: PAXLOVID-treated subjects. Red: Placebo-treated subjects.
Note: Viral RNA results of detected/<LLOQ were assigned a value of 1.7 $\log_{10}$ copies/mL, and results of undetected RNA were assigned a value of 0 copies/mL.
Note: Analysis includes sites with viral RNA data from ≥10 subjects.
Abbreviations: CI, confidence interval; LLOQ, lower limit of quantitation; log, logarithm; RNA, ribonucleic acid; SITEID, site identifier

While an unusually high rate of undetected viral RNA results at a given site could indicate false or improper sampling from study volunteers, it might also be explained at least partly by the immunologic characteristics of the population, or even characteristics of the virus circulating at the time. Of note, the protocols allowed for up to 5 days from a positive RT-PCR test prior to randomization, so it is feasible for some study volunteers to test positive for SARS-CoV-2 infection but have undetected viral RNA by the time of randomization.

As expected, sites with larger percentages of subjects with undetected viral RNA at baseline also tended to have higher percentages of subjects with positive baseline serostatus (Figure 103). Nevertheless, even among sites with the highest seropositivity rates there was a wide range of percentages of subjects with undetected viral RNA at baseline. Two sites from EPIC-HR (1389 and 1402) and 3 sites from EPIC-SR (1144, 1401, 1418) are noted for having ≥90% of subjects with undetected viral RNA at baseline, and not surprisingly, for nearly all subjects with undetected viral RNA at baseline, viral RNA levels remained undetected at all subsequent study points.

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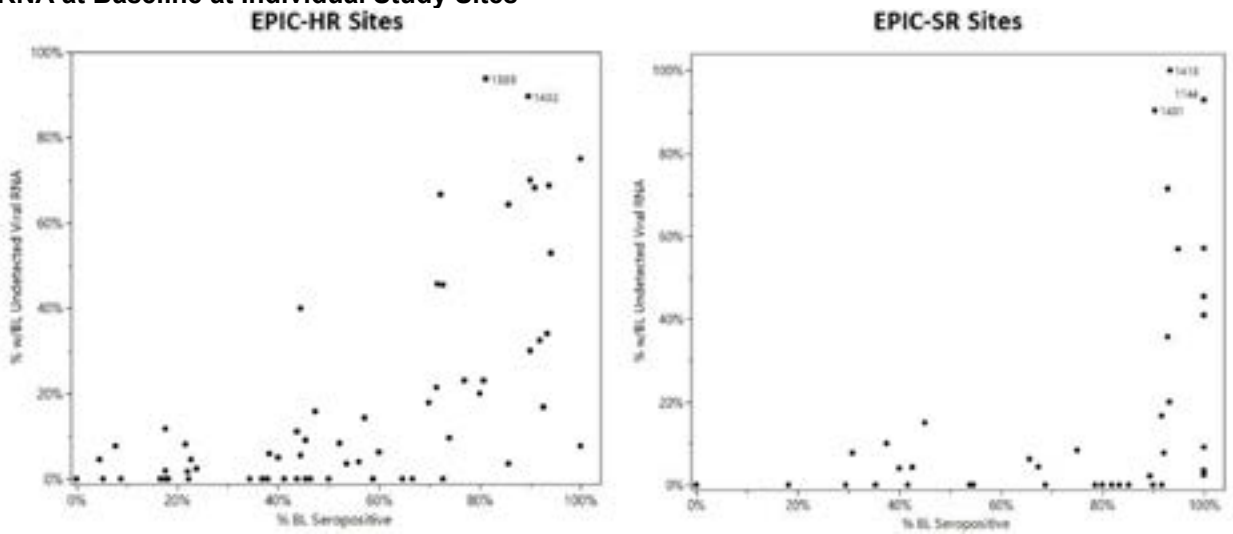
Figure 103. Association Between Frequencies of SARS-CoV-2 Seropositivity and Undetected Viral RNA at Baseline at Individual Study Sites



Source: FDA analysis of ADMC and ADSL datasets.
Analysis includes sites with viral RNA data from ≥10 subjects.
Abbreviations: BL, baseline; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; w/, with

The noted sites with ≥90% of subjects with undetected viral RNA at baseline are all from the same Miami, FL, USA geographic area. EPIC-HR site 1389 is the same as EPIC-SR site 1401 (PI: Hernandez, Miami Lakes, FL, USA), and EPIC-HR site 1402 is the same as EPIC-SR site 1418 (PI: De La Vega, Hialeah Gardens, FL, USA). The third noted site (EPIC-SR site 1144) corresponds to EPIC-HR site 1147 (PI: Benitez, Hialeah, FL, USA), which had 68% of subjects in EPIC-HR with undetected viral RNA at baseline (91% seropositive). Interestingly, nearly all of the other sites with relatively low viral RNA levels across visits were also from the Miami, FL USA geographic area, including EPIC-HR sites 1318 (Miami, FL; same as 1388 in EPIC-SR), 1395 (Miami, FL), 1458 (Cutler Bay, FL), 1471 (Miami, FL), and 1505 (Miami, FL; same as 1520 in EPIC-SR). Notable exceptions in this same region are EPIC-HR 1274 and EPIC-SR 1281 (censored PI: Gonzalez/Martinez, Cutler Bay, FL) which had lower rates of baseline undetected viral RNA of 17% and 41%, respectively, despite high reported seropositivity rates of 93% and 100%, respectively. Another site that had low mean viral RNA levels across all visits was EPIC-HR 1362 (Bangalore, India), which is consistent with the Applicant's observations regarding some sites in India. Note that all EPIC-SR data from U.S. sites were from the 2021/Pre-Omicron period, which overlapped with the EPIC-HR enrollment period.

Given the close geographic clustering of sites with high frequencies of subjects with low or undetected viral RNA, it is reasonable to hypothesize a number of factors that could have caused or contributed to these observations, such as the immunologic status of the population, false positive screening test results, a virus lineage that tended to shed into the NP space at lower levels or for a shorter duration, the presence of genetic polymorphisms in the virus lineage that impacted the sensitivity of the qRT-PCR assay, or improper collection, handling or storage of samples. In response to an inquiry about these findings, the Applicant reported that sites with high frequencies of subjects with low or undetected viral RNA not only had high rates of SARS-CoV-2 seropositivity at baseline, but they also had higher quantitative levels of S-specific binding antibody. Therefore, the Applicant concluded that these observations reflect an expected inverse relationship between viral RNA level and the presence/level of anti-SARS-CoV-2

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antibodies. No subjects at the sites with the highest frequencies of subjects with undetected viral RNA at baseline (EPIC-HR 1389, 1402; EPIC-SR 1144, 1401, 1418) reached the hospitalization/death endpoint. Furthermore, the inclusion of a subset of study subjects, irrespective of treatment arm, with undetected viral RNA at all study visits would not have a substantial impact on analyses of viral shedding or rebound. Therefore, no censoring or further investigations of these sites were considered.

18.5.4. Conclusions on Virology Data Anomalies and Approach to Censoring Data

The extensive analyses of viral RNA shedding patterns and viral nucleotide sequences summarized above indicate that virology data from sites EPIC-HR 1274/EPIC-SR 1281 (Gonzalez/Martinez) and EPIC-SR site 1157 (Medzhidiev) are highly unusual and implausible, raising concerns about data quality or integrity from these sites. Given these concerning data patterns, the review team determined that these sites should be censored from all key efficacy, safety, and virology analyses.

The viral RNA and sequencing anomalies from EPIC-SR site 1197 (2022 enrollment period) were not as pronounced as those observed at the other noted sites. Nevertheless, the totality of data from this site indicate it is somewhat of an outlier in terms of similarities in viral RNA shedding patterns and viral RNA sequences between subjects within the site, as well as instances of identical or nearly identical viral sequences between this site and EPIC-SR site 1157. As a conservative approach, we recommended that data from EPIC-SR site 1197 (2022 enrollment period) similarly be censored from all key analyses, or at minimum for all virology-focused analyses.

Specific cause(s) of these virology data anomalies remain unknown. The fact that the anomalies appear to be restricted to three specific sites indicates a site-specific problem, such as mishandling of samples at the study sites prior to shipment to the central laboratory. However, it also seems somewhat improbable that similar problems occurred at three different study sites across two different countries over a ~one-year period, with two of the sites (both in Bulgaria) having subjects with identical or nearly identical viral nucleotide sequences.

The Applicant has concluded that central laboratory non-compliance, aliquoting, or run batch errors could not account for the viral RNA shedding patterns or viral sequencing concordance observed (discussed in (Pfizer 2022q)). The Applicant provided analyses of viral RNA results from EPIC-SR site 1157 (Medzhidiev), which were conducted across 17 different assay runs indicating that the viral RNA anomalies observed did not occur over a single assay run, and any sample mishandling that contributed to the patterns observed likely occurred upstream of the assay runs. Similarly, in the case of EPIC-HR site 1274/EPIC-SR site 1281 (Gonzalez/Martinez), samples were collected over a 5-month period (July-November 2021), and the Applicant concluded that the viral RNA shedding and sequencing data abnormalities could not be explained by concordance with batch run date of either qRT-PCR or viral sequencing since abnormalities were observed across multiple runs. Furthermore, the quality control data from viral sequencing runs did not indicate contamination or failed run issues. However, the Applicant did not provide data that excludes potential sample mishandling or mis-labeling at some early step in sample aliquoting or preparation (e.g., RNA extraction) that was batched by study site,

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and occurred downstream of sample collection at the site but prior to any qRT-PCR or sequencing assay runs.

Sample mishandling directly at the study site could explain the results from site EPIC-HR 1274/EPIC-SR 1281 (Gonzalez/Martinez). This site had evidence of highly implausible symptom reporting data, (b) (7)(A) The intentional spiking or splitting of virology samples directly at the study site would be consistent with other findings at the site and could explain the virology data anomalies observed.

Importantly, regardless of the specific cause(s), there is no indication that any of the anomalies or potential mishandling of samples was in any manner related to specific treatment assignment. All conclusions on viral RNA shedding, rebound, and resistance remain unchanged regardless of how the data are censored from these study sites.

During the review another site that participated in both EPIC-HR and EPIC-SR, EPIC-HR 1470/EPIC-SR 1488 (PI: Hernandez), was closed during the conduct of the trials due to concerns about trial oversight, and existing subjects at the site were transferred to a nearby site (EPIC-HR 1276/EPIC-SR 1282; PI: Diaz). Issues at the original site were unrelated to any clinical virology data anomalies. The review team decided to censor all data from subjects who started at the EPIC-HR 1470/EPIC-SR 1488 site from all key analyses. See integrated review Section 6.3 for details.

In conclusion, the following sites/subjects were censored from all key clinical virology analyses of the EPIC-HR and EPIC-SR trials:

- EPIC-HR: Sites 1274 (Gonzalez/Martinez, n = 95 treated) and 1470 (including subjects [IDs that start with 1470] who transferred to 1276, n = 38 treated).
- EPIC-SR Pre-Omicron, data through December 19, 2021 cut-off: Sites 1281 (Gonzalez/Martinez, n = 46 treated), and 1488 (including subjects [IDs which start with 1488] who transferred to site 1282, n = 31 treated).
- EPIC-SR Post-Omicron, 2022 data: Sites 1157 (Medzhidiev, n = 47 treated) and 1197 (Haytova, 2022 enrollees only, n = 18 treated).
- Total number of subjects censored: 275 treated (133 in EPIC-HR, 142 in EPIC-SR; 137 PAXLOVID-treated, 138 placebo-treated).

19. Clinical Microbiology

Not applicable.

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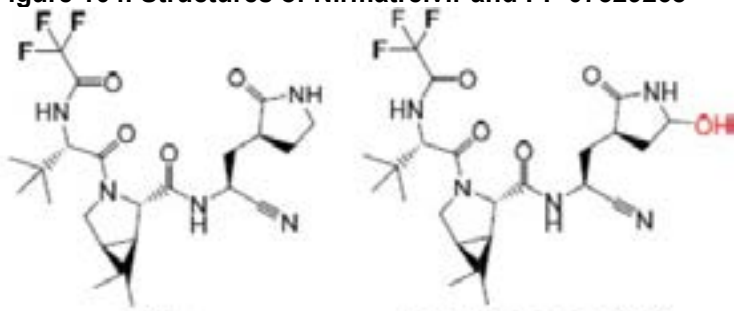
20. Mechanism of Action/Drug Resistance

20.1. Mechanism of Action

Inhibition of Recombinant SARS-CoV-2 M^{pro} in a Biochemical Assay (Pfizer 2022j)

The Applicant determined the ability of NIR and PF-07329268 (also referred to as M4) to inhibit recombinant SARS-CoV-2 (Wuhan-Hu-1) M^{pro} in a fluorescence resonance energy transfer (FRET)-based biochemical assay. PF-07329268 (Figure 104) is the primary oxidative metabolite of NIR in human and monkey liver microsomes, human and monkey hepatocytes, and monkey plasma. These experiments used 15 nM (~500 ng/mL) recombinant SARS-CoV-2 M^{pro}, 0.3 to 30,000 nM or 1 to 1,000 nM inhibitor, and 25,000 nM of a peptide substrate corresponding to the nsp4/nsp5 cleavage site (Dabcyl-KTSAVLQ↓SGFRKME-Edans). NIR inhibited the activity of recombinant SARS-CoV-2 M^{pro} with a geometric mean IC_{50} value of 19.2 nM and a geometric mean K_i value of 3.1 nM (Table 210). The metabolite PF-07329268 inhibited SARS-CoV-2 M^{pro} with a geometric mean IC_{50} value of 17.5 nM and a geometric mean K_i value of 3.2 nM.

Figure 104. Structures of Nirmatrelvir and PF-07329268



Source: Adapted from (Pfizer 2020a), p. 18.
Abbreviations: M4, metabolite 4 (PF-07329268); NIR, nirmatrelvir

Table 210. NIR and PF-07329268 Activity Against Recombinant SARS-CoV-2 M^{pro} in a Biochemical Assay

Compound	n	Geomean IC_{50} (nM)	CI (nM)	Geomean K_i (nM)	CI (nM)
NIR	6	19.2	13.5–25.0	3.1	1.3–4.9
PF-07329268	2	17.5	15.3–20.0[a]	3.2	2.4–4.2[a]

Source: (Pfizer 2022j), p. 9.
[a] The range is reported instead of CI since n=2.
Abbreviations: CI, 95% confidence interval; Geomean, geometric mean; IC_{50}, half-maximal inhibitory concentration; K_i, inhibition constant; M^{pro}, main protease; n, number of experiments; NIR, nirmatrelvir; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Inhibition of Recombinant SARS-CoV-2 M^{pro} Enzymes With Substitutions in a Biochemical Assay (Pfizer 2022h)

Using the FRET-based biochemical assay, the Applicant determined the ability of NIR to inhibit recombinant SARS-CoV-2 M^{pro} containing 94 single substitutions and 21 combinations of

substitutions. These substitutions were tested because they: 1) represent naturally occurring or laboratory engineered substitutions at residues in direct contact or close proximity (<5 Å) with NIR, as determined by the Applicant's co-crystal structural analysis, 2) were identified as naturally occurring polymorphisms in M^{pro}, or 3) were associated with MHV or SARS-CoV-2 resistance to NIR in cell culture. These experiments were performed with 30 to 2,000 nM M^{pro} (depending on the catalytic efficiency of the enzyme), a maximum NIR concentration of 1,000 to 100,000 nM, and 30,000 nM of peptide substrate. In this set of experiments, NIR inhibited wild-type (WT, Wuhan-Hu-1) SARS-CoV-2 M^{pro} with a geometric mean K_i value of 0.9 nM (Table 211).

Results could not be obtained for M^{pro} H41Y, C145F/I, and H163A substitutions because the enzymes were catalytically inactive. These 3 residues directly contact NIR. Of the other single substitutions tested, 19/90 resulted in ≥3-fold higher geometric mean K_i values compared to WT: Y54A, F140A/L/S, G143S, S144A/E/T, H164N, E166A/G/V, H172Y, A173S/V, R188G, Q192L/P, and V297A (Table 211). Most of these residues directly contact or are located in close proximity (<5 Å) of NIR, except for A173S/V and V297A. The M^{pro} P132H substitution, which is a prevalent polymorphism in SARS-CoV-2 Omicron variants, did not affect NIR activity (K_i value fold-change: 0.7). In addition, 14/21 of the substitution combinations resulted in ≥3-fold higher geometric mean K_i values compared to WT. In most of these combinations, the primary M^{pro} substitution(s) responsible for the reduced activity of NIR appeared to be F140L, S144A, E166A/V, H172Y, and A173V.

Table 211. NIR Activity Against SARS-CoV-2 M^{pro} Enzymes With Substitutions in a Biochemical Assay

M^{pro} Enzyme	Contact?[a]	Enzyme (nM)	Max NIR (nM)	K_i Geomean (nM)	K_i Lower 95% CI (nM)	K_i Upper 95% CI (nM)	n	p-Value (vs. WT)[b]	K_i Fold Change (vs. WT)
WT	N/A	30	1,000	0.9	0.5	1.7	9	N/A	N/A
A7S	No	60	10,000	<0.8	<0.1	9.0	5	0.49	<0.9
A7T	No	70	10,000	<0.7	<0.1	8.8	5	0.46	<0.8
A7V	No	70	10,000	<0.8	<0.1	9.4	5	0.49	<0.9
G15S	No	55	1,000	1.4	0.5	4.3	4	0.11	1.6
T21I	No	40	1,000	1.4	0.2	9.6	3	0.17	1.6
T21I+L50F+ A193P+S301P	**No/No/No /No**	**150**	**10,000**	**6.5**	**2.1**	**19.8**	**3**	**0.0004**	**7.3**
T21I+S144A	**No/Yes**	**125**	**10,000**	**17.5**	**8.6**	**35.5**	**3**	**<0.0001**	**20**
T21I+S144A+T304I	**No/Yes/No**	**250**	**10,000**	**45.8**	**20.6**	**102**	**6**	**<0.0001**	**51**
T21I+E166V	**No/Yes**	**600**	**100,000**	**9,710**	**8,650**	**10,900**	**3**	**<0.0001**	**11,000**
T21I+A173V	**No/No**	**125**	**10,000**	**13.1**	**10.4**	**16.5**	**3**	**<0.0001**	**15**
T21I+A173V+T304I	**No/No/No**	**200**	**100,000**	**49.1**	**22.7**	**107**	**3**	**<0.0001**	**55**
T21I+A260V+T304I	No/No/No	200	10,000	<2.6	0.5	14.3	7	0.09	<2.9
T21I+T304I	No/No	60	10,000	<1.6	0.5	5.7	7	0.13	<1.8
L30F	No	150	10,000	<1.1	0.1	11.1	5	0.35	<1.3
H41Y[c]	Yes	--	--	--	--	--	--	--	--
T45I	No	30	1,000	1.8	1.1	3.1	4	0.01	2.1
M49I	Yes	45	1,000	0.2	<0.1	0.6	3	0.001	0.2
M49L	Yes	60	1,000	<0.5	0.2	1.2	4	0.10	<0.5
M49T	Yes	125	1,000/10,000	0.8	<0.1	32.2	3	0.39	0.9
L50F	No	60	1,000	0.2	<0.1	1.0	3	0.02	0.2
L50F+F140L+ L167F+T304I	**No/Yes/Yes/ No**	**300**	**100,000**	**169**	**114**	**252**	**3**	**<0.0001**	**190**
L50F+E166A+L167F	**No/Yes/Yes**	**300**	**10,000**	**187**	**109**	**321**	**3**	**<0.0001**	**210**
L50F+E166V	**No/Yes**	**500**	**100,000**	**4,020**	**2,250**	**7,170**	**3**	**<0.0001**	**4,500**
L50F+A173V	No/No	60	10,000	<1.7	0.2	12.2	4	0.16	<1.9
L50F+T304I	No/No	100	10,000	1.1	<0.1	25.0	4	0.37	1.3
Y54A	**Yes**	**500**	**10,000**	**22.0**	**14.2**	**34.3**	**4**	**<0.0001**	**25**
E55L	No	250	1,000/10,000	<0.6	0.3	1.3	7	0.26	<0.7
E55L+S144A	**No/Yes**	**250**	**10,000**	**49.8**	**23.8**	**104**	**3**	**<0.0001**	**56**
A70T	No	200	1,000/10,000	<0.3	0.2	0.5	5	0.007	<0.4
G71S	No	30	1,000	0.7	0.4	1.4	3	0.20	0.8

M^{pro} Enzyme	Contact?[a]	Enzyme (nM)	Max NIR (nM)	K_i Geomean (nM)	K_i Lower 95% CI (nM)	K_i Upper 95% CI (nM)	n	p-Value (vs. WT)[b]	K_i Fold Change (vs. WT)
L75F	No	30	1,000	0.3	0.1	0.6	4	0.004	0.3
M82I	No	125	10,000	<1.7	0.1	20.9	5	0.23	<1.9
M82R	No	225	10,000	<0.8	0.1	4.4	5	0.50	<0.9
Q83K	No	30	1,000	0.9	0.3	2.5	4	0.37	1.0
K88R	No	30	1,000/10,000	0.4	0.2	1.0	4	0.13	0.5
L89F	No	60	1,000	1.8	0.5	7.1	4	0.08	2.1
K90R	No	30	1,000	1.1	0.2	5.8	5	0.35	1.2
K90R+K100R	No/No	60	1,000	<0.8	<0.1	6.3	3	0.48	<0.9
K90R+P252L	No/No	40	1,000	0.7	0.6	1.0	3	0.39	0.8
P108S	No	30	1,000	2.6	1.8	3.8	4	0.001	2.9
G109R	No	750	10,000	<0.8	<0.1	7.8	5	0.49	<0.9
P132H	No	60	1,000	0.6	0.2	2.3	4	0.08	0.7
P132L	No	60	1,000	1.0	0.2	4.6	3	0.32	1.1
P132S	No	100	1,000	0.6	<0.1	4.1	4	0.19	0.6
P132H+T169S	No/No	60	1,000	1.0	0.3	3.9	4	0.33	1.1
T135I	No	45	1,000	2.0	0.9	4.5	4	0.02	2.3
T135I+T304I	**No/No**	**100**	**10,000**	**<4.6**	**0.7**	**31.6**	**7**	**0.04**	**<5.1**
F140A	**Yes**	**250**	**10,000**	**18.3**	**3.4**	**99.3**	**7**	**0.002**	**21**
F140L	**Yes**	**40**	**1,000**	**6.8**	**2.0**	**22.8**	**5**	**0.002**	**7.6**
F140L+A173V	**Yes/No**	**125**	**10,000**	**85.0**	**69.8**	**103**	**3**	**<0.0001**	**95**
F140S	**Yes**	**400**	**10,000**	**227**	**86.3**	**599**	**4**	**<0.0001**	**260**
L141F	Yes	50	10,000	1.7	0.4	7.4	3	0.07	1.9
N142L	Yes	35	1,000	1.0	0.3	4.0	5	0.33	1.2
N142S	Yes	30	1,000	<0.7	0.3	1.8	6	0.36	<0.8
G143S	**Yes**	**300**	**1,000/10,000**	**3.2**	**0.2**	**46.9**	**5**	**0.21**	**3.6**
S144A	**Yes**	**250**	**10,000**	**41.3**	**18.7**	**91.2**	**3**	**<0.0001**	**46**
S144E	**Yes**	**1,250**	**10,000**	**427**	**238**	**769**	**4**	**<0.0001**	**480**
S144T	**Yes**	**1,250**	**10,000**	**151**	**49.8**	**461**	**3**	**<0.0001**	**170**
C145F[c]	Yes	--	--	--	--	--	--	--	--
C145I[c]	Yes	--	--	--	--	--	--	--	--
D153H	No	60	10,000	1.1	<0.1	61.8	3	0.40	1.3
D153Y	No	60	10,000	1.1	0.1	8.7	4	0.45	1.3
V157A	No	125	10,000	<1.0	0.2	4.2	4	0.36	<1.1
S158P	No	300	10,000	1.1	0.3	4.3	4	0.27	1.3
C160F	No	60	10,000	0.5	<0.1	9.8	3	0.31	0.6

M^{pro} Enzyme	Contact?[a]	Enzyme (nM)	Max NIR (nM)	K_i Geomean (nM)	K_i Lower 95% CI (nM)	K_i Upper 95% CI (nM)	n	p-Value (vs. WT)[b]	K_i Fold Change (vs. WT)
H163A[c]	Yes	--	--	--	--	--	--	--	--
H164N	**Yes**	**250**	**10,000**	**<6.0**	**2.0**	**18.3**	**8**	**0.002**	**<6.7**
M165I	Yes	60	1,000	<0.7	<0.1	5.4	4	0.41	<0.8
E166A	**Yes**	**250**	**10,000**	**31.2**	**15.1**	**64.3**	**6**	**<0.0001**	**35**
E166G	**Yes**	**500**	**10,000**	**<5.6**	**0.2**	**130**	**4**	**0.07**	**<6.2**
E166V	**Yes**	**2,000**	**100,000**	**6,880**	**5,670**	**8,360**	**3**	**<0.0001**	**7,700**
L167F	Yes	250	10,000	<0.8	<0.1	61.7	3	0.49	<0.9
L167I	Yes	60	1,000	1.6	0.5	5.3	3	0.06	1.8
P168R	Yes	60	1,000	1.7	0.7	4.1	4	0.06	1.9
P168S	Yes	30	1,000	0.5	<0.1	3.1	4	0.25	0.6
T169I	No	60	10,000	<1.2	<0.1	25.1	3	0.31	<1.4
H172Y	**Yes**	**500**	**1,000/10,000**	**225**	**130**	**391**	**4**	**<0.0001**	**250**
H172Y+P252L	**Yes/No**	**750**	**100,000**	**161**	**33.3**	**782**	**3**	**<0.0001**	**180**
A173S	**No**	**30**	**10,000**	**3.7**	**1.2**	**11.3**	**4**	**0.006**	**4.1**
A173T	No	70	10,000	<1.6	<0.1	84.8	4	0.30	<1.8
A173V	**No**	**200**	**10,000**	**14.3**	**2.4**	**83.6**	**4**	**0.003**	**16**
A173V+T304I	**No/No**	**250**	**10,000**	**24.5**	**5.5**	**109**	**6**	**0.0004**	**28**
V186A	Yes	100	10,000	<0.8	0.1	5.6	3	0.46	<0.8
V186G	Yes	500	10,000	<1.2	<0.1	28.4	4	0.36	<1.4
R188G	**Yes**	**250**	**100,000**	**33.7**	**18.3**	**62.0**	**3**	**<0.0001**	**38**
R188M	Yes	60	1,000	0.9	0.4	2.3	4	0.37	1.0
Q189K	Yes	500	1,000/10,000	<1.5	0.3	6.5	6	0.18	<1.6
T190A	Yes	60	1,000	0.5	<0.1	8.3	3	0.17	0.6
T190I	Yes	30	1,000	0.6	0.2	1.8	3	0.23	0.7
A191T	Yes	30	1,000	<0.7	0.3	2.0	4	0.40	<0.8
A191V	Yes	30	1,000	<0.7	0.4	1.4	5	0.37	<0.8
Q192L	**Yes**	**625**	**10,000**	**26.3**	**14.7**	**46.8**	**3**	**<0.0001**	**29**
Q192P	**Yes**	**1,000**	**10,000**	**<6.9**	**0.2**	**213**	**4**	**0.15**	**<7.8**
A193P	No	125	10,000	0.8	<0.1	26.1	3	0.49	0.9
T196A	No	60	10,000	1.1	0.1	10.2	4	0.25	1.2
T196K	No	60	10,000	<0.3	ND	ND	5	0.003	<0.3
T196M	No	60	10,000	0.7	<0.1	20.5	4	0.13	0.8
T196R	No	60	10,000	<0.5	0.3	0.9	9	0.15	<0.6
V212F	No	30	1,000	0.4	0.2	0.8	6	0.06	0.5
I213L	No	60	1,000	0.4	<0.1	12.9	3	0.09	0.5

M^{pro} Enzyme	Contact?[a]	Enzyme (nM)	Max NIR (nM)	K_i Geomean (nM)	K_i Lower 95% CI (nM)	K_i Upper 95% CI (nM)	n	p-Value (vs. WT)[b]	K_i Fold Change (vs. WT)
L220F	No	30	1,000	<0.8	0.3	2.0	5	0.47	<0.9
A234V	No	30	1,000	1.4	0.6	3.0	5	0.09	1.6
D248E	No	30	1,000	1.3	0.2	7.7	4	0.25	1.4
P252L	No	30	1,000/10,000	<0.8	0.3	1.9	6	0.43	<0.9
L253V	No	60	1,000	<0.6	0.3	1.3	7	0.34	<0.7
A260V	No	40	1,000	0.5	0.1	2.1	4	0.12	0.6
A266V	No	60	1,000	1.3	0.3	4.7	5	0.21	1.4
G278R	No	60	10,000	<0.7	0.3	1.8	5	0.36	<0.8
G278V	No	60	10,000	2.1	0.3	15.1	3	0.08	2.4
V296I	No	125	10,000	<0.7	0.2	1.9	6	0.35	<0.7
V297A	**No**	**60**	**10,000**	**2.6**	**0.2**	**44.0**	**5**	**0.15**	**3.0**
V297F	No	60	10,000	<2.5	<0.1	94.9	4	0.13	<2.8
S301P	No	125	10,000	0.2	ND	ND	1	0.003	0.2
G302C	No	125	10,000	1.6	0.3	7.2	4	0.13	1.8
T304I	No	80	1,000	0.9	0.4	2.0	4	0.42	1.0

Source: Adapted from (Pfizer 2022h), p. 16-17.
Note: Bolded rows indicates substitutions that resulted in ≥3-to-<10-fold increases in geomean K_i values. Bolded and shaded rows indicate substitutions that resulted in ≥10-fold increases in geomean K_i values.
[a.] This column indicates residues in direct contact or close proximity (<5 Å) with NIR based on the Applicant's co-crystal structural analysis.
[b.] p-values were determined by t-test of log Ki values with one tail and unequal variance.
[c.] No data (inactive enzyme).
Abbreviations: CI, confidence interval; K_i, inhibition constant; M^{pro}, main protease; n, number of experiments; N/A, not applicable; WT, wild-type.

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The Applicant also determined the catalytic efficiency (k_{cat}/K_m) of these M^{pro} enzymes in the absence of NIR. These experiments were performed with variable concentrations of M^{pro} and a maximum peptide substrate concentration of 250,000 nM. WT SARS-CoV-2 M^{pro} had a catalytic efficiency (k_{cat}/K_m) of 25,500 $M^{-1}s^{-1}$ (Table 212). Of the 33 M^{pro} enzymes with ≥3-fold higher geometric mean K_i values, 31/33 (all except A173S and V297A) had ≥3-fold lower geometric mean k_{cat}/K_m values, indicating reduced catalytic efficiency. These results indicate that most M^{pro} substitutions that lead to reduced NIR activity also result in reduced catalytic efficiency of the enzyme. However, the extent to which these results are predictive of virus replication kinetics in cell culture or in SARS-CoV-2-infected individuals is unclear. Furthermore, these findings do not take into account the possibility that SARS-CoV-2 could acquire additional compensatory substitutions that further improve the catalytic activity of NIR-resistant M^{pro} enzymes.

Table 212. Catalytic Efficiency of SARS-CoV-2 M^{pro} Enzymes With Substitutions in a Biochemical Assay

M^{pro}	Contact?[a]	k_{cat}/K_m Geomean ($M^{-1}s^{-1}$)	k_{cat}/K_m Lower 95% CI ($M^{-1}s^{-1}$)	k_{cat}/K_m Upper 95% CI ($M^{-1}s^{-1}$)	n	p-Value (vs. WT)[b]	k_{cat}/K_m Fold Change (vs. WT)
WT	N/A	25,500	18,300	35,600	15	N/A	N/A
A7S	No	12,800	5,140	31,900	4	0.04	2.0
A7T	No	7,150	6,080	8,400	3	<0.0001	3.6
A7V	No	6,350	3,830	10,500	3	<0.0001	4.0
G15S	No	21,300	12,000	37,700	6	0.26	1.2
T21I	No	16,800	13,400	21,100	3	0.01	1.5
T21I+L50F+ A193P+S301P	**No/No/No/No**	**7,800**	**4,060**	**15,000**	**3**	**0.0004**	**3.3**
T21I+S144A	**No/Yes**	**6,640**	**3,900**	**11,300**	**3**	**<0.0001**	**3.8**
T21I+S144A+T304I	**No/Yes/No**	**2,760**	**1,150**	**6,600**	**3**	**0.0002**	**9.2**
T21I+E166V	**No/Yes**	**1,270**	**883**	**1,820**	**3**	**<0.0001**	**20**
T21I+A173V	**No/No**	**7,200**	**4,170**	**12,400**	**3**	**<0.0001**	**3.5**
T21I+A173V+T304I	**No/No/No**	**5,920**	**3,640**	**9,640**	**3**	**<0.0001**	**4.3**
T21I+A260V+T304I	No/No/No	4,470	2,560	7,820	3	<0.0001	5.7
T21I+T304I	No/No	14,900	10,800	20,600	3	0.004	1.7
L30F	No	2,490	316	19,700	3	0.01	10
T45I	No	29,800	18,500	48,000	8	0.27	0.9
M49I	Yes	15,500	7,170	33,600	4	0.16	1.6
M49L	Yes	14,900	10,200	21,900	6	0.01	1.7
M49T	Yes	6,700	4,790	9,380	5	<0.0001	3.8
L50F	No	12,000	5,170	27,900	5	0.007	2.1
L50F+F140L+ L167F+T304I	**No/Yes/Yes/No**	**2,780**	**1,430**	**5,410**	**3**	**<0.0001**	**9.2**
L50F+E166A+L167F	**No/Yes/Yes**	**1,110**	**917**	**1,340**	**3**	**<0.0001**	**23**
L50F+E166V	**No/Yes**	**703**	**346**	**1,430**	**4**	**<0.0001**	**36**
L50F+A173V	No/No	10,100	2,780	36,900	3	2.5	0.03
L50F+T304I	No/No	8,340	6,590	10,600	3	<0.0001	3.1
Y54A	**Yes**	**507**	**150**	**1,710**	**4**	**0.0003**	**50**
E55L	No	8,680	3,840	19,600	5	0.008	2.9
E55L+S144A	**No/Yes**	**3,720**	**850**	**16,200**	**4**	**0.01**	**6.9**
A70T	No	11,700	3,270	41,600	4	0.07	2.2
G71S	No	15,700	6,150	40,300	3	0.07	1.6
L75F	No	33,400	13,900	80,400	3	0.17	0.8

M^{pro}	Contact?[a]	k_{cat}/K_m Geomean ($M^{-1}s^{-1}$)	k_{cat}/K_m Lower 95% CI ($M^{-1}s^{-1}$)	k_{cat}/K_m Upper 95% CI ($M^{-1}s^{-1}$)	n	p-Value (vs. WT)[b]	k_{cat}/K_m Fold Change (vs. WT)
M82I	No	5,320	2,550	11,100	3	0.0002	4.8
M82R	No	4,560	1,730	12,000	3	0.001	5.6
Q83K	No	32,900	17,000	63,600	4	0.18	0.8
K88R	No	28,300	12,100	65,700	4	0.38	0.9
L89F	No	15,900	10,500	24,200	9	0.03	1.6
K90R	No	28,400	16,000	50,400	9	0.36	0.9
K90R+K100R	No/No	9,620	2,310	40,000	3	0.12	2.7
K90R+P252L	No/No	11,900	2,820	50,200	3	0.07	2.1
P108S	No	27,100	18,000	40,800	10	0.41	0.9
G109R	No	722	246	2,120	5	0.0001	35
P132H	No	17,800	3,690	85,800	3	0.22	1.4
P132L	No	12,700	4,230	38,200	3	0.04	2.0
P132S	No	4,790	716	32,100	3	0.02	5.3
P132H+T169S	No/No	11,800	8,310	16,900	5	0.0009	2.2
T135I	No	17,000	10,100	28,600	5	0.06	1.5
T135I+T304I	**No/No**	**6,350**	**3,130**	**12,900**	**3**	**0.0003**	**4.0**
F140A	**Yes**	**2,060**	**102**	**41,800**	**3**	**0.03**	**12**
F140L	**Yes**	**6,890**	**1,790**	**26,500**	**3**	**0.02**	**3.7**
F140L+A173V	**Yes/No**	**3,120**	**2,660**	**3,670**	**3**	**<0.0001**	**8.2**
F140S	**Yes**	**833**	**574**	**1,210**	**3**	**<0.0001**	**31**
L141F	Yes	20,000	10,200	39,100	3	0.15	1.3
N142L	Yes	48,000	27,900	82,700	5	0.02	1.4
N142S	Yes	18,300	9,340	35,900	5	0.14	1.9
G143S	**Yes**	**1,310**	**537**	**3,210**	**5**	**0.0001**	**19**
S144A	**Yes**	**6,570**	**2,390**	**18,000**	**3**	**0.004**	**3.9**
S144E	**Yes**	**69.0**	**49.3**	**96.5**	**4**	**<0.0001**	**370**
S144T	**Yes**	**88.7**	**47.9**	**164**	**4**	**<0.0001**	**290**
D153H	No	15,300	3,970	58,900	4	0.16	1.7
D153Y	No	12,500	3,800	40,900	4	0.07	2.0
V157A	No	8,660	5,950	12,600	6	0.0001	2.9
S158P	No	2,790	2,110	3,700	6	<0.0001	9.1
C160F	No	14,100	4,760	41,700	3	0.06	1.8
H164N	**Yes**	**1,350**	**229**	**7,980**	**3**	**0.005**	**19**
M165I	Yes	15,300	7,130	33,000	6	0.08	1.7
E166A	**Yes**	**2,420**	**645**	**9,080**	**3**	**0.003**	**11**
E166G	**Yes**	**1,440**	**847**	**2,450**	**4**	**<0.0001**	**18**
E166V	**Yes**	**283**	**224**	**357**	**5**	**<0.0001**	**90**
L167F	Yes	2,200	391	12,300	3	0.007	12
L167I	Yes	14,200	7,970	25,200	8	0.03	1.8
P168R	Yes	15,900	11,500	22,000	5	0.01	1.6
P168S	Yes	40,900	29,200	57,200	5	0.02	0.6
T169I	No	14,500	4,950	42,400	3	0.07	1.8
H172Y	**Yes**	**427**	**173**	**1,050**	**5**	**<0.0001**	**60**
H172Y+P252L	**Yes/No**	**950**	**712**	**1,270**	**3**	**<0.0001**	**27**
A173S	**No**	**12,200**	**6,130**	**24,100**	**3**	**0.007**	**2.1**
A173T	No	4,280	1,860	9,880	3	0.0004	6.0
A173V	**No**	**4,460**	**2,910**	**6,830**	**6**	**<0.0001**	**5.7**
A173V+T304I	**No/No**	**2,740**	**1,290**	**5,810**	**3**	**<0.0001**	**9.3**
V186A	Yes	8,410	4,840	14,600	3	0.0002	3.0

M^{pro}	Contact?[a]	k_{cat}/K_m Geomean ($M^{-1}s^{-1}$)	k_{cat}/K_m Lower 95% CI ($M^{-1}s^{-1}$)	k_{cat}/K_m Upper 95% CI ($M^{-1}s^{-1}$)	n	p-Value (vs. WT)[b]	k_{cat}/K_m Fold Change (vs. WT)
V186G	Yes	1,540	1,120	2,120	5	<0.0001	17
R188G	**Yes**	**4,870**	**2,270**	**10,400**	**3**	**0.0002**	**5.2**
R188M	Yes	11,500	8,500	15,400	6	0.0003	2.2
Q189K	Yes	2,330	1,740	3,120	7	<0.0001	11
T190A	Yes	6,150	5,160	7,340	5	<0.0001	4.1
T190I	Yes	22,100	15,300	31,900	5	0.25	1.2
A191T	Yes	23,300	15,100	36,000	6	0.35	1.1
A191V	Yes	43,100	18,500	100,000	6	0.09	0.6
Q192L	**Yes**	**292**	**126**	**679**	**4**	**<0.0001**	**87**
Q192P	**Yes**	**539**	**282**	**1,030**	**4**	**<0.0001**	**47**
A193P	No	7,160	3,780	13,500	3	0.0002	3.6
T196A	No	10,100	4,170	24,300	4	0.02	2.5
T196K	No	14,500	11,400	18,500	3	0.001	1.8
T196M	No	13,000	5,980	28,100	3	0.02	2.0
T196R	No	14,200	5,880	34,400	4	0.06	1.8
V212F	No	26,700	13,000	54,800	5	0.44	1.0
I213L	No	16,100	7,160	36,200	3	0.06	1.6
L220F	No	23,800	9,530	59,400	3	0.40	1.1
A234V	No	24,100	14,300	40,500	8	0.42	1.1
D248E	No	20,500	8,200	51,500	5	0.29	1.2
P252L	No	30,800	11,500	83,000	4	0.31	0.8
L253V	No	10,400	4,780	22,700	5	0.01	2.5
A260V	No	10,100	3,290	30,800	3	0.02	2.5
A266V	No	20,700	3,440	125,000	3	0.34	1.2
G278R	No	16,200	8,420	31,200	3	0.04	1.6
G278V	No	16,100	6,430	40,100	3	0.07	1.6
V296I	No	12,100	2,350	62,300	3	0.09	2.1
V297A	**No**	**10,700**	**7,040**	**16,200**	**4**	**0.0005**	**2.4**
V297F	No	11,100	7,260	17,000	4	0.0008	2.3
S301P	No	7,210	3,820	13,600	3	0.0002	3.5
G302C	No	7,770	5,340	11,300	6	<0.0001	3.3
T304I	No	9,200	6,390	13,200	6	0.0001	2.8

Source: Adapted from (Pfizer 2022h), p. 18-19.
Note: Bolded rows indicates substitutions that resulted in ≥3-to-<10-fold increases in geomean K_i values. Bolded and shaded rows text indicate substitutions that resulted in ≥10-fold increases in geomean K_i values..
[a.] This column indicates residues in direct contact or close proximity (<5 Å) with NIR based on the Applicant's co-crystal structural analysis.
[b.] p-values were determined by t-test (details not provided).
Abbreviations: CI, confidence interval; k_{cat}, first-order rate constant; K_i, inhibition constant; K_m, Michaelis constant (substrate concentration at half the maximum velocity); M^{pro}, main protease; n, number of experiments; N/A, not applicable; WT, wild-type

Inhibition of Recombinant M^{pro} Enzymes from Six Other Human CoVs in Biochemical Assays (Pfizer 2021d)

Using FRET-based biochemical assays, the Applicant determined the ability of NIR to inhibit recombinant M^{pro} enzymes from 6 other human coronaviruses: SARS-CoV-1, MERS-CoV, HCoV-OC43, HCoV-HKU1, HCoV-NL63, and HCoV-229E. SARS-CoV-1, MERS-CoV, HCoV-OC43, and HCoV-HKU1 are betacoronaviruses, like SARS-CoV-2, whereas HCoV-NL63 and HCoV-229E are alphacoronaviruses. These experiments were performed with 12.5 to 100 nM recombinant M^{pro}, a maximum NIR concentration of 30,000 nM, and

12,500 to 25,000 nM of peptide substrates. For SARS-CoV-1, MERS-CoV, HCoV-OC43, and HCoV-HKU1 (betacoronaviruses), the SARS-CoV-2 nsp4/nsp5 peptide substrate was used, but for HCoV-NL63 and HCoV-229E (alphacoronaviruses), their respective nsp4/nsp5 peptide substrates were used. NIR inhibited the activity of all 6 M^{pro} enzymes tested, with geometric mean IC_{50} values of 28.9 to 479 nM (Table 213). However, relative to SARS-CoV-2 M^{pro} (geometric mean IC_{50} value: 19.2 nM), there was a ≥10-fold increase in geometric mean IC_{50} values for MERS-CoV and HCoV-NL63 M^{pro} enzymes, indicating reduced NIR activity.

Table 213. NIR Activity Against Other Human CoV M^{pro} Enzymes in Biochemical Assays

M^{pro}	n	Enzyme (nM)	Substrate (nM)	Geomean IC_{50} (nM)	95% CI
SARS-CoV-1	3	25	25,000	28.9	24.4-34.2
MERS-CoV	3	100	25,000	402	218-741
HCoV-OC43	3	25	12,500	77.7	31.2-194
HCoV-HKU1	3	12.5	12,500	39.1	25.6-59.8
HCoV-NL63	3	50	12,500	479	242-949
HCoV-229E	3	50	12,500	113	41.7-304

Source: Adapted from (Pfizer 2021d), p. 9, 13.
Abbreviations: CI, confidence interval; CoV, coronavirus; Geomean, geometric mean; IC_{50}, half-maximal inhibitory concentration; M^{pro}, main protease; n, number of experiments; NIR, nirmatrelvir.

Inhibition of Other Proteases in Biochemical Assays (Pfizer 2021d)

Using FRET-based biochemical assays, the Applicant determined the ability of NIR to inhibit 7 human proteases (caspase 2, cathepsins B/D/L, elastase, thrombin a, and chymotrypsin), 1 bovine protease (chymotrypsin), and 1 viral protease (HIV-1). These proteases are unrelated to SARS-CoV-2 M^{pro}. Caspase 2 and cathepsins B/L are cysteine proteases, like SARS-CoV-2 M^{pro}, whereas the others are aspartic or serine proteases (Table 214). Cathepsins B/L have been implicated in SARS-CoV-2 entry (Zhao et al. 2021), and dual inhibitors of SARS-CoV-2 M^{pro} and cathepsins B/L have been identified (Sacco et al. 2020). These experiments were performed with 0.01 to 20 nM enzyme, a maximum NIR concentration of 10,000 or 100,000 nM, and 2,000 to 750,000 nM of peptide substrate. NIR did not inhibit any of the proteases tested up to 10,000 or 100,000 nM (Table 214). These findings indicate that the activity of NIR may be restricted to M^{pro} enzymes.

Table 214. NIR Activity Against Other Proteases in Biochemical Assays

Protease	n	Type	Enzyme (nM)	Substrate (nM)	IC_{50} (nM)
Caspase 2	2	Cysteine	10	5,000	>100,000
Cathepsin B	3	Cysteine	1.2	15,000	>100,000
Cathepsin D	2	Aspartic	1	2,000	>100,000
Cathepsin L	3	Cysteine	0.25	10,000	>100,000
Elastase	2	Serine	0.6	10,000	>100,000
Thrombin a	2	Serine	0.01	10,000	>100,000
Chymotrypsin	2	Serine	2	750,000	>10,000
Bovine chymotrypsin	2	Serine	0.5	10,000	>100,000
HIV-1	2	Aspartic	20	10,000	>100,000

Source: Adapted from (Pfizer 2021d), p. 10, 13.
Abbreviations: HIV-1, human immunodeficiency virus type-1; IC_{50}, half-maximal inhibitory concentration; n, number of experiments; NIR, nirmatrelvir

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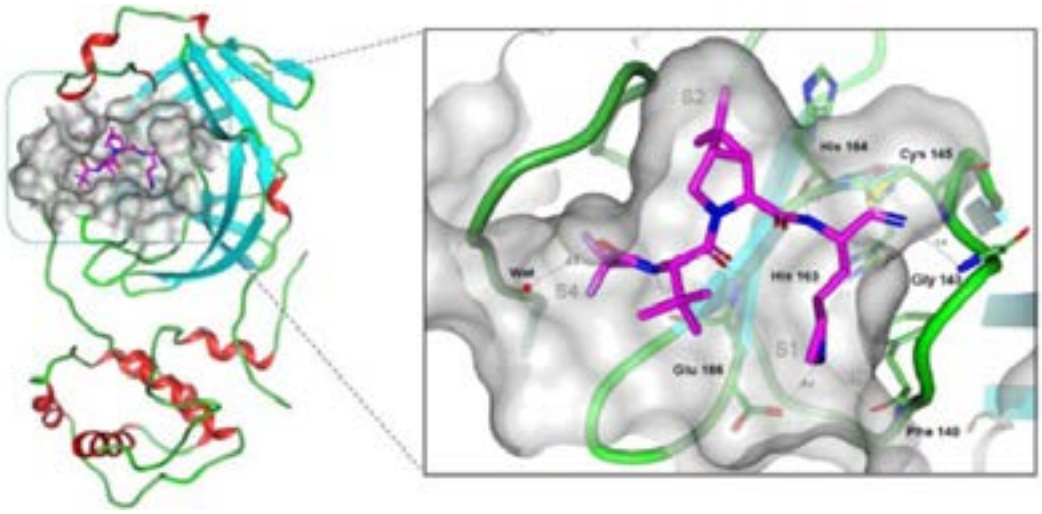
X-Ray Co-Crystal Structure of NIR Bound to Recombinant SARS-CoV-2 M^{pro} (Pfizer 2022s)

Using X-ray crystallography, the Applicant determined the co-crystal structure of NIR bound to recombinant SARS-CoV-2 M^{pro} (Wuhan-Hu-1, with an additional glycine residue on the N-terminus) at 1.7 Å resolution. NIR was found to bind to the active site of SARS-CoV-2 M^{pro}, forming interactions that are analogous to enzyme-substrate contacts (Figure 105). The warhead nitrile carbon of NIR covalently binds to the sulfur atom from C145, generating a thioimidate complex, while the imine nitrogen hydrogen bonds with the main chain NH of G143. The lactam of NIR binds to the S1 pocket of M^{pro} and hydrogen bonds with the side chains of H163 and E166, as well as the main chain CO of F140. In addition, the central amide NH of NIR hydrogen bonds to the CO of H164. The dimethyl aza-bicyclohexane moiety of NIR binds to the hydrophobic S2 pocket, while the trifluoroacetamide moiety of NIR binds to the S4 pocket. The dimethylpropyl moiety of NIR is exposed to solvent.

Figure 105. Co-Crystal Structural Analysis of NIR Bound to SARS-CoV-2 M^{pro}



Source: (Pfizer 2022s), p. 8.
Note: NIR binds to the substrate site of SARS-CoV-2 M^{pro} and forms a covalent bond with the catalytic cysteine residue, C145. Furthermore, NIR occupies the S1, S2, and S4 binding pockets of the active site. Residues that form hydrogen bonds (dashed lines) with NIR are labeled.
Abbreviations: Cys, cysteine; Glu, glutamic acid; Gly, glycine; His, histidine; M^{pro}, main protease; NIR, nirmatrelvir; Phe, phenylalanine; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Sequence Conservation of NIR Contact Residues in SARS-CoV-2 M^{pro} (Pfizer 2022r)

Based on co-crystal structural analysis, the Applicant identified 23 SARS-CoV-2 M^{pro} residues that directly contact or are located in close proximity (<5 Å) of NIR (Table 215). Of these, 11/23 residues directly contact NIR, while 12/23 are located in close proximity but do not directly contact NIR. The Applicant assessed the conservation of these residues in SARS-CoV-2 using the EpiCoV sequence database hosted by GISAID (accessed November 30, 2022; n = 12,664,696 sequences). Note that sequence databases are affected by differences in the amount of sequencing conducted across countries and geographical regions. All 23 residues were highly conserved, with polymorphism frequencies ≤0.1%. The most common polymorphisms were M49I (n = 1,950), V186F (n = 2,193), T190I (n = 2,032), and A191V (n = 9,140). M49I, T190I,

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and A191V did not affect NIR activity in a biochemical assay, while V186F was not tested, although V186A/G did not affect NIR activity in a biochemical assay. Several of these naturally occurring M^{pro} polymorphisms were associated with NIR resistance in cell culture (typically in combination with other M^{pro} substitutions) in studies conducted by the Applicant or others, including F140L (n = 4), S144A (n = 12), E166A/V (n = 9 each), L167F (n = 5), H172Y (n = 12), V186A (n = 47), R188G (n = 15), and A191V (n = 9,140) (Zhou et al. 2022b; Iketani et al. 2023; Jochmans et al. 2023).

Table 215. Sequence Conservation of SARS-CoV-2 M^{pro} Residues That Contact or Are Located in Close Proximity (<5 Å) of NIR

M^{pro} Residue	# Sequences With Polymorphisms	Percentage of Sequences With Polymorphisms	Polymorphisms in ≥100 Sequences	Distance From NIR (Å)	Interaction With NIR
H41	199	0.002%	H41Q	3.5	Catalytic residue, hydrophobic contact
M49	2,127	0.02%	M49I	3.8	Side chain hydrophobic contact
Y54	15	0.0001%	none	3.7	No direct interaction
F140	22	0.0002%	none	3.2	Backbone hydrogen bond
L141	52	0.0004%	none	3.9	No direct interaction
N142	278	0.002%	N142S	3.8	No direct interaction
G143	26	0.0002%	none	3.0	Backbone hydrogen bond
S144	42	0.0003%	none	3.6	No direct interaction
C145	24	0.0002%	none	1.9	Catalytic residue, covalent bond
H163	15	0.0001%	none	2.8	Side chain hydrogen bond
H164	14	0.0001%	none	3.0	Backbone hydrogen bond
M165	139	0.001%	M165I	2.8	Side chain hydrophobic contact
E166	52	0.0004%	none	3.6	Backbone and side chain hydrogen bonds
L167	16	0.0001%	none	3.5	Side chain hydrophobic contact
P168	497	0.004%	P168S	3.3	Side chain hydrophobic contact
H172	56	0.0004%	none	3.5	No direct interaction
V186	3,551	0.03%	V186F/G/I	4.6	No direct interaction
D187	113	0.0009%	none	3.7	No direct interaction
R188	561	0.004%	R188K/S	3.7	No direct interaction
Q189	146	0.001%	none	3.8	No direct interaction
T190	2,156	0.02%	T190I	2.8	No direct interaction
A191	10,178	0.08%	A191S/T/V	4.7	No direct interaction
Q192	111	0.0009%	none	3.5	No direct interaction

Source: Adapted from (Pfizer 2022r), p. 10-16.
Yellow text and red text indicate Mpro residues at which substitutions resulted in ≥3-to-<10-fold and ≥10-fold increases in geomean Ki values, respectively, in a biochemical assay.
Abbreviations: Mpro, main protease; NIR, nirmatrelvir

Other Studies Related to NIR Mechanism of Action

- In the Duveau study, the ability of NIR to inhibit SARS-CoV-2 M^{pro}, SARS-CoV-2 papain-like protease, and 21 human cysteine proteases was determined using biochemical assays. The activity of NIR was selective for SARS-CoV-2 M^{pro} (Duveau and Thomas 2022).
- In Greasley et al., the Applicant solved the co-crystal structure of NIR bound to SARS-CoV-2 Omicron M^{pro} (P132H) and determined that there were no significant differences in the structure relative to WT M^{pro} (Greasley et al. 2022).
- In Kneller et al., Yang et al., and Zhao et al., the co-crystal structure of NIR bound to SARS-CoV-2 M^{pro} was independently determined (Kneller et al. 2022; Yang et al. 2022; Zhao et al.

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2022). In (Yang et al. 2022), the 3 structures were compared to each other and 2 structures published by the Applicant (Owen et al. 2021). All 5 structures were highly similar, but several M^{pro} residues had variable orientations, including 3 residues that contact NIR or have been associated with NIR resistance in cell culture (M49, L50, P168).

20.2. Nonclinical Virology

20.2.1. Antiviral Activity in Cell Culture

NIR Activity Against SARS-CoV-2 WA1/2020 in Vero E6 Cells (Pfizer 2021h)

The activity of NIR and PF-07329268 (the primary oxidative metabolite of NIR) against SARS-CoV-2 USA-WA1/2020 was investigated in Vero E6 (African green monkey kidney) cells by cytopathic effect (CPE) reduction assay. Vero E6 cells were infected at a multiplicity of infection (MOI) of ~0.002, and compounds were added at the time of infection. CPE reduction was measured 3 days post-infection using the CellTiter-Glo Luminescent Cell Viability Assay (Promega). Cell viability was measured in uninfected cells treated with NIR in parallel under matched conditions. These experiments were performed in the presence and absence of 2,000 nM CP-100356, a P-gp inhibitor. According to the Applicant, NIR is a P-gp substrate, and Vero E6 cells express high levels of P-gp, such that NIR has enhanced activity in Vero E6 cells treated with CP-100356. In the absence of CP-100356, NIR inhibited SARS-CoV-2 replication with geometric mean EC_{50} and EC_{90} values of 4,480 and 9,460 nM, respectively (Table 216). In the presence of CP-100356, NIR inhibited SARS-CoV-2 replication with geometric mean EC_{50} and EC_{90} values of 74.5 and 155 nM, respectively. Thus, NIR had 60-61-fold more potent activity in the presence of CP-100356. In uninfected cells, NIR did not affect cell viability up to the maximum concentration tested (10,000 or 100,000 nM), resulting in average selectivity index (SI) values of >21.5 and >1,250 in the absence and presence of CP-100356, respectively. PF-07329268 also had more potent activity in the presence of CP-100356, but PF-07329268 had ~9.3-fold weaker activity than NIR in the presence of CP-100356.

Table 216. Activity of NIR and PF-07329268 (±CP-100356) Against SARS-CoV-2 in Vero E6 Cells

NIR				NIR + CP-100356			
Geomean EC_{50} nM (95% CI)	Geomean EC_{90} nM (95% CI)	Geomean CC_{50} nM	SI	Geomean EC_{50} nM (95% CI)	Geomean EC_{90} nM (95% CI)	Geomean CC_{50} nM	SI
4,480, n = 20 (3,550-5,650)	9,460, n = 20 (7,600-11,800)	>100,000 or >10,000, n = 10	>21.5	74.5, n = 20 (66.5-83.4)	155, n = 20 (138-173)	>100,000 or >10,000, n = 10	>1,250

PF-07329268				PF-07329268 + CP-100356			
Geomean EC_{50} nM (95% CI)	Geomean EC_{90} nM (95% CI)	Geomean CC_{50} nM	SI	Geomean EC_{50} nM (95% CI)	Geomean EC_{90} nM (95% CI)	Geomean CC_{50} nM	SI
>3,333 or >3,000, n = 4 (ND)	>3,333 or >3,000, n = 4 (ND)	>3,333 or >3,000, n = 2	ND	690, n = 3 (210 – 2,270)	1,440, n = 3 (437 – 4,720)	>3,333 or >3,000, n = 2	>5.1

Source: Adapted from (Pfizer 2021h), p. 12.
Note: CP-100356 is a P-gp inh bitor that was added to a final concentration of 2,000 nM.
Abbreviations: CC_{50}, 50% cytotoxic concentration; CI, confidence interval; EC_{50}, half maximal effective concentration; EC_{90}, 90% maximal effective concentration; Geomean, geometric mean; n, number of experiments; ND, no data; NIR, nirmatrelvir; SI, selectivity index (CC_{50} value/EC_{50} value)

NIR and Ritonavir Activity Against SARS-CoV-2 WA1/2020 in A549-ACE2 Cells (Pfizer 2022i)

The activity of NIR, ritonavir, and NIR + ritonavir against SARS-CoV-2 was investigated in A549-ACE2 cells using a luciferase reporter assay. A549-ACE2 cells are human alveolar epithelial cells engineered to stably express human angiotensin converting enzyme-2 (ACE2), the receptor for SARS-CoV-2. These experiments were performed using a recombinant SARS-CoV-2 (USA-WA1/2020-based) reporter virus that encodes NanoLuc luciferase (Promega) in place of ORF7 (Xie et al. 2020b). Cells were infected at an MOI of ~0.01, and compounds were added 10 minutes post-infection. NIR and ritonavir alone were tested at final concentrations of 0.1 to 3,000 nM. In NIR+ritonavir combination experiments, NIR was tested at concentrations of 15 to 3,000 nM, and ritonavir was tested at concentrations of 176 to 3,000 nM. These experiments were performed in the absence of CP-100356 (P-gp inhibitor). Luciferase activity was measured at 72 hr post-infection. Cell viability was measured in uninfected cells treated with NIR or ritonavir in parallel using the CellTiter-Glo Luminescent Cell Viability Assay (Promega). NIR inhibited SARS-CoV-2 replication with geometric mean EC_{50} and EC_{90} values of 77.9 and 215 nM, respectively (Table 217), similar to the geometric mean EC_{50} and EC_{90} values of 74.5 and 155 nM observed in Vero E6 cells treated with CP-100356.

These findings indicate that A549-ACE2 cells express low levels of P-gp. NIR was not cytotoxic at the maximum concentration tested (3,000 nM), resulting in an SI value >38.5. Ritonavir alone had no antiviral activity or cytotoxicity up to the maximum concentration tested (3,000 nM). In NIR + ritonavir combination experiments, NIR alone had an EC_{50} value of 233 nM. In the presence of ritonavir, NIR had EC_{50} values ranging from 151 to 450 nM (Table 218). There was no clear concentration-dependent effect of ritonavir on NIR activity, although a small decrease in NIR activity was observed at the highest concentrations of ritonavir tested (2,000 to 3,000 nM). Combination cytotoxicity was not measured. Overall, these results indicate that ritonavir does not have activity against SARS-CoV-2 in the absence or presence of NIR.

Table 217. Activity of NIR Alone and Ritonavir Alone Against SARS-CoV-2 in A549-ACE2 Cells (Without P-gp Inhibitor)

NIR				Ritonavir		
Geomean EC_{50} nM (95% CI)	Geomean EC_{90} nM (95% CI)	Geomean CC_{50} nM	SI	Geomean EC_{50} nM	Geomean EC_{90} nM	Geomean CC_{50} nM
77.9 (50.5-120), n=28	215 (146 to 317), n=28	>3,000, n=14	>38.5	>3,000, n=2	>3,000, n=2	>3,000, n=1

Source: Adapted from (Pfizer 2022i), p. 15.
Abbreviations: CC_{50}, 50% cytotoxic concentration; CI, confidence interval; EC_{50}, half maximal effective concentration; EC_{90}, 90% maximal effective concentration; Geomean, geometric mean; n, number of experiments; NIR, nirmatrelvir; P-gp, P-glycoprotein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SI, selectivity index (CC_{50} value/EC_{50} value)

Table 218. Activity of NIR + Ritonavir Against SARS-CoV-2 in A549-ACE2 Cells (Without P-gp Inhibitor)

Ritonavir (nM)	NIR EC_{50} (nM)	Lower 95% CI (nM)	Upper 95% CI (nM)
0	233	202	268
176	168	140	202
263	185	157	216
395	201	183	221
593	262	216	318
889	151	132	173
1,330	161	125	207
2,000	336	296	380
3,000	450	379	534

Source: Adapted from , (Pfizer 2022i) p. 18.
Abbreviations: CI, confidence interval; EC_{50}, half maximal effective concentration; NIR, nirmatrelvir; P-gp, P-glycoprotein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

NIR Activity Against SARS-CoV-2 in Differentiated Normal Human Bronchial Epithelial (dNHBE) Cells (Pfizer 2021g)

The activity of NIR against SARS-CoV-2 (USA-WA1/2020) was further investigated in dNHBE cells (MatTek EpiAirway). According to the manufacturer, EpiAirway is a 3-dimensional mucociliary tissue model consisting of dNHBE cells cultured at the air-liquid interface. The model exhibits human-relevant tissue structure and cell morphology and consists of organized keratin 5-positive basal cells, mucus-producing goblet cells, functional tight junctions, and beating cilia. The dNHBE cells used by the Applicant were derived from a single donor, who was a 23-year-old, healthy, non-smoking, Caucasian male. Cells were infected at an MOI of ~0.001, and NIR was added at the time of infection. Depending on the experiment, NIR was tested at concentrations of 10 to 10,000 nM, 10 to 500 nM, or 8 to 5,000 nM. These experiments were performed in the absence of CP-100356 (P-gp inhibitor). Virus was applied to the apical side, while NIR was added to the apical and basal sides of the cultures. Following an initial 2 hr incubation with virus and NIR, the apical medium was removed, and the basal medium was replaced with fresh NIR-containing medium. The cells were then maintained at the air-liquid interface, and viruses in the apical compartment were harvested 3- and 5-days post-infection by washing the surface with pre-warmed culture medium. Virus titers in apical washes (expressed as $TCID_{50}$/mL) were then determined by CPE assay in Vero 76 cells. Three independent experiments were performed. NIR had activity against SARS-CoV-2 in dNHBE cells with geometric mean EC_{50} and EC_{90} values of 32.6-61.8 nM and 56.1-181 nM, respectively

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(Table 219). These values are similar to those reported in Vero E6 (+CP-100356) and A549-ACE2 (-CP-100356) cells.

Table 219. Activity of NIR Against SARS-CoV-2 in dNHBE Cells (Without P-gp Inhibitor)

	EC_{50} (nM)				EC_{90} (nM)			
Virus Collection Day	N=1	N=2	N=3	Geomean (95% CI)	N=1	N=2	N=3	Geomean (95% CI)
3	75.7	67.8	46.1	61.8 (32.4 - 118)	157	141	268	181 (76.9 - 425)
5	55.5	23.1	27.1	32.6 (10.2 - 104)	92.4	43.6	44.0	56.1 (19.2 - 164)

Source: Adapted from (Pfizer 2021g), p. 14.
CI, confidence interval; dNHBE, differentiated normal human bronchial epithelial cells; EC_{50}, half-maximal effective concentration; Geomean, geometric mean; N, replicate number; NIR, nirmatrelvir; P-gp, P-glycoprotein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

NIR Activity Against SARS-CoV-2 Variants in Vero E6 P-gp Knockout and Vero E6-TMPRSS2 Cells (Pfizer 2022e; Pfizer 2022k)

The activity of NIR against SARS-CoV-2 variants was determined in Vero E6 P-gp knockout and Vero E6-TMPRSS2 cells. Vero E6 P-gp knockout cells were generated by the Applicant (details not provided). Vero E6-TMPRSS2 cells were obtained from (b) (4) and stably express human transmembrane protease serine 2 (TMPRSS2), a cellular protease involved in SARS-CoV-2 entry (Hoffmann et al. 2020). Vero E6-TMPRSS2 cells are known to be more susceptible to SARS-CoV-2 infection than Vero E6 cells (Matsuyama et al. 2020). In total, 10 SARS-CoV-2 isolates were tested in at least one cell line: USA-WA1/2020, Alpha, Beta (x2), Gamma, Delta, Lambda, Mu, Omicron BA.1, and Omicron BA.2. Some of these isolates had polymorphisms in M^{pro} (Table 220), but none had polymorphisms in any M^{pro} cleavage sites. In Vero E6 P-gp knockout cells, NIR activity was tested by CPE reduction and qRT-PCR assays, whereas only CPE reduction assay was performed in Vero E6-TMPRSS2 cells. In Vero E6-TMPRSS2 cells, NIR activity was tested in the presence of 2,000 nM CP-100356 (P-gp inhibitor). For the CPE reduction assay, cells were infected at MOIs of 0.03 to 0.04, and NIR was added at the time of infection. CPE reduction was measured 72 hr post-infection using the CellTiter-Glo Luminescent Cell Viability Assay (Promega). For the qRT-PCR assay, cells were infected at an MOI of 0.04, and compounds were added at the time of infection. Cells were lysed 48 hr post-infection, and intracellular SARS-CoV-2 RNA levels were measured by qRT-PCR of nsp10.

In these assays, NIR inhibited SARS-CoV-2 USA-WA1/2020 replication with geometric mean EC_{50} values of ~32 to 96 nM (Table 220), similar to the values reported in other cell types. NIR had activity against all tested SARS-CoV-2 variants. Two Beta isolates had 3.0- to 4.4-fold reduced susceptibility to NIR (based on geometric mean EC_{50} values) in some assays. Both isolates had the M^{pro} K90R polymorphism, and one isolate also had the M^{pro} P252L polymorphism, which has been associated with reduced NIR susceptibility in cell culture (Iketani et al. 2023). The K90R substitution did not affect NIR activity in a biochemical assay or in cell culture when engineered into recombinant SARS-CoV-2 (see below). NIR retained activity against the Omicron BA.1 and BA.2 variants (geometric mean EC_{50} value fold-changes ≤1.1).

Table 220. NIR Activity Against SARS-CoV-2 Variants in Vero E6 P-gp Knockout and Vero E6-TMPRSS2 Cells

		Vero E6 P-gp Knockout (CPE)			Vero E6-TMPRSS2 With P-gp Inhibitor (CPE)			Vero E6 P-gp Knockout (qRT-PCR)		
Variant	M^{pro} Polymorphs	Geomean EC_{50} (nM) Range	Geomean EC_{90} (nM) Range	EC_{50} FC	Geomean EC_{50} (nM) Range	Geomean EC_{90} (nM) Range	EC_{50} FC	Geomean EC_{50} (nM) Range	Geomean EC_{90} (nM) Range	EC_{50} FC
WA1/2020 (n=3)	N/A	96.3 (86.7–110)	195 (174–225)	N/A	71.2 (51.7–92.1)	147 (105–191)	N/A	32.2 (15.6–90.6)	371 (311–463)	N/A
B.1.1.7 Alpha (n=3)	none	75.3 (58.7–90.5)	186 (172–199)	0.8	170 (145–182)	364 (309–399)	2.4	41.0 (39.1-45.2)	213 (106–595)	1.3
B.1.351 Beta (n=4)	K90R	ND	ND	ND	ND	ND	ND	141 (103-272)	533 (276-757)	4.4[a]
B.1.351 Beta (n=3-4)	K90R, P252L	171 (138–207)	363 (288–441)	1.8	217 (175–243)	460 (378–517)	3.0[a]	127.2 (39.8–220)	456 (344–683)	4.0[a]
P.1 Gamma (n=3)	none	87.7 (68.2–121)	222 (187–251)	0.9	204 (137–250)	430 (287–533)	2.9	24.9 (15.8–33.0)	153 (107–209)	0.78
B.1.617.2 Delta (n=2-3)	none	ND	ND	ND	82.2 (71.0–98.2)	168 (147–205)	1.2	15.9 (8.7–37.0)	26.0b (18.2–33.7)	0.5
C.37 Lambda (n=3-4)	G15S	59.5 (51.2–66.6)	171 (129–297)	0.6	93.0 (87.3–97.7)	193 (181–203)	1.3	21.2 (12.2–30.8)	127 (60.2–482)	0.7
B.1.621 Mu (n=3)	none	65.1 (62.0-68.5)	134 (129-139)	0.7	138 (101-203)	292 (212-427)	1.9	25.7 (21.9-30.2)	57.4 (51.4-69.2)	0.8
Omicron BA.1 (n=3)	P132H	ND	ND	ND	ND	ND	ND	16.2 (9.4-30.5)	ND	0.5
Omicron BA.2 (n=3)	P132H	ND	ND	ND	79 (63-98)	150 (125-185)	1.1	ND	ND	ND

Source: Adapted from (Pfizer 2022e), p. 14 and (Pfizer 2022k), p. 16-17.
[a.] EC_{50} value fold-changes ≥3.
[b.] Mathematic average, not geomean.
Abbreviations: CPE, cytopathic effect; EC_{50}, half-maximal effective concentration; EC_{90}, 90% maximal effective concentration; FC, fold change relative to WA1/2020; Geomean, geometric mean; M^{pro}, main protease; n, number of experiments; N/A, not applicable; ND, not determined; NIR, nirmatrelvir; P-gp, P-glycoprotein; Polymorphs, polymorphisms; qRT-PCR, quantitative reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

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Subsequently, the Applicant determined the activity of NIR against SARS-CoV-2 USA-WA1/2020, BA.2, BA.2.12.1, BA.4, and BA.5 variants in Vero E6-TMPRSS2 cells by qRT-PCR assay of intracellular SARS-CoV-2 RNA. Relative to USA-WA1/2020, the BA.2, BA.2.12.1, BA.4, and BA.5 isolates contained the M^{pro} P132H polymorphism, but none of the isolates had any other polymorphisms in M^{pro} or M^{pro} cleavage sites. NIR activity was tested in the presence of 2,000 nM CP-100356 (P-gp inhibitor). Cells were infected at an MOI of 0.04, with compounds added at the time of infection. Cells were lysed 48 hr post-infection, and intracellular SARS-CoV-2 RNA levels were determined by qRT-PCR. NIR retained activity against the SARS-CoV-2 Omicron sub-variants BA.2, BA.2.12.1, BA.4, and BA.5, with fold-changes in geometric mean EC_{50} and EC_{90} values <1 relative to USA-WA1/2020 (Table 221).

Table 221. NIR Activity Against SARS-CoV-2 Omicron Subvariants in Vero E6-TMPRSS2 Cells (With P-gp Inhibitor)

Variant	M^{pro} Polymorphs	n	Geomean EC_{50} (nM) Range	EC_{50} Fold-Change	Geomean EC_{90} (nM) Range	EC_{90} Fold-Change
USA-WA1/2020	N/A	7	70 (49 – 98)	N/A	211 (123 – 478)	N/A
Omicron BA.2	P132H	5	65 (52 – 78)	0.9	132 (95 – 162)	0.6
Omicron BA.2.12.1	P132H	5	40 (34 – 44)	0.6	114 (72 – 408)	0.5
Omicron BA.4	P132H	3	39 (19 – 54)	0.6	98 (92 – 104)	0.5
Omicron BA.5	P132H	5	44 (29 – 117)	0.6	178 (109 – 451)	0.8

Source: Adapted from (Pfizer 2022k), p. 17.
Abbreviations: EC_{50}, half-maximal effective concentration; EC_{90}, 90% maximal effective concentration; Geomean, geometric mean; M^{pro}, main protease; n, number of experiments; N/A, not applicable; P-gp, P-glycoprotein; Polymorphs, polymorphisms; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

NIR Activity Against SARS-CoV-2 Variants in Vero-TMPRSS2 and HeLa-ACE2 Cells (Pfizer 2022d)

The activity of NIR against SARS-CoV-2 variants was also determined in Vero-TMPRRS2 and HeLa-ACE2 cells. Both cell lines were obtained from [redacted] (b) (4) Vero-TMPRRS2 are Vero cells stably expressing human TMPRSS2, while HeLa-ACE2 cells are HeLa (human cervical carcinoma) cells stably expressing human ACE2. In total, 6 variants were tested: USA-WA1/2020, mouse-adapted (MA) WA1/2020, Alpha, Beta, Delta, and Omicron BA.1. Relative to USA-WA1/2020, the Beta and BA.1 isolates contained the M^{pro} K90R and P132H polymorphisms, respectively, but none of the isolates had any other polymorphisms in M^{pro} or M^{pro} cleavage sites. Cells were infected at MOIs of 0.025 (Vero-TMPRSS2) or 0.25 (HeLa-ACE2), with NIR added 2 hr before infection. In Vero-TMPRSS2 cells, NIR activity was tested in the presence of 2,000 nM CP-100356 (P-gp inhibitor). Cells were incubated for 48 hr, washed, fixed, and immunostained for the SARS-CoV-2 nucleocapsid (N) protein. The percentages of infected cells were determined using a Celigo imaging cytometer (Nexcelom). The effect of NIR on cell viability in uninfected cells was examined in parallel by MTT assay (Roche). NIR had activity against all SARS-CoV-2 variants (Table 222). In Vero-TMPRSS2 cells, the Beta isolate had 3.2-fold reduced susceptibility to NIR (based on EC_{50} value). NIR was not cytotoxic up to

the maximum concentration tested (10,000 nM), resulting in SI values of >82.6->588 in Vero-TMPRSS2 cells and >44.4->143 in HeLa-ACE2 cells.

Table 222. NIR Activity Against SARS-CoV-2 Variants in Vero-TMPRSS2 and HeLa-ACE2 Cells

		Vero-TMPRSS2 (+CP-100356, n=1)				HeLa-ACE2 (-CP-100356, n=2)			
Variant	M^{pro} Polymorphs	EC_{50} (nM)	EC_{90} (nM)	EC_{50} Fold-Change	CC_{50}	Mean EC_{50} (nM)	Mean EC_{90} (nM)	EC_{50} Fold-Change	CC_{50}
WA1/2020	N/A	38	45	N/A	>10,000	207	802	N/A	>10,000
MA WA1/2020	none	17	34	0.5	>10,000	128	275	0.6	>10,000
B.1.1.7 Alpha	none	22	49	0.6	>10,000	118	236	0.6	>10,000
B.1.351 Beta	K90R	121	138	3.2[a]	>10,000	225	762	1.1	>10,000
B.1.617.2 Delta	none	73	133	1.9	>10,000	169	1,134	0.8	>10,000
Omicron BA.1	P132H	23	51	0.6	>10,000	70	203	0.3	>10,000

Source: Adapted from (Pfizer 2022d), p. 12.
[a.] EC_{50} value fold-change ≥3.
Abbreviations: CC_{50}, 50% cytotoxic concentration; EC_{50}, half-maximal effective concentration; EC_{90}, 90% maximal effective concentration; n, number of experiments; N/A, not applicable; Polymorphs, polymorphisms; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

NIR Activity Against SARS-CoV-2 Delta Clinical Isolates in Vero E6-TMPRSS2 Cells (Pfizer 2022f)

In this report, the Applicant determined the activity of NIR against 4 clinical isolates of the SARS-CoV-2 Delta variant in Vero E6-TMPRSS2 cells treated with 2,000 nM CP-100356 (P-gp inhibitor). NIR retained activity against the 4 Delta isolates, with geometric mean EC_{50} value fold-changes ≤2.1 compared to the control virus (WA1/2020).

NIR Activity Against Other Human CoVs in Cell Culture (Pfizer 2021f; Pfizer 2021e; Pfizer 2021c)

The activity of NIR against 3 other human coronaviruses was determined in cell culture: SARS-CoV-1, MERS-CoV, and HCoV-229E. SARS-CoV-1 and MERS-CoV are betacoronaviruses, like SARS-CoV-2, whereas HCoV-229E is an alphacoronavirus.

The activity of NIR against SARS-CoV-1 (Toronto-2) was determined in Vero E6 cells by CPE reduction assay in the absence and presence of 2,000 nM CP-100356 (P-gp inhibitor). In the absence of CP-100356, NIR inhibited SARS-CoV-1 replication with geometric mean EC_{50} and EC_{90} values of 12,300 and 25,500 nM, respectively. In the presence of CP-100356, NIR inhibited SARS-CoV-1 replication with geometric mean EC_{50} and EC_{90} values of 151 and 317 nM, respectively. These values are ~2.0 to 2.7-fold higher than those reported for SARS-CoV-2 (WA1/2020) in the same cell line. NIR was not cytotoxic in uninfected Vero E6 cells up to the maximum concentration tested (100,000 nM).

The activity of NIR against MERS-CoV (EMC/2012) was investigated in Vero 81 (STAT1 knockout) cells by CPE reduction assay in the absence and presence of 1,000 nM CP-100356 (P-gp inhibitor). In the absence of CP-100356, NIR inhibited MERS-CoV replication with geometric mean EC_{50} and EC_{90} values of 5,410 and 11,600 nM, respectively. In the presence of CP-100356, NIR inhibited MERS-CoV replication with geometric mean EC_{50} and EC_{90} values of 166 and 351 nM, respectively. NIR activity against SARS-CoV-2 was not determined in Vero 81 cells, but these values are ~1.2- to 2.3-fold higher than those reported for SARS-CoV-2

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(WA1/2020) in Vero E6 cells (+CP-100356). NIR was not cytotoxic in uninfected Vero 81 cells up to the maximum concentration tested (100,000 nM).

The activity of NIR against HCoV-229E (ATCC VR-740) was investigated in MRC-5 (human fetal lung fibroblast) cells by CPE reduction assay in the absence of CP-100356. The Applicant previously demonstrated that the activity of another M^{pro} inhibitor (PF-00835231) against HCoV-229E in MRC-5 cells was not affected by CP-100356, indicating that this cell line expresses low levels of P-gp (Boras et al. 2021). NIR inhibited HCoV-229E replication with geometric mean EC_{50} and EC_{90} values of 190 and 620 nM, respectively. NIR activity against SARS-CoV-2 was not determined in MRC-5 cells, but these values are ~2.6-4.0-fold higher than those reported for SARS-CoV-2 (WA1/2020) in Vero E6 cells (+CP-100356). NIR was not cytotoxic in MRC-5 cells up to the maximum concentration tested (100,000 nM).

NIR Activity Against Human Picornaviruses in Cell Culture (Pfizer 2021b)

The activity of NIR against two human picornaviruses was determined in cell culture: enterovirus 71 (EV71, Shenzhen/120F1/09) and human rhinovirus 1B (HRV1B, ATCC VR-1645). Picornaviruses encode 3C proteases that are structurally related to coronavirus M^{pro}. NIR activity against EV71 and HRV1B was determined in human rhabdomyosarcoma and H1 HeLa cells, respectively, by CPE reduction assay. These experiments were performed in the absence of CP-100356. NIR did not inhibit EV71 or HRV1B replication at the maximum concentration tested (100,000 nM). NIR also did not have cytotoxicity in uninfected cells up to the maximum concentration tested (100,000 nM). These results indicate that the activity of NIR may be limited to coronaviruses. Positive controls for antiviral activity were not included.

Other Studies Related to NIR Antiviral Activity in Cell Culture

NIR retained activity against the SARS-CoV-2 Alpha, Beta, Gamma, Delta, Omicron BA.1, BA.1.1, BA.2, BA.2.12.1, BA.2.75, BA.4, BA.5, BQ.1.1, and/or XBB variants in cell culture (Abdelnabi et al. 2022; Bojkova et al. 2022a; Bojkova et al. 2022b; Li et al. 2022; Ohashi et al. 2022; Saito et al. 2022; Takashita et al. 2022a; Takashita et al. 2022b; Takashita et al. 2022c; Vangeel et al. 2022; Imai et al. 2023). These findings indicate that NIR has broad activity against SARS-CoV-2 variants.

20.2.2. Antiviral Activity in Cell Culture in the Presence of Serum

The Applicant did not directly determine the impact of serum on NIR antiviral activity. However, in (Pfizer 2020b), the Applicant measured the binding of NIR (300 to 10,000 nM) to proteins in human, cynomolgus monkey, and rat plasma by equilibrium dialysis. NIR was found to be 67 to 70%, 50 to 61%, and 51 to 53% bound to proteins from human, cynomolgus monkey, and rat plasma, respectively. Based on these results and the EC_{90} value of NIR against SARS-CoV-2 in dNHBE cells (181 nM), the Applicant estimated the plasma protein-adjusted EC_{90} value to be 585 nM (292 ng/mL), which was selected as the target plasma exposure (C_{min}) for clinical studies.

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20.2.3. Antiviral Cytotoxicity/Selectivity Index

As described above, NIR did not have cytotoxicity in uninfected cells up to the maximum concentration tested in any cell type, resulting in CC_{50} values >3,000 nM in A549-ACE2 (-CP-100356) cells, >10,000 nM in Vero-TMPRSS2 (+CP-100356) and HeLa ACE2 (-CP-100356) cells, and >100,000 nM in Vero E6 (±CP-100356), Vero 81 (+CP-100356), MRC-5 (-CP-100356), human rhabdomyosarcoma (-CP-100356), and H1 HeLa (-CP-100356) cells. NIR had favorable selectivity index (SI) values (CC_{50} value/EC_{50} value) against SARS-CoV-2 of >38.5 (A549-ACE2, -CP-100356), >44.4->143 (HeLa-ACE2, -CP-100356), >82.6->588 (Vero-TMPRSS2, +CP-100356), and >1,250 (Vero E6, +CP-100356). NIR had favorable SI values against SARS-CoV-1, MERS-CoV, and HCoV-229E of >662 (Vero E6, +CP-100356), >602 (Vero 81, +CP-100356), and >526 (MRC-5, -CP-100356), respectively.

20.2.4. Combination Antiviral Activity in Cell Culture

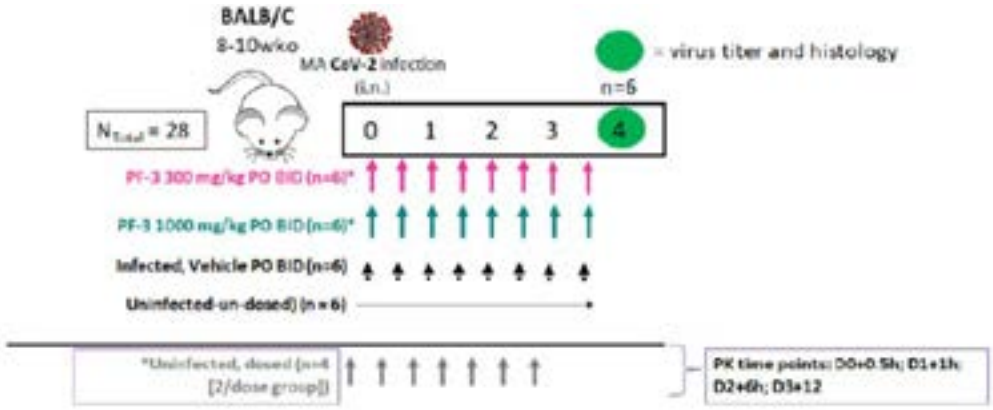
As described above, the Applicant investigated the activity of NIR in combination with ritonavir in A549-ACE2 cells. The Applicant did not provide reports on the activity of NIR in combination with other antivirals approved or authorized by the FDA for the treatment of COVID-19, such as remdesivir (Veklury) or molnupiravir (Lagevrio). However, NIR is not expected to have antagonistic activity with these products in cell culture as they have distinct targets. In Zhou et al., NIR and remdesivir did not have antagonistic activity against SARS-CoV-2 in cell culture (Zhou et al. 2022b). Likewise, in Gidari et al. and Rosenke et al., NIR and molnupiravir did not have antagonistic activity against SARS-CoV-2 in cell culture or in rhesus macaques, respectively (Gidari et al. 2022; Rosenke et al. 2023). Note that this does not rule out a potential effect of molnupiravir-mediated mutagenesis affecting NIR resistance development, given the random mutagenic effects of molnupiravir throughout the SARS-CoV-2 genome (FDA 2022a; FDA 2022b).

20.2.5. Antiviral Activity in Animal Models

NIR Activity in SARS-CoV-2 MA10-Infected BALB/c Mice (Pfizer 2021j)

The activity of NIR was evaluated against mouse-adapted (MA) SARS-CoV-2 MA10 in BALB/c mice in two independent studies. In BALB/c mice, SARS-CoV-2 MA10 causes severe, and in some cases lethal, lung disease (Leist et al. 2020). The extent of lethality depends on the infectious dose and age of the mice. SARS-CoV-2 MA10 does not encode any M^{pro} substitutions. In each study, 8-to-10-week-old female mice were inoculated intranasally with 10^5 $TCID_{50}$ of SARS-CoV-2 MA10 (Figure 106). NIR was orally administered twice daily (BID) at 300 or 1,000 mg/kg starting at 4 hours post-infection on Day 0 and continuing to Day 3. Thus, dosing modeled prophylaxis, not treatment of symptomatic disease. Mice were weighed daily to measure infection-associated weight loss and were euthanized on Day 4 for determination of lung virus titers, histopathology, and immunohistochemistry. Virus titers ($TCID_{50}$/mL) were determined by CPE assay in Vero 76 cells. With this experimental design, mice were not followed for a sufficient duration to assess the impact of NIR through the full course of disease. Uninfected, untreated and infected, vehicle-treated mice were included as controls. In addition, uninfected animals were treated with NIR for PK studies.

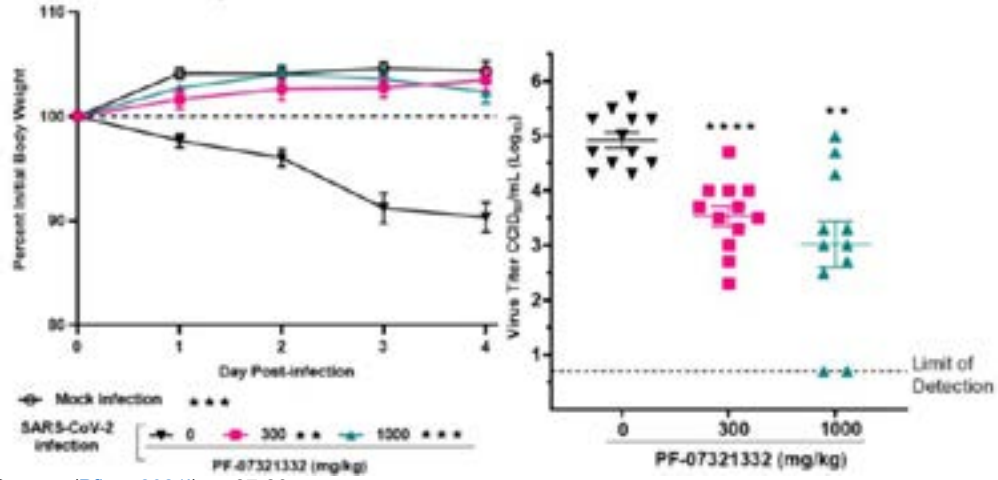
Figure 106. Experimental Design to Test Efficacy of NIR in SARS-CoV-2 MA10-Infected BALB/c Mice



Source: (Pfizer 2021j), p. 11.
Abbreviations: BID, twice daily; D, day; h, hour; i.n., intranasal; MA, mouse-adapted; n, number of animals; NIR, nirmatrelvir; N_{total}, total number of animals; PF-3, nirmatrelvir; PK, pharmacokinetics; PO, dosed orally; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; wko, weeks old

Infected, vehicle-treated mice lost ~10% of their initial body weight through Day 4 (Figure 107). In contrast, uninfected mice and infected, NIR-treated mice gained body weight over the course of the experiment. In infected, vehicle-treated mice, the mean lung virus titer was 4.9 $\log_{10}$ $TCID_{50}$/mL on Day 4. In infected mice treated with NIR at 300 or 1,000 mg/kg BID, mean lung virus titers were 3.5 $\log_{10}$ and 3.0 $\log_{10}$ $TCID_{50}$/mL, respectively, on Day 4. Thus, NIR resulted in 1.4 $\log_{10}$ and 1.9 $\log_{10}$ reductions in mean lung virus titers at 300 or 1,000 mg/kg BID, respectively. Results were generally consistent between studies 1 and 2.

Figure 107. Effects of NIR on Bodyweight and Lung Virus Titers in SARS-CoV-2 MA10-Infected BALB/c Mice (Studies 1 and 2 Combined)



Source: (Pfizer 2021j), p. 27-28.
Note: p-values were determined by ANOVA with Dunnett's post-test, and values are relative to infected, vehicle-treated mice.
** indicates p <0.01
*** indicates p <0.001
**** indicates p <0.0001
Abbreviations: $CCID_{50}$, median cell culture infectious dose; PF-07321332, nirmatrelvir.

In study 1, lung histopathology analyses were inconclusive due to poor quality of samples from infected, vehicle-treated mice. In study 2, blinded assessments of lungs from infected, vehicle-

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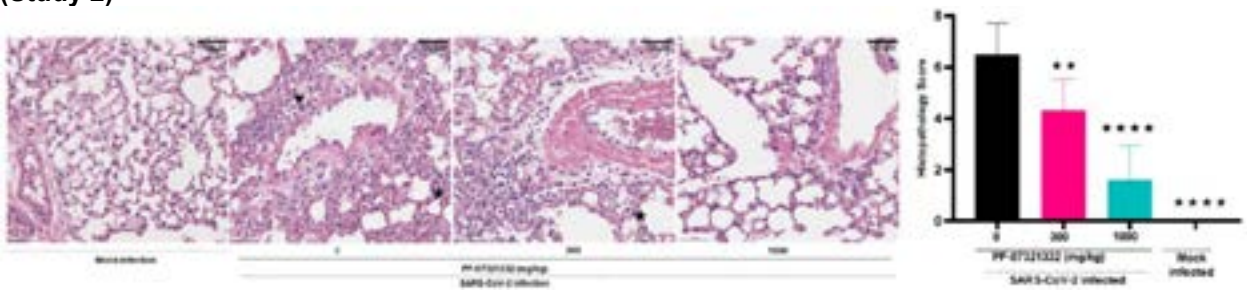
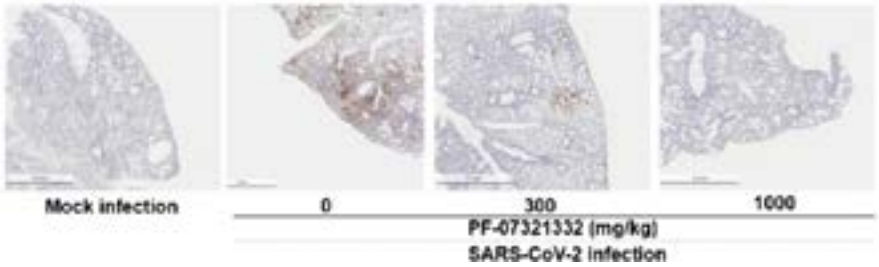
treated mice showed evidence of increased perivascular inflammation, bronchial or bronchiolar epithelial degeneration or necrosis, bronchial or bronchiolar inflammation, cellular debris in alveolar lumen, alveolar inflammation, and thickening of the alveolar septum compared to infected, NIR-treated mice and uninfected mice. Most of the infected mice exhibited multifocal pulmonary lesions, but infected, NIR-treated mice developed significantly fewer lesions than infected, vehicle-treated mice (Figure 108). Thus, NIR reduced lung tissue damage through Day 4 due to virus replication and limited cellular infiltration. In addition, immunohistochemistry of lung sections was performed using an anti-SARS-CoV-2 nucleocapsid (N) antibody (Figure 109). NIR treatment resulted in dose-dependent decreases in N protein staining, showing that NIR reduced viral replication in the lungs on Day 4.

Figure 108. Effect of NIR on Lung Histopathology in SARS-CoV-2 MA10-Infected BALB/c Mice (Study 2)



Source: (Pfizer 2021j), p. 31-32.
Note: Left, Hematoxylin- and eosin-stained lung sections focusing on perivascular damage and alveolar inflammation. Right, lung histopathology scores.
Note: Four parameters were evaluated in a blinded manner with a 5-point scoring system: perivascular inflammation, bronchial or bronchiolar epithelial degeneration or necrosis, bronchial or bronchiolar inflammation, and alveolar inflammation.
Note: p-values were determined by one-way ANOVA with Dunnett's post-test, and values are relative to infected, vehicle-treated mice.
** indicates p <0.01
**** indicates p <0.0001
Abbreviations: NIR, nirmatrelvir; PF-07321332, nirmatrelvir; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Figure 109. Effect of NIR on SARS-CoV-2 Nucleocapsid Staining in SARS-CoV-2 MA10-Infected BALB/c Mice (Study 2)



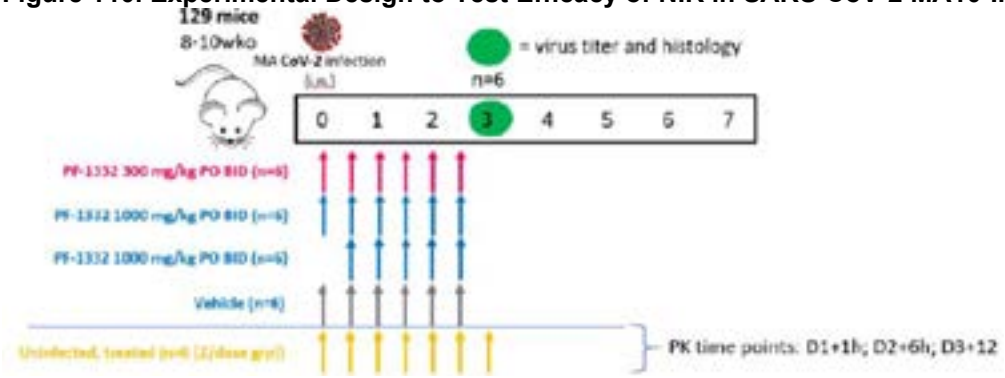
Source: (Pfizer 2021j), p. 32.
Note: Immunohistochemistry images indicating the presence of SARS-CoV-2 nucleocapsid protein (brown stain).
Abbreviations: NIR, nirmatrelvir; PF-07321332, nirmatrelvir; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

PK studies were also performed using a separate group of uninfected, NIR-treated animals. Minimal unbound plasma concentrations (C_{min}) of NIR at 12 hr post-last dose were 0.9x and 4.2x higher (for 300 and 1,000 mg/kg BID, respectively) than the EC_{90} value of NIR against SARS-CoV-2 in dNHBE cells (181 nM). These results show that NIR has antiviral activity at C_{min} unbound plasma exposures $\geq EC_{90}$ value in BALB/c mice. However, the higher dose of NIR (1,000 mg/kg) had better activity.

NIR Activity in SARS-CoV-2 MA10-Infected 129 Mice (Pfizer 2021i)

The activity of NIR was also evaluated against SARS-CoV-2 MA10 in 129 mice, which are immunocompetent mice that are more susceptible to SARS-CoV-1 infection than BALB/c mice (Gretebeck and Subbarao 2015). Female 8-to-10-week-old mice were inoculated intranasally with $2.5x10^4$ pfu of SARS-CoV-2 MA10. NIR was orally administered at 300 or 1,000 mg/kg BID starting at 4 hr (300 or 1,000 mg/kg) or 12 hr (1,000 mg/kg) post-infection on Day 0 and continuing to Day 2 (Figure 110). Thus, dosing modeled prophylaxis, not treatment of symptomatic disease. Mice were weighed daily to measure infection-associated weight loss and were euthanized on Day 3 for determination of lung virus titers and histopathology. Virus titers ($TCID_{50}$/mL) were determined by CPE assay in Vero 76 cells. With this experimental design, mice were not followed for a sufficient duration to assess the impact of NIR through the full course of disease. Uninfected, untreated and infected, vehicle-treated mice were included as controls. In addition, uninfected animals were treated with NIR for PK studies.

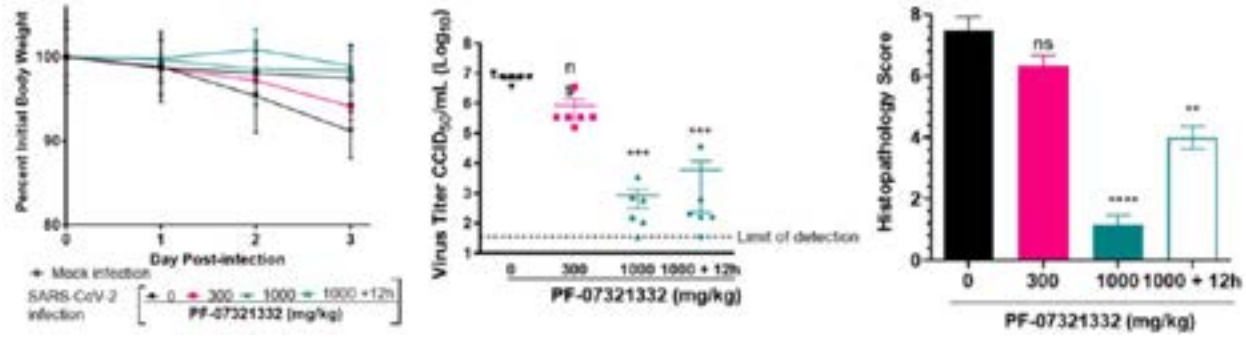
Figure 110. Experimental Design to Test Efficacy of NIR in SARS-CoV-2 MA10-Infected 129 Mice



Source: (Pfizer 2021i), p. 9.
Abbreviations: BID, twice daily; D, day; h, hour; i.n., intranasal; MA, mouse-adapted; n, number of animals; NIR, nirmatrelvir; PF-1332, nirmatrelvir; PK, pharmacokinetics; PO, dosed orally; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; wko, weeks old

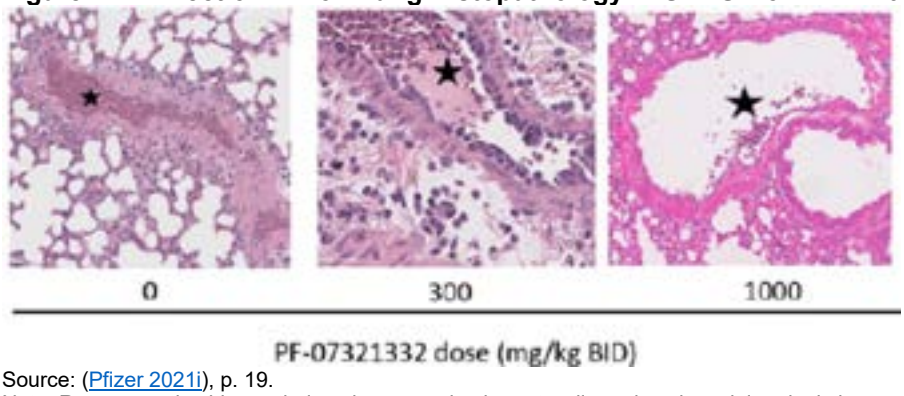
In this study, infected vehicle-treated mice lost ~9% bodyweight by Day 3 (Figure 111). NIR prevented weight loss at the 1,000 mg/kg dose, although the Applicant did not indicate whether these findings were statistically significant. The mean lung virus titer in infected, vehicle-treated mice was 6.8 log_{10} $TCID_{50}$/mL on Day 3. NIR resulted in 1.1 log and 4.2 to 4.3 log_{10} reductions in mean lung virus titers at 300 and 1,000 mg/kg BID, respectively, although only the results with the 1,000 mg/kg dose were statistically significant. Lastly, NIR at 1,000 mg/kg resulted in reduced lung histopathology in blinded assessments on Day 3, especially when treatment was initiated at 4 hr post-infection (Figure 111 and Figure 112).

Figure 111. Effects of NIR on Bodyweight, Lung Virus Titers, and Lung Histopathology in SARS-CoV-2 MA10-Infected 129 Mice



Source: (Pfizer 2021i), p. 17-19.
Note: For lung histopathology, four parameters were evaluated in a blinded manner with a 5-point scoring system: perivascular inflammation, bronchial or bronchiolar epithelial degeneration or necrosis, bronchial or bronchiolar inflammation, and alveolar inflammation.
Note: vehicle-treated mice. p-values were determined by Kruskal-Wallis test and relative to vehicle-treated mice.
** indicates p <0.01
*** indicates p <0.001
**** indicates p <0.0001
Abbreviations: $CCID_{50}$, median cell culture infectious dose; h, hour; log, logarithm; NIR, nirmatrelvir; ns, not significant; PF-07321332, nirmatrelvir; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Figure 112. Effect of NIR on Lung Histopathology in SARS-CoV-2 MA10-Infected 129 Mice



Source: (Pfizer 2021i), p. 19.
Note: Representative histopathology images using hematoxylin and eosin staining depicting perivascular inflammation from the untreated/infected 0 mg/kg control, 300 mg/kg BID and 1000 mg/kg BID treatment groups.
Abbreviations: BID, twice daily; NIR, nirmatrelvir; PF-07321332, nirmatrelvir; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

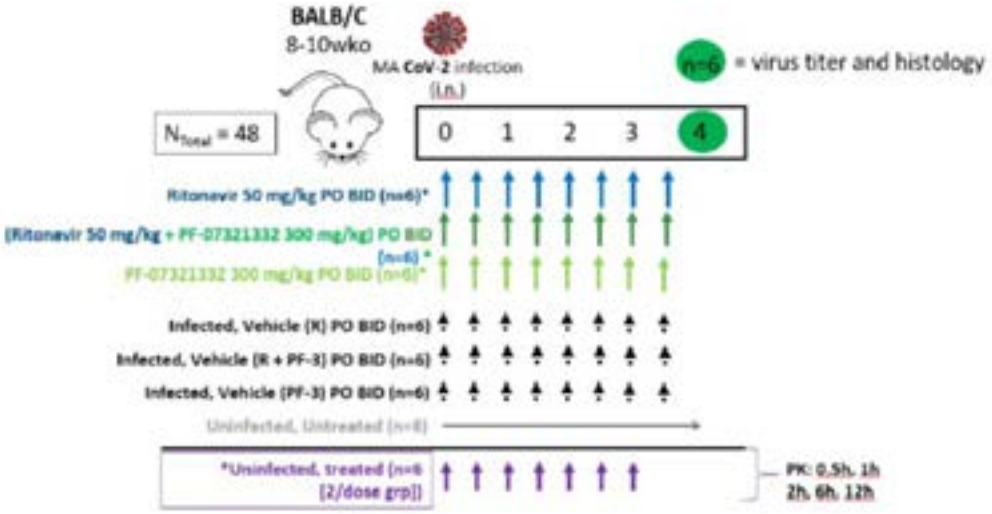
PK studies were also performed using a separate group of uninfected, NIR-treated animals. Minimal unbound plasma concentrations (C_{min}) of NIR at 12 hr post-last dose were 3.5× and 25× higher (for 300 and 1,000 mg/kg BID, respectively) than the EC_{90} value of NIR against SARS-CoV-2 in dNHBE cells (181 nM).

NIR + Ritonavir Activity in SARS-CoV-2 MA10-Infected BALB/c Mice (Pfizer 2022m)

The activity of NIR, ritonavir, and NIR+ritonavir was evaluated against SARS-CoV-2 MA10 in BALB/c mice in two independent studies. In each study, 8-to-10-week-old female mice were inoculated intranasally with 10^5 $TCID_{50}$ of SARS-CoV-2 MA10 (Figure 113). Mice were orally treated with NIR (300 mg/kg BID), ritonavir (50 mg/kg BID), or NIR+ritonavir (300 mg/kg BID and 50 mg/kg BID, respectively) starting at 4 hours post-infection on Day 0 and continuing to

Day 3. Thus, dosing modeled prophylaxis, not treatment of symptomatic disease. Mice were euthanized on Day 4 for determination of lung virus titers, histopathology, and immunohistochemistry. Virus titers ($TCID_{50}$/mL) were determined by CPE assay in Vero 76 cells. With this experimental design, mice were not followed for a sufficient duration to assess the impact of NIR through the full course of disease. Uninfected, untreated and infected, vehicle-treated mice were included as controls. In addition, uninfected were treated with NIR, ritonavir, or NIR+ritonavir for PK studies.

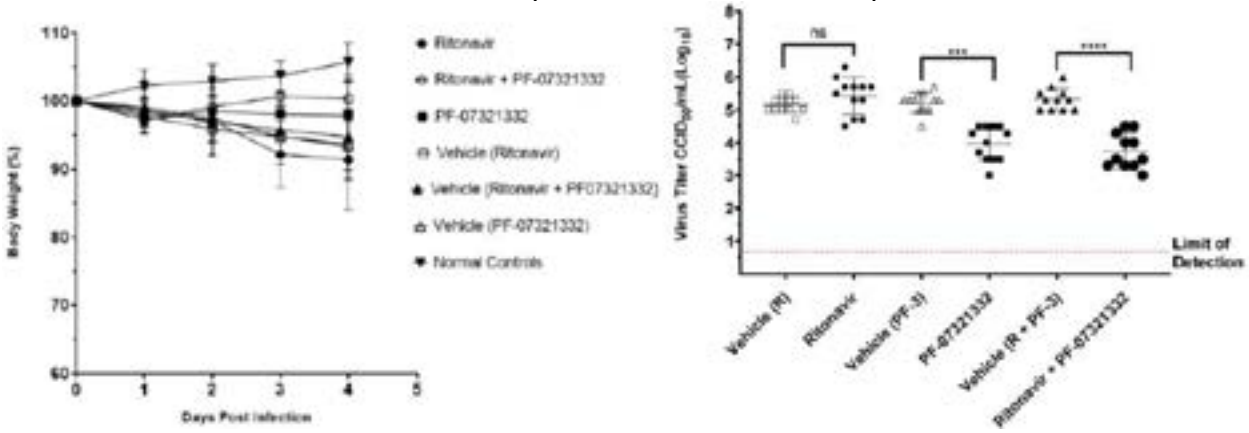
Figure 113. Experimental Design to Test Efficacy of NIR, Ritonavir, and NIR + Ritonavir in SARS-CoV-2 MA10-Infected BALB/c Mice



Source: (Pfizer 2022m), p. 10.
Abbreviations: BID, twice daily; h, hour; i.n., intranasal; MA, mouse-adapted; n, number of animals; NIR, nirmatrelvir; N_{total}, total number of animals; PF-3/PF-07321332, nirmatrelvir; PK, pharmacokinetics; PO, dosed orally; R, ritonavir; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; wko, weeks old

Infected mice treated with ritonavir alone or vehicle lost ~10% of their initial body weight through Day 4, while uninfected mice gained body weight over the course of the experiment (Figure 114). Infected mice treated with NIR or NIR+ritonavir lost less weight than those treated with ritonavir or vehicle, although the Applicant did not indicate whether these findings were statistically significant. In vehicle-treated mice, mean lung virus titers were 5.2-5.3 log_{10} $TCID_{50}$/mL on Day 4. In ritonavir-treated mice, the mean lung virus titer was 5.4 log_{10} $TCID_{50}$/mL; thus, ritonavir alone did not have antiviral activity. In NIR-treated mice, the mean lung virus titer was 4.0 log_{10} $TCID_{50}$/mL; thus, NIR alone resulted in a 1.2 log_{10} reduction in virus titer relative to vehicle control. In mice treated with NIR + ritonavir, the mean lung virus titer was 3.7 log_{10} $TCID_{50}$/mL; thus, NIR + ritonavir resulted in a 1.6 log_{10} reduction in virus titer relative to vehicle control. The Applicant did not indicate whether the difference in lung viral titers between NIR and NIR + ritonavir was statistically significant. Results were generally consistent between the two studies.

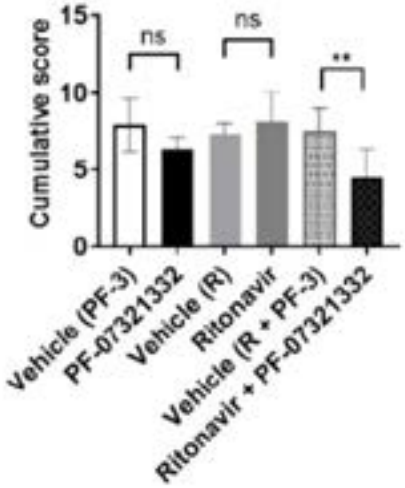
Figure 114. Effects of NIR, Ritonavir, and NIR + Ritonavir on Body Weight and Lung Virus Titers in SARS-CoV-2 MA10-Infected BALB/c Mice (Studies 2 and 3 Combined)



Source: (Pfizer 2022m), p. 27, 30.
Note: p-values were determined by non-parametric one-way ANOVA with Kruskal-Wallis post-test.*** indicates p <0.001 and **** indicates p <0.0001 relative to infected vehicle-treated mice.
Abbreviations: CCID50, median cell culture infectious dose; log, logarithm; NIR, nirmatrelvir; ns, not significant; PF-3/PF-07321332, nirmatrelvir; R, ritonavir; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

In contrast to results from report 105036, NIR alone did not reduce mean lung histopathology scores in blinded assessments on Day 4 in this study (Figure 115). Ritonavir alone did not affect mean lung histopathology scores either. However, NIR+ritonavir significantly reduced the mean lung histopathology score. The Applicant also provided representative lung histopathology and immunohistochemistry images for studies 2 and 3 (data not shown).

Figure 115. Effects of NIR, Ritonavir, and NIR + Ritonavir on Lung Histopathology Scores in SARS-CoV-2 MA10-Infected BALB/c Mice (Studies 2 and 3 Combined)



Source: (Pfizer 2022m), p. 33.
Note: Four parameters were evaluated in a blinded manner with a 5-point scoring system: perivascular inflammation, bronchial or bronchiolar epithelial degeneration or necrosis, bronchial or bronchiolar inflammation, and alveolar inflammation.
Note: p-values were determined by non-parametric one-way ANOVA with Kruskal-Wallis post-test.
** indicates p <0.01.
Abbreviations: NIR, nirmatrelvir; ns, not significant; PF-3/PF-07321332, nirmatrelvir; R, ritonavir; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

PK studies were also performed using a separate group of uninfected, treated animals. In study 2, minimal unbound plasma concentrations (C_{min}) of NIR at 12 hours post-last dose were 0.9x and

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8x higher (for NIR and NIR + ritonavir, respectively) than the EC_{90} value of NIR against SARS-CoV-2 in dNHBE cells (181 nM). In study 3, C_{min} values at 12 hours post-last dose were 2.9x and 28x higher (for NIR and NIR + ritonavir, respectively) than the EC_{90} value. These results show that ritonavir significantly increased NIR plasma exposures in BALB/c mice.

Other Studies Related to NIR Antiviral Activity in Animal Models

In Abdelnabi et al., NIR was shown to have antiviral activity in Syrian hamsters infected with the SARS-CoV-2 Beta or Delta variants (Abdelnabi et al. 2022). In addition, NIR prevented transmission of SARS-CoV-2 Delta from infected, NIR-treated hamsters to co-housed, uninfected hamsters. NIR dosing (125-250 mg/kg BID) was initiated at the time of infection in these experiments. In Uraki et al., NIR was shown to have antiviral activity in Syrian hamsters infected with the SARS-CoV-2 Omicron BA.2 variant. NIR dosing (1,000 mg/kg BID) was initiated 24 hours post-infection (Uraki et al. 2022).

20.3. Drug Resistance

20.3.1. Resistance Development in Cell Culture

Selection of NIR-Resistant MHV in Cell Culture (Pfizer 2021a)

To identify M^{pro} residues associated with NIR resistance, the Applicant initially selected for NIR resistance in cell culture using mouse hepatitis virus (MHV) A59 (ATCC VR-764), a betacoronavirus used as a surrogate for SARS-CoV-2. In L929 (mouse fibroblast) cells, NIR inhibited MHV replication in a CPE reduction assay with EC_{50} values of 847 and 395 nM in the absence and presence of 2,000 nM CP-100356 (P-gp inhibitor), respectively. These results indicate that NIR may have reduced activity against MHV M^{pro} relative to SARS-CoV-2 M^{pro}, in agreement with a published study (Heilmann et al. 2023). Overall, MHV M^{pro} and SARS-CoV-2 M^{pro} have ~51% amino acid identity. In addition, MHV M^{pro} has several amino acid differences near the NIR binding site relative to SARS-CoV-2 M^{pro}, including N142C, H164Q, M165L, P168S, V186R, R188A, T190V, and A191V. Thus, the extent to which NIR resistance substitutions in MHV are predictive of resistance substitutions in SARS-CoV-2 is unclear.

To select for NIR resistance, MHV was serially passaged 11× in L929 cells with increasing concentrations of NIR. This experiment was performed in the absence of CP-100356. The initial MOI was 0.001 (specific number of infectious units unknown), and the initial concentration of NIR was 420 nM, which represents ~0.5xEC_{50} value (847 nM). The final concentration of NIR was 42,340 nM, which represents ~50xEC_{50} value. This experiment was performed using a single virus stock. Each passage lasted 2 to 3 days, and the virus titer was determined after each passage by plaque assay in L929 cells. MOIs varied among passages from 0.001 to 1.1. M^{pro} and M^{pro} cleavage site substitutions were identified by whole-genome Illumina sequencing of viral RNA from passages 2-9 and 33 plaque-purified viruses (13 from passage 9, 20 from passage 10). Virus titer was not detected after passage 11.

In viruses from passages 2 to 9, 4 M^{pro} substitutions were detected at a frequency >3%: P55L, S144A, F213L, and A250V (Table 223). In SARS-CoV-2 M^{pro}, the residues at these positions are E55, S144, I213, and P252, respectively. In addition, one substitution (ORF1ab S4470N) was

observed in an M^{pro} cleavage site at passage 2 but not in any later passages. The frequencies of these substitutions were not provided. Of the plaque-purified viruses, all 33 viruses contained the M^{pro} P55L and S144A substitutions (Table 224). In addition, 3 viruses contained other low-frequency (3-5%) M^{pro} substitutions: one with P15A, one with T50K and T129M, and one with F126L. In SARS-CoV-2 M^{pro}, the residues at these positions are G15 (P15A), L50 (T50K), Y126 (F126L), and A129 (T129M). The F213L and A250V M^{pro} substitutions were not detected in any of the plaque-purified viruses. None of the plaque-purified viruses had substitutions in M^{pro} cleavage sites.

Table 223. Sequencing of MHV Passaged in the Presence of NIR

Passage	NIR nM (×EC_{50})	MHV M^{pro} Substitutions ≥3%
2	850 (1)	F213L, A250V
3	1,060 (1.25)	P55L, F213L, A250V
4	2,120 (2.5)	P55L, F213L, A250V
5	2,540 (3)	P55L, F213L, A250V
6	3,390 (4)	P55L, F213L, A250V
7	4,230 (5)	P55L, F213L, A250V
8	8,470 (10)	P55L, F213L, A250V
9	25,410 (30)	P55L, S144A, F213L, A250V

Source: Adapted from (Pfizer 2021a), p. 17.
Abbreviations: EC_{50}, half-maximal effective concentration; MHV, murine hepatitis virus; M^{pro}, main protease; NIR, nirmatrelvir

Table 224. Sequencing of Plaque-Purified MHV Passaged in the Presence of NIR

Passage	NIR nM (×EC_{50})	# of Plaques	MHV M^{pro} Substitutions ≥3% (# Plaques)
9	25,410 (30)	13	T50K (1/13), P55L (13/13), T129M (1/13), S144A (13/13)
10	33,870 (40)	20	P15A (1/20), P55L (20/20), F126L (1/20), S144A (20/20)

Source: Adapted from (Pfizer 2021a), p. 17-18.
Abbreviations: EC_{50}, half-maximal effective concentration; MHV, murine hepatitis virus; M^{pro}, main protease; NIR, nirmatrelvir

For 4 plaque-purified viruses, virus titers and susceptibility to NIR were determined (Table 225). Virus titers were determined in the absence of NIR by plaque assay in L929 cells. NIR activity was determined in the presence of 2,000 nM CP-100356 by qRT-PCR assay in L929 cells. All 4 viruses contained M^{pro} P55L and S144A substitutions. One virus also contained a low-frequency (3-5%) P15A substitution, while another virus contained low-frequency (3-5%) T50K and T129M substitutions. All 4 viruses had reduced susceptibility to NIR, with 4.4 to 4.9-fold higher EC_{50} values relative to the parental virus. These results indicate that the M^{pro} P55L and/or S144A substitutions likely confer reduced susceptibility to NIR. These results do not rule out the possibility that the other substitutions (e.g., P15A, T50K, F126L, and T129M) further enhance resistance, as these substitutions were present at low frequencies (3 to 5%). The Applicant did not confirm these results with recombinant viruses.

Table 225. Activity of NIR Against Plaque-Purified MHV With M^{pro} Substitutions

Passage	NIR nM (×EC_{50})	M^{pro} Substitutions	Titer (pfu/mL)	Titer FC	Geomean EC_{50} nM (Range)	EC_{50} FC
Parent Virus	N/A	N/A	1.5E+06	N/A	600 (400-1,000)	N/A
9	25,410 (30)	P55L, S144A	1.3E+05	12	2,630 (1,400-3,900)	4.4
9	25,410 (30)	T50K, P55L, T129M, S144A	1.3E+04	120	2,930 (2,000-4,500)	4.9
10	33,870 (40)	P55L, S144A	7.3E+04	21	2,650 (1,600-3,800)	4.4
10	33,870 (40)	P15A, P55L, S144A	2.5E+04	60	2,800 (1,600-4,400)	4.7

Source: Adapted from (Pfizer 2021a), p. 16.
Abbreviations: EC_{50}, half-maximal effective concentration; FC, fold-change; Geomean, geometric mean; M^{pro}, main protease; MHV, murine hepatitis virus; N/A, not applicable; NIR, nirmatrelvir; pfu, plaque-forming units.

In total, 8 M^{pro} substitutions were observed in NIR-selected MHV: P15A, T50K, P55L, F126L, T129M, S144A, F213L, and A250V. In SARS-CoV-2 M^{pro}, the residues at these positions are G15, L50, E55, Y126, A129, S144, I213, and P252, respectively. SARS-CoV-2 M^{pro} substitutions at some of these positions have been associated with NIR resistance in cell culture, including L50F, S144A, and P252L, usually in combination with other substitutions (see below, (Zhou et al. 2022b; Iketani et al. 2023; Jochmans et al. 2023)). In the SARS-CoV-2 M^{pro}/NIR co-crystal structure, none of these residues directly contact NIR, although S144 is located in close proximity (~3.6 Å).

Selection of NIR-Resistant SARS-CoV-2 in Vero E6 P-gp Knockout Cells (Pfizer 2022g)

In addition to MHV selection, the Applicant selected NIR-resistant SARS-CoV-2 (USA-WA1/2020) in Vero E6 P-gp knockout cells. SARS-CoV-2 was serially passaged 9 times under 5 different passaging schemes with constant or increasing NIR concentrations. In scheme #1, the NIR concentration was kept constant at 150 nM (1xEC_{50}). In schemes #2-4, the NIR concentration was progressively increased from 150 nM (1×EC_{50}) to either 1,314 nM (9xEC_{50}), 3,066 nM (21xEC_{50}), or 7,300 nM (50xEC_{50}). In scheme #5, the NIR concentration was kept constant at 370 nM (1xEC_{90}). These experiments were conducted using a single virus stock. In addition, for schemes #1-4, the first passage was the same (i.e., the virus was split after the first passage). Cells were infected at an MOI of 0.01 for the first passage and variable MOIs thereafter. Each passage lasted 2 to 8 days, depending on the amount of time required to generate >50% CPE in the culture. When sufficient CPE was detected, viral supernatants were collected and used to infect cells for the next passage. Virus titers ($TCID_{50}$/mL) after each passage were determined by CPE assay in Vero E6 P-gp knockout cells. Virus was passaged in the absence of NIR as a control.

After each passage, viral RNA was extracted, and M^{pro} and M^{pro} cleavage site substitutions with frequencies ≥3% were identified by whole-genome Illumina sequencing. In schemes #1-4, which shared the first virus passage, an M^{pro} T304I substitution was identified after passage 1 (Table 226). In scheme #1, T304I gradually increased in frequency, but no other M^{pro} substitutions were observed. In schemes #2-4, T304I increased in frequency more quickly, followed by acquisition of an A173V substitution, which increased to >90% frequency in a single passage. In scheme #3, L50F (20-21%) and T135I (6%) substitutions were also observed after passages 8 to 9. In scheme #5, T304I was identified first, followed by T21I and S144A substitutions. L50F (6%), T135I (7%), and A191V (5%) were also observed after passages 4 to 5 but not after later passages. Virus that was passaged in the absence of NIR did not acquire any

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M^{pro} substitutions. In total, 7 distinct M^{pro} substitutions were identified: T21I, L50F, T135I, S144A, A173V, A191V, and T304I. In addition, the substitution frequencies indicate that some viruses had multiple M^{pro} substitutions, e.g., T21I+T304I, A173V+T304I, and T21I+S144A+T304I.

Table 226. Sequencing of SARS-CoV-2 Passaged in the Presence of NIR in Vero E6 P-gp Knockout Cells

	M^{pro} Substitutions ≥3% (Frequency)				
Passage	**Scheme #1**	**Scheme #2**	**Scheme #3**	**Scheme #4**	**Scheme #5**
1	T304I (12%)	T304I (12%)	T304I (12%)	T304I (12%)	none
2	T304I (15%)	T304I (45%)	T304I (45%)	T304I (45%)	T304I (5%)
3	T304I (38%)	T304I (79%)	T304I (79%)	T304I (79%)	T304I (77%)
4	T304I (66%)	T304I (83%)	T304I (81%)	T304I (81%)	T21I (31%), L50F (6%), T135I (7%), T304I (81%)
5	T304I (68%)	T304I (74%)	A173V (12%), T304I (74%)	A173V (12%), T304I (74%)	T21I (78%), L50F (6%), S144A (43%), A191V (5%), T304I (71%)
6	T304I (73%)	A173V (5%), T304I (75%)	A173V (93%), T304I (74%)	A173V (93%), T304I (74%)	T21I (99%), S144A (94%), T304I (73%)
7	T304I (75%)	A173V (93%), T304I (76%)	A173V (93%), T304I (77%)	A173V (89%), T304I (79%)	T21I (100%), S144A (95%), T304I (77%)
8	T304I (82%)	A173V (98%), T304I (80%)	L50F (21%), T135I (6%), A173V (98%), T304I (81%)	ND	T21I (100%), S144A (100%), T304I (83%)
9	T304I (80%)	A173V (97%), T304I (80%)	L50F (20%), A173V (98%), T304I (79%)	ND	T21I (100%), S144A (100%), T304I (81%)

Source: Adapted from (Pfizer 2022g), p. 30-31.
Abbreviations: M^{pro}, main protease; ND, no data, as viruses could not be recovered; NIR, nirmatrelvir; P-gp, P-glycoprotein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

To determine whether the selected viruses had reduced susceptibility to NIR, the Applicant plaque-purified a total of 88 viruses from scheme #3, passage 7 and scheme #5, passages 4-5. The viruses were screened by Sanger sequencing to identify M^{pro} substitutions. Six viruses with different M^{pro} substitutions were selected for additional analysis. These viruses were further propagated in the absence and presence of NIR to produce virus stocks and prevent reversion of M^{pro} substitutions. The virus stocks were then sequenced by whole-genome Illumina sequencing to confirm the presence of the expected substitutions. NIR activity was then determined against the 6 viruses in Vero E6 P-gp knockout cells by nsp10 qRT-PCR assay. In most cases, the viruses further propagated in the presence of NIR were used for these experiments. However, the virus propagated in the absence of NIR was used for T304I.

The 6 viruses tested had M^{pro} T304I, T21I+T304I, L50F+T304I, T135I+T304I, A173V+T304I, or T21I+S144A+T304I substitutions (Table 227). For most viruses, the expected M^{pro} substitutions had frequencies ≥97%, but the L50F and T304I substitutions had frequencies of 49% and 80-82%, respectively. In response to an Information Request, the Applicant indicated that the T304I results may have been affected by a sequencing artifact. When sequencing was repeated with a different methodology, the T304I frequency in plaque-purified viruses was 99-100%. The Applicant did not comment on whether sequencing artifacts may have also been

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responsible for the low frequency of L50F (49%) in plaque-purified virus. Relative to the parental virus (USA-WA1/2020, historical aggregate of 23 experiments), all 6 viruses had significantly reduced susceptibility to NIR. The virus with the T304I substitution alone had 3.4-fold reduced susceptibility to NIR (based on geometric mean EC_{50} value). The viruses with T21I + T304I, L50F + T304I, T135I + T304I, and A173V + T304I double substitutions had 3.8- to 20.2-fold reduced susceptibility to NIR, while the virus with the T21I + S144A + T304I triple substitution had 27.8-fold reduced susceptibility to NIR. All of the viruses remained fully susceptible to remdesivir. Overall, these results indicate that most of the M^{pro} substitutions contributed to NIR resistance, with the possible exception of T135I.

Table 227. Activity of NIR Against Plaque-Purified SARS-CoV-2 With M^{pro} Substitutions

		EC_{50} (nM)					EC_{90} (nM)				
M^{pro} Substitutions (Frequency)	n	GMean	95% CI Low Bound	95% CI High Bound	Fold-Change	p-value	GMean	95% CI Low Bound	95% CI High Bound	Fold-Change	p-value
none (control)	23	34.8	25.7	47.0	N/A	N/A	154	118	200	N/A	N/A
T304I (82%)	3	118	24.2	574	3.4	0.02	420	143	1,232	2.7	0.02
T21I (100%), T304I (81%)	3	275	136	554	7.9	<0.001	568	279	1,159	3.7	0.002
L50F (49%), T304I (80%)	4	205	72.4	582	5.9	<0.001	783	496	1,236	5.1	<0.001
T135I (100%), T304I (80%)	4	134	62.0	288	3.8	0.002	353	153	814	2.3	0.04
A173V (97%), T304I (82%)	3	702	150	3,287	20.2	<0.001	1,631	512	5,190	10.6	<0.001
T21I (100%), S144A (100%), T304I (82%)	4	967	438	2,136	27.8	<0.001	2,548	1,517	4,280	16.6	<0.001

Source: Adapted from (Pfizer 2022g), p. 35.
Note: P-values were determined by one-way ANOVA with Dunnett's post-test to compare EC_{50} values of each virus to the control virus (WA1/2020).
Abbreviations: CI, confidence interval; EC_{50}, half-maximal effective concentration; EC_{90}, 90% effective concentration; GMean, geometric mean; M^{pro}, main protease; n, number of experiments; N/A, not applicable; SARS-CoV-2, severe acute respiratory syndrome 2

Of the 7 distinct M^{pro} substitutions observed (T21I, L50F, T135I, S144A, A173V, A191V, and T304I), 6/7 (all except T135I) have been associated with NIR resistance in cell culture by other groups, usually in combination with other M^{pro} substitutions (Zhou et al. 2022b; Iketani et al. 2023; Jochmans et al. 2023). In addition, the T21I + T304I, L50F + T304I, A173V + T304I, and T21I + S144A + T304I double or triple substitutions have all been associated with NIR resistance in other studies, although other M^{pro} substitutions were present as well in some cases. In biochemical assays (Section 20.1), the S144A and A173V substitutions significantly affected NIR activity (K_i fold-change ≥3), while the T21I, L50F, T135I, A191V, and T304I substitutions did not. Of the substitution combinations, the T135I + T304I, A173V + T304I, and T21I + S144A + T304I substitutions significantly affected NIR activity, while the T21I + T304I and L50F + T304I substitutions did not. Notably, the T304I substitution is located near the C-terminus of M^{pro}, which overlaps the nsp5/nsp6 M^{pro} cleavage site. T304I is located in the P3 position of the cleavage site and may affect binding of the nsp5/nsp6 cleavage site or M^{pro} autocleavage (Iketani et al. 2023). The finding that T304I did not affect NIR activity in biochemical assays (in which T304I was introduced into M^{pro} but not the peptide substrate) is

consistent with this hypothesis. M^{pro} substitutions at several other cleavage sites were also observed (not shown) but only sporadically and at low frequencies (3-6%).

These studies had several limitations. The findings were not confirmed with recombinant viruses. Replication kinetics in the absence of NIR were not determined. Alternative resistance pathways may have been missed, as a single virus stock was used to initiate the infections, and the first passage was shared for 4/5 passaging schemes. No data were provided regarding the structural or mechanistic basis of resistance.

Selection of NIR-Resistant SARS-CoV-2 in A549-ACE2 Cells (Pfizer 2022c)

The Applicant also selected NIR-resistant SARS-CoV-2 (USA-WA1/2020) in A549-ACE2 cells. The activity of NIR against SARS-CoV-2 WA1/2020 in A549-ACE2 cells was first determined by virus yield reduction assay. A549-ACE2 cells were infected in the presence of NIR for 2 days, followed by collection of supernatants and virus titration in Vero E6 cells by plaque assay. NIR had an EC_{50} value of ~50 nM in this assay. SARS-CoV-2 was serially passaged 7 times with NIR concentrations increasing from 300 nM ($6xEC_{50}$) to 2,500 nM ($50xEC_{50}$). These experiments were conducted using a single virus stock. Cells were infected at an MOI of 0.1 for passages 1-2, 0.01 for passage 3, and 0.001 for passages 4 to 7. Each passage lasted 3 to 6 days. After each passage, virus titers (pfu/mL) were determined by plaque assay in Vero E6 cells. In addition, viral RNA was extracted after each passage, and M^{pro} and M^{pro} cleavage site substitutions were identified by whole-genome Illumina sequencing.

After passage 3, an A173V M^{pro} substitution was detected at a high frequency (96%, Table 228). The A173V M^{pro} substitution remained predominant through passage 7, and no other major M^{pro} substitutions were detected. However, several M^{pro} substitutions were sporadically observed at low frequencies (3-9%), including I78F, K90R, S144A, and L205V. Virus titers were low after passages 6 to 7. The passaged viruses were also found to form smaller plaques in A549-ACE2 cells (in the absence of NIR), possibly indicating a replication defect. Thus, passage 6 and 7 viruses were plaque-purified and expanded in A549-ACE2 cells (in the absence of NIR), and 10 plaques were sequenced. The plaque-purified viruses were found to contain F140L + A173V M^{pro} substitutions. It is unclear why the F140L substitution was only detected in plaque-purified viruses.

Table 228. Sequencing of SARS-CoV-2 Passaged in the Presence of NIR in A549-ACE2 Cells

Passage	NIR (nM)	EC_{50} Multiples	Sample Description	M^{pro} Substitutions ≥50% (Frequency)
1	300	6×	Pooled Sample	none
2	300	6×	Pooled Sample	none
3	1,250	25×	Pooled Sample	A173V (96%)
4	1,250	25×	Pooled Sample	A173V (96%)
	2,000	40×	Pooled Sample	A173V (94%)
5	2,000	40×	Pooled Sample	A173V (93%)
	2,500	50×	Pooled Sample	A173V (88%)

Passage	NIR (nM)	EC_{50} Multiples	Sample Description	M^{pro} Substitutions ≥50% (Frequency)
6	2,000	40×	Pooled Sample	A173V (86%)
			Plaque-Purified	F140L (99%)+A173V (97%)
	2,500	50×	Pooled Sample	A173V (71%)
			Plaque-Purified	F140L (99%)+A173V (96%)
7	2,000	40×	Pooled Sample	A173V (85%)
			Plaque-Purified	F140L (98%)+A173V (96%)
	2,500	50×	Pooled Sample	A173V (65%)
			Plaque-Purified	F140L (99%)+A173V (98%)

Source: Adapted from (Pfizer 2022c), p. 17.
Abbreviations: EC_{50}, half-maximal effective concentration; M^{pro}, main protease; NIR, nirmatrelvir; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

The activity of NIR against two passaged viruses was determined in Vero E6-TMPRSS2 cells by nsp10 qRT-PCR assay. These experiments were performed in the presence of 2,000 nM CP-100356 (P-gp inhibitor). NIR inhibited replication of the parental virus (SARS-CoV-2 WA1/2020) with a geometric mean EC_{50} value of 61 nM (Table 229). NIR had similar activity against the P5 virus with the A173V substitution, indicating that the A173V substitution alone may not confer significant NIR resistance, as reported by others (Zhou et al. 2022b; Iketani et al. 2023). However, NIR had significantly reduced activity against the P7 virus with F140L+A173V substitutions, with a 10.1-fold higher EC_{50} value. This virus remained fully susceptible to remdesivir.

Table 229. Activity of NIR Against SARS-CoV-2 With M^{pro} Substitutions

Virus (M^{pro} Substitutions)	N	EC_{50} (nM) Geomean	EC_{50} (nM) Fold-Change	EC_{50} (nM) p-value	EC_{90} (nM) Geomean	EC_{90} (nM) Fold-Change	EC_{90} (nM) p-value
Control (none)	3	61	N/A	N/A	327	N/A	N/A
P5 (A173V)	3	57	0.9	0.88	130	0.4	0.006
P7 (F140L+A173V)	3	614	10.1	<0.001	1,308	4.0	<0.001

Source: Adapted from (Pfizer 2022c), p. 18.
Notes: P-values were determined by Dunnett t-test.
Abbreviations: EC_{50}, half-maximal effective concentration; EC_{90}, 90% maximal effective concentration; Mpro, main protease; N/A, not applicable; NIR ,nirmatrelvir; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Both the F140L and A173V M^{pro} substitutions have been associated with NIR resistance in cell culture by independent groups (Zhou et al. 2022b; Iketani et al. 2023). However, the F140L + A173V double substitution has not been observed by others. In biochemical assays (Section 20.1), the F140L, A173V, and F140L + A173V substitution led to 7.6-, 16-, and 95-fold higher K_i values, respectively, indicating that both substitutions contribute to resistance. These studies had several limitations. The findings were not confirmed with recombinant viruses. Replication kinetics in the absence of NIR were not determined. Alternative resistance pathways may have been missed, as a single virus stock was used to initiate the infections. No data were provided regarding the structural or mechanistic basis of resistance.

NIR Activity Against Recombinant SARS-CoV-2 Encoding M^{pro} Substitutions (Pfizer 2022l)

To determine the impact of M^{pro} substitutions on NIR activity in cell culture, the Applicant generated recombinant SARS-CoV-2 (WA1/2020-based) viruses using a previously described system (Xie et al. 2020a). The Applicant attempted to generate viruses with Mpro $G1^{5S,}$ Y54A,

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E55L, E55L + S144A, L89F, K90R, F140A, S144A/E/L/P/T, H164N, E166A/V, H172Y, and Q189K substitutions. The E166V substitution was chosen because it was identified in several NIR-treated participants in trial EPIC-HR. The L89F and K90R substitutions were chosen because they represent naturally occurring polymorphisms that were not expected to affect NIR activity. The other substitutions were chosen because they significantly affected NIR activity in a biochemical assay and/or were identified in NIR-selected MHV. These substitutions were chosen prior to completion of the Applicant's studies on NIR-selected SARS-CoV-2 in cell culture and the publication of similar studies by independent groups. Only S144A, E166A/V, and H172Y have been associated with SARS-CoV-2 resistance to NIR in cell culture (Zhou et al. 2022b; Iketani et al. 2023; Jochmans et al. 2023).

The Applicant successfully generated 9/17 recombinant viruses with M^{pro} substitutions, while 8/17 viruses could not be generated because: 1. virus was not recovered, or 2. virus was recovered but did not encode the expected M^{pro} substitution (Table 230). In 2 cases (H164N and E166A), the initial virus recovered contained a mixture of sequences, but viruses encoding only the desired substitution were obtained by plaque purification. All virus stocks, whether produced by bulk passaging or plaque purification, were analyzed by Illumina sequencing to confirm the presence of only the desired substitutions.

The activity of NIR against recombinant SARS-CoV-2 viruses was tested in Vero E6 P-gp knockout cells by N qRT-PCR assay. Cells were infected at an MOI of 0.04 in the presence of NIR and incubated for 48 hr, followed by in-plate lysis and qRT-PCR. NIR inhibited the replication of WT SARS-CoV-2 (WA1/2020) with a mean EC_{50} value of 37 nM (Table 230). Of the 9/17 viruses successfully generated, only the virus with the E166A substitution had significantly reduced susceptibility to NIR, with an ~3.3-fold higher EC_{50} value. The virus with the S144A substitution had a 2.5-fold higher EC_{50} value, although the difference was not statistically significant. The S144A and E166A substitutions led to 46- and 35-fold reduced NIR activity in a biochemical assay (Table 211), respectively.

Table 230. Activity of NIR Against Recombinant SARS-CoV-2 With M^{pro} Substitutions

		EC_{50} (nM)			EC_{90} (nM)		
Virus	n	Mean	Fold-Change	p-Value	Mean	Fold-Change	p-value
WT	18	37	N/A	N/A	100	N/A	N/A
G15S	3	26	0.7	0.97	64	0.6	0.91
Y54A[a]	--	--	--	--	--	--	--
E55L	4	66	1.8	0.59	133	1.3	0.99
E55L+S144A[b]	--	--	--	--	--	--	--
L89F	3	48	1.3	1.00	212	2.1	0.41
K90R	3	56	1.5	0.94	113	1.1	1.00
F140Aa	--	--	--	--	--	--	--
S144A	4	94	2.5	0.08	195	1.9	0.41
S144E[a]	--	--	--	--	--	--	--
S144L[a]	--	--	--	--	--	--	--
S144P[a]	--	--	--	--	--	--	--
S144T[a]	--	--	--	--	--	--	--
H164N	3	71	1.9	0.58	158	1.6	0.91

		EC_{50} (nM)			EC_{90} (nM)		
Virus	n	Mean	Fold-Change	p-Value	Mean	Fold-Change	p-value
E166A	5	122	3.3	0.004	535	5.3	<0.001
E166V[a]	--	--	--	--	--	--	--
H172Y[a]	--	--	--	--	--	--	--
Q189K	4	8	0.2	<0.001	24	0.2	0.002

Source: Adapted from (Pfizer 2022l), p. 24.
Note: P-values were determined by Dunnett t-test.
[a.] No data (viruses could not be recovered)
[b.] Experiments in progress.
Abbreviations: EC_{50}, half-maximal effective concentration; EC_{90}, 90% maximal effective concentration; M^{pro}, main protease; n, number of experiments; N/A, not applicable; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WT, wild-type

In another report, NIR had a 2.2-fold higher EC_{50} value against recombinant SARS-CoV-2 with the M^{pro} S144A substitution, similar to the 2.5-fold change observed by the Applicant (Iketani et al. 2023). Thus, the S144A substitution alone confers only slightly reduced susceptibility to NIR. In two other reports, recombinant SARS-CoV-2 with the M^{pro} E166V substitution was successfully generated and found to have significantly reduced susceptibility to NIR, with 25-288-fold higher EC_{50} values (Zhou et al. 2022b; Iketani et al. 2023). The main limitation of the Applicant's study is that most of the M^{pro} substitutions (and combinations of substitutions) that were identified in NIR-selected SARS-CoV-2 (by the Applicant and others) have not yet been tested.

Other Studies Related to NIR Resistance in Cell Culture

- In Iketani et al., SARS-CoV-2 WA1/2020 was passaged in Vero E6 cells in the presence of NIR (Iketani et al. 2023). Three cultures were passaged. Culture #1 acquired 5 M^{pro} substitutions (T21I, C160F, A173V, V186A, T304I) and had 28.5-fold reduced susceptibility to NIR (based on EC_{50} value). Culture #2 acquired 4 M^{pro} substitutions (T21I, L50F, A193P, S301P) and had 28.8-fold reduced susceptibility to NIR. Culture #3 acquired 4 M^{pro} substitutions (L50F, F140L, L167F, T304I) and had 54.7-fold reduced susceptibility to NIR. SARS-CoV-2 was also passaged in Huh7-ACE2 cells in 480 wells, leading to the identification of 53 NIR-resistant cultures. Fourteen M^{pro} substitutions were identified in at least 2 cultures: T21I, L50F, P108S, S144A, E166A/V, T169I, H172Y, A173V, V186A, R188G, P252L, S301P, and T304I. Note that the S301P and T304I substitutions overlap the P6 and P3 positions, respectively, of the nsp5/nsp6 cleavage site.
- In Jochmans et al., (preprint), SARS-CoV-2 GHB-0302 was passaged in Vero E6 cells in the presence of the M^{pro} inhibitor ALG-097161 (Jochmans et al. 2023). The passaged virus acquired M^{pro} L50F, E166A, and L167F substitutions and was cross-resistant to NIR, with a 51-fold higher EC_{50} value. Recombinant SARS-CoV-2 (WA1/2020-based) with the L50F, E166A + L167F, and L50F + E166A + L167F substitutions had 1.5-, 10.0-, and 29-fold higher EC_{50} values, respectively, than WT virus.
- In Zhou et al., SARS-CoV-2 /DK-AHH1/2020 was passaged in Vero E6 cells in the presence of NIR or the HCV NS3/4A protease inhibitor boceprevir (Zhou et al. 2022b). Boceprevir is known to have activity against SARS-CoV-2 M^{pro} (Ma et al. 2020). Two viruses passaged in the presence of boceprevir were found to have reduced susceptibility to NIR (5-6-fold higher EC_{50} values): one with M^{pro} L50F, C160F, A173V, and A191V substitutions and one with M^{pro} L50F and A173V substitutions. Another virus passaged in the presence of NIR acquired

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M^{pro} T21I and T304I substitutions and had 4-6-fold higher EC_{50} values. One additional virus passaged in the presence of NIR acquired M^{pro} L50F and E166V substitutions and had 78-175-fold higher EC_{50} values.

- Table 231 contains a list of all SARS-CoV-2 M^{pro} substitutions that were associated with NIR resistance in cell culture, either in the Applicant's studies or the studies described above. These substitutions were observed in numerous combinations. Refer to the cited studies for lists of all combinations that have been identified to date.

Table 231. SARS-CoV-2 M^{pro} Substitutions Associated With NIR Resistance in Cell Culture Across Different Studies

M^{pro} Substitution	Contact[1]	Biochemical Assay K_i Fold-Change	Applicant's Selection Studies	(Iketani et al. 2023)	(Jochmans et al. 2023)	(Zhou et al. 2022b)
T21I	No	1.6	X	X		X
L50F	No	0.2	X	X	X	X
P108S	No	2.9		X		
T135I	No	2.3	X			
F140L	Yes	7.6	X	X		
S144A	Yes	46	X	X		
C160F	No	0.6		X		X
E166A/V	Yes	35/7,700		X	X	X
L167F	Yes	<0.9		X	X	
T169I	No	<1.4		X		
H172Y	Yes	250		X		
A173V	No	16	X	X		X
V186A	Yes	<0.8		X		
R188G	Yes	38		X		
A191V	Yes	<0.8	X			X
A193P	No	0.9		X		
P252L	No	<0.9		X		
S301P[2]	No	0.2[e]		X		
T304I[2]	No	1.0[e]	X	X		X

Source: FDA analysis and pooled summary of Applicant's nonclinical virology/resistance reports and noted literature references.
[1.] This column indicates residues in direct contact or close proximity (<5 Å) with NIR based on the Applicant's co-crystal structural analysis.
[2.] Note that S301P and T304I overlap the P6 and P3 positions, respectively, of the nsp5/nsp6 cleavage site located at the C-terminus of M^{pro}.
Note: Shading indicates substitutions that were observed in at least 2 studies.
Note: Biochemical data are from (Pfizer 2022h). For (Iketani et al. 2023), M^{pro} substitutions associated with NIR resistance in Huh7-ACE2 cells are only listed if they were observed in ≥2 cultures.
Abbreviations: K_i, inh bition constant; M^{pro}, main protease; ND, no data; NIR, nirmatrelvir; nsp, nonstructural protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

20.3.2. Cross-Resistance

Currently, NIR (in combination with ritonavir) is the only authorized M^{pro} inhibitor for the treatment of COVID-19. As described above, remdesivir retains activity against NIR-resistant SARS-CoV-2 in cell culture, as expected based on these products' distinct mechanisms of action. Similar findings have been reported by others (Zhou et al. 2022b; Iketani et al. 2023). The Applicant has not investigated the activity of NIR against SARS-CoV-2 viruses that are resistant to other antivirals approved or authorized by the FDA for COVID-19. However, NIR is expected to retain activity against such viruses due to its distinct mechanism of action. NIR is known to

exhibit partial cross-resistance with other SARS-CoV-2 M^{pro} inhibitors under development (Iketani et al. 2023).

20.3.3. Drug Resistance in Clinical Studies

Refer to Section 18: Clinical Virology.

20.4. Updated Nonclinical Virology/Resistance Data

Late in the review cycle, and after reviewing the data described in the sections above, the Applicant submitted the following nonclinical virology data on the activity of nirmatrelvir against additional SARS-CoV-2 Omicron sub-variants and phenotyping of M^{pro} substitutions using biochemical assays and recombinant viruses.

Nirmatrelvir Activity Against Additional SARS-CoV-2 Omicron Sub-Variants

In Report 042713 (v8), the Applicant determined the activity of NIR against SARS-CoV-2 USA-WA1/2020, BA.4.6, BF.7 (x2), BQ.1, BQ.1.11, and XBB.1.5 variants in Vero E6-TMPRSS2 cells by qRT-PCR, using the method described in Section 20.2.1 (Pfizer 2023c). NIR activity was tested in the presence of 2,000 nM CP-100356 (P-gp inhibitor). NIR retained activity against the
SARS-CoV-2 Omicron sub-variants BA.4.6, BF.7 (x2), BQ.1, BQ.1.11, and XBB.1.5, with fold-changes in geometric mean EC_{50} and EC_{90} values ≤1.5 relative to USA-WA1/2020 (Table 232).

Table 232. NIR Activity Against Additional SARS-CoV-2 Omicron Subvariants in Vero E6-TMPRSS2 Cells (With P-gp Inhibitor)

Variant	M^{pro} Polymorphism	n	Geomean EC_{50} (nM) (Range)	EC_{50} FC	Geomean EC_{90} (nM) (Range)	EC_{90} FC
USA-WA1/2020	N/A	30	99 (42-228)	N/A	218 (86-478)	N/A
Omicron BA.4.6	P132H	3	146 (116-200)	1.5	294 (239-414)	1.3
Omicron BF.7	P132H+T243I	4	76 (58-104)	0.8	157 (119-213)	0.7
Omicron BF.7	P132H+P252L+F294L	5	108 (59-190)	1.1	240 (174-397)	1.1
Omicron BQ.1	P132H	3	104 (79-126)	1.1	215 (158-266)	1.0
Omicron BQ.1.11	P132H	2[a]	90 (55-124)	0.9	190 (121-259)	0.9
Omicron XBB.1.5	P132H	6	113 (37-200)	1.1	228 (79-385)	1.0

Source: Adapted from (Pfizer 2023c), p. 19-20.
a. Mathematical average (n=2), not geomean.
Abbreviations: EC_{50}, half-maximal effective concentration; EC_{90}, 90% maximal effective concentration; FC, fold-change; Geomean, geometric mean; M^{pro}, main protease; n, number of experiments; N/A, not applicable; P-gp, P-glycoprotein; Polymorphs, polymorphisms; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Phenotypic Analysis of Additional M^{pro} Substitutions

In Report 121015 (v7), the Applicant determined the activity of NIR against recombinant SARS-CoV-2 M^{pro} enzymes with several additional substitutions in biochemical assays, using the method described in Section 20.1 (Pfizer 2023b). In total, 12 new enzymes were tested, which had
P108L, V186F, A193T/V, V202F/G/L, W207L, A260S/T, K269R, or T21I + C160F + A173V +

V186A + T304I substitutions. These substitutions were tested because they were: a) associated with PAXLOVID treatment in EPIC-HR, b) associated with nirmatrelvir resistance in cell culture, or c) were observed at nirmatrelvir contact or close proximity residues in the GISAID sequence database. Of these, only T21I + C160F + A173V + V186A + T304I significantly affected nirmatrelvir activity, with a 28-fold higher geometric mean K_i value compared to WT enzyme. The other substitutions did not significantly affect nirmatrelvir activity, with the following geometric mean K_i value fold-changes: P108L (0.3), V186F (0.5), A193T/V (0.5/0.4), V202F/G/L (0.6/0.4/0.3), W207L (0.7), A260S/T (0.3/0.5), and K269R (0.7).

In Report 024518 (v5), the Applicant determined the activity of NIR against recombinant SARS-CoV-2 viruses with several additional M^{pro} substitutions in Vero E6 P-gp knockout or Vero E6-TMPRSS2 cells (+2,000 nM CP-100356, P-gp inhibitor), using the method described in Section 20.3.1 (Pfizer 2023d). The Applicant attempted to generate 14 viruses, which had M^{pro} F140I/L/S, S144A, E166G, A173S/T, A191V, Q192L, T304I, E55L + S144A, S144A + T304I, E166G + L232I, and T21I + A260V + T304I substitutions. Of these, 4/14 viruses (F140I/S, A173T, and A191V) could not be generated because the virus could not be recovered or lacked the desired substitutions. Of the 10/14 viruses successfully recovered, 6/10 had significantly reduced susceptibility to NIR, with the following mean EC_{50} value fold-changes relative to WA1-2020: F140L (4.1), S144A (5.3), A173S (3.2), E55L + S144A (6.5), S144A + T304I (3.1), and T21I + A260V+T304I (3.2). NIR retained activity (EC_{50} value fold-change <3) against the other 4/10 viruses, with the following mean EC_{50} value fold-changes: E166G (1.1), Q192L (1.2), T304I (1.4), and E166G+L232I (2.9).

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22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

Please refer to Section 6.3.1.

23. Labeling: Key Changes and Considerations

Prescribing Information

Prescribing Information Labeling Review

Applicant's proposed labeling submitted on June 29, 2022, was compared with final agreed upon labeling. This review summarizes the major label changes and provides a cross reference to other sections of the Integrated Review for additional details and rationale for the labeling changes. Edits to highlights and table of contents were made to capture changes to the full prescribing information.

General Changes to Prescribing Information

BOXED WARNING

The following Boxed Warning to alert healthcare providers of the significant drug interactions with PAXLOVID was added. See Section 7.7.1 for additional detail.

WARNING: SIGNIFICANT DRUG INTERACTIONS WITH PAXLOVID

- **PAXLOVID includes ritonavir, a strong CYP3A inhibitor, which may lead to greater exposure of certain concomitant medications, resulting in potentially severe, life-threatening, or fatal events *[see Contraindications (4), Warnings and Precautions (5.1), and Drug Interactions (7)].***
- **Prior to prescribing PAXLOVID: 1) Review all medications taken by the patient to assess potential drug-drug interactions with a strong CYP3A inhibitor like PAXLOVID and 2) Determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring *[see Drug Interactions (7)].***
- **Consider the benefit of PAXLOVID treatment in reducing hospitalization and death, and whether the risk of potential drug-drug interactions for an individual patient can be appropriately managed *[see Warnings and Precautions (5.1), Drug Interactions (7), and Clinical Studies (14)].***

1 INDICATIONS AND USAGE

Indications statement was modified (b) (4) See Section 8.3 for additional detail.

Limitations of Use: Removed the LOU [redacted] See Section 6.3.5 for additional detail.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Information

Included additional description of the two different dose packs available for PAXLOVID to avoid potential medication error.

[redacted]

4 CONTRAINIDCATIONS

Added the following under the drug interaction contraindication to alert healthcare providers of important qualifications related to list of contraindicated drugs listed in this section: There are certain other drugs for which concomitant use with PAXLOVID should be avoided and/or dose adjustment, interruption, or therapeutic monitoring is recommended. Drugs listed in this section are a guide and not considered a comprehensive list of all drugs that may be contraindicated with PAXLOVID. The healthcare provider should consult other appropriate resources such as the prescribing information for the interacting drug for comprehensive information on dosing or monitoring with concomitant use of a strong CYP3A inhibitor [redacted] *[see Drug Interactions (7.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Adverse Reactions Due to Drug Interactions

- Highlighted [redacted], life-threatening, and/or fatal adverse reaction due to drug interactions with calcineurin inhibitors (e.g., tacrolimus, cyclosporine) and calcium channel blockers.
- Provided risk mitigation steps to healthcare provider to avoid potentially significant drug interactions including review all medications taken by the patient to assess potential drug-drug interactions and determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring.
- Added benefit risk statement of considering the benefit of PAXLOVID versus risk of potential DDI.

5.2 Hypersensitivity Reactions

- Added serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson syndrome (SJS)). See Section 7.6.3.3 for additional detail.

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6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

- [redacted] (b) (4) was removed. See Section 7.6.2 for additional detail. Added safety data from EPIC-SR (vaccinated or unvaccinated subjects at standard risk of fully vaccinated subjects with at least 1 risk factor for progression to severe disease).
- Moved adverse reactions reported under EUA [redacted] (b) (4) to subsection 6.1 Clinical Trials Experience and added the following additional events: anaphylaxis, Toxic Epidermal Necrolysis, Stevens-Johnsons syndrome, headache, hypertension, and vomiting.

7 DRUG INTERACTIONS

7.3 Established and Other Potentially Significant Drug Interactions

Added the following additional drug interactions to Table 1. Established and Other Potentially Significant Drug Interactions: tamsulosin, apixaban, primidone, clonazepam, rifapentine, silodosin, eplerenone, ivabradine, aliskiren, ticagrelor, vorapaxar, clopidogrel, cilostazol, lumacaftor/ivacaftor, elexacaftor/tezacaftor/ivacaftor, tezacaftor/ivacaftor, saxagliptin, voclosporin, everolimus, tofacitinib, upadacitinib, lomitapide, eletriptan, ubrogepant, Rimegepant, finerenone, darifenacin, hydrocodone, oxycodone, meperidine, suvorexant, aripiprazole, brexpiprazole, cariprazine, iloperidone, lumateperone, pimavanserin, naloxegol, tadalafil, riociguat, avanafil, vardenafil, buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem, tolvaptan with appropriate clinical comments.

Most of these additions mirrored additions to the EUA Fact Sheet for Healthcare Providers during the course of the NDA review (please see the EUA review memos for more details).

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

[redacted] (b) (4) has been removed and replaced with the following statement: The optimal dose of PAXLOVID has not been established in pediatric patients.

8.5 Geriatric Use

The following statement was added: No overall differences in safety were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in safety between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Changed mechanism of action (MoA) to nirmatrelvir is a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antiviral drug. Additional details moved to Section 12.4 for consistency with other antiviral drug labels.

12.2 Pharmacodynamics

Removed [redacted], and a high-level summary of clinical antiviral activity was added to Section 12.4 Microbiology.

12.3 Pharmacokinetics

[redacted] The predicted Day 5 nirmatrelvir exposure parameters in adult subjects with mild-to-moderate COVID-19 who were treated with PAXLOVID in EPIC-HR are presented in Table 3 of the USPI. Additional PK parameters from healthy subjects were added to Table 2 of the USPI including food effect and the percentage of dose excreted as total (unchanged drug) in feces and urine.

12.4 Microbiology

Section was modified and expanded to describe MoA (details moved from 12.1, see above), add updated data on nirmatrelvir antiviral activity against different SARS-CoV-2 variants, add high level summary of clinical antiviral activity [redacted], remove [redacted] re-organized and included additional details on potential resistance-associated substitutions, describe resistance-associated substitutions detected in subjects with viral RNA rebound, and include a brief summary of analyses of symptom rebound. See Sections 18 and 20 for additional detail.

[redacted]

14 CLINICAL STUDIES

14.1 Efficacy in Subjects at High Risk for Progressing to Severe COVID-19

- Included COVID-19 related hospitalization through Day 28 in Table 8 USPI, the efficacy table for EPIC-HR.
- Added secondary endpoint of all-cause mortality through Week 24 for PAXLOVID and placebo in footnote of Table 8 of USPI.
- Added data on COVID-19 related hospitalization or death from any cause through Day 28, with confidence interval, in subjects who were SARS-CoV-2 seropositive at baseline.
- See Section 6.2.1.4 for additional detail.

14.2 [redacted] Unvaccinated Subjects Without a Risk Factor for Progression to Severe COVID-19 or Subjects Fully Vaccinated Against COVID-19 With at Least One Factor for Progression to Severe COVID-19

- Removed [redacted] and included statement that primary endpoint of the trial was the difference in time to sustained alleviation of all

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targeted COVID-19 signs and symptoms through Day 28 among PAXLOVID versus placebo recipients was not met.

- Added the following: In an exploratory analysis of the subgroup of fully vaccinated subjects with at least 1 risk factor for progression to severe disease, a non-statistically significant numerical reduction relative to placebo for the secondary endpoint of COVID-19 related hospitalization or death from any cause through Day 28 was observed.
- See Section 6.2.2.4 for additional detail.

14.3 Post-Exposure Prophylaxis

Removed [redacted] (b) (4) and included the following: The primary endpoint for this trial was not met. PAXLOVID is not indicated for post-exposure prophylaxis of COVID-19. See Section 6.2.3.4 for additional detail.

Packaging

The proposed packaging of the PAXLOVID commercial product, including the carton labeling and container labels, was reviewed for areas of vulnerability that may lead to medication errors. The final packaging incorporated Agency recommendations to maximize safe use. Differences between the commercial packaging and the PAXLOVID packaging under EUA include the following:

- Each carton will contain ten single dose blister cards, rather than five blister cards containing both the morning and the evening dose.
- Bolding, font size, and language were adjusted and arrows were added to the container labels to further clarify dosing instructions.
- The size, color, language, and placement of language on the carton labeling were adjusted to further distinguish the dose pack for patients with moderate renal impairment from the dose pack for patients with normal renal function or mild renal impairment.
- The carton labeling was revised to include the following alert to patients: “Find out about medicines that should not be taken with Paxlovid.”

For further details, please refer to the Office of Surveillance and Epidemiology (OSE) Label and Labeling Reviews by Melina Fanari, Madhuri Patel, and Mishale Mistry from September 1 and December 12, 2022, and the OSE Reviews of Revised Label and Labeling by Melina Fanari and Madhuri Patel from January 9 and May 2, 2023 (DARRTS ID: 5077785 2022).[20]

[20] The referenced documents contain proprietary data obtained by FDA and cannot be released to the public. The information contained within is the result of an OSE review as part of PAXLOVID, NDA 217188. The source documents can only be accessed by authorized individuals.

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23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- USPI
- Patient package insert (PPI)
- Carton and container labeling

24. Postmarketing Requirements and Commitments

24.1. Postmarketing Requirements

The following postmarketing requirements (PMRs) will be issued at the time of approval (note that wording changes may occur between those listed below and in the approval letter):

24.1.1. Pediatric Research Equity Act PMR 4392-1

Conduct a study to evaluate the safety, tolerability, pharmacokinetics, and treatment response of PAXLOVID in pediatric subjects 6 to less than 18 years of age and weighing 20 kg or higher, with mild-to-moderate coronavirus disease 2019 (COVID-19).

24.1.2. Pediatric Research Equity Act PMR 4392-2

Conduct a study to evaluate the safety, tolerability, pharmacokinetics, and treatment response of PAXLOVID in pediatric subjects 2 to less than 6 years of age, with mild-to-moderate coronavirus disease 2019 (COVID-19).

24.1.3. Pediatric Research Equity Act PMR 4392-3

Conduct a study to evaluate the safety, tolerability, pharmacokinetics, and treatment response of PAXLOVID in pediatric subjects from birth to less than 2 years of age, with mild-to-moderate coronavirus disease 2019 (COVID-19).

24.1.4. PMR 4392-4

Conduct studies to characterize the phenotypic effects of the following amino acid substitutions on nirmatrelvir anti-SARS-CoV-2 activity: M^{pro} substitutions G11V, L30I, T45N, A94V, T98I/R/del, V104I, W207/R/del, F223L, H246Y; M^{pro} cleavage site substitutions A3571V, V3855I, A5328S/V, S6799A. M^{pro} substitutions can be evaluated in biochemical assays using recombinant M^{pro} proteins or cell culture assays using recombinant SARS-CoV-2 viruses or replicons. The M^{pro} cleavage site substitutions should be evaluated in cell culture assays using recombinant SARS-CoV-2 viruses or replicons.

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24.1.5. PMR 4392-5

Conduct a study to monitor genomic database(s) for the emergence of SARS-CoV-2 variants with amino acid polymorphisms in M^{pro} or M^{pro} cleavage sites. Conduct surveillance activities on at least a monthly basis. Conduct phenotypic analysis for any M^{pro} or M^{pro} cleavage site polymorphisms that are detected at a frequency ≥1% either globally or in the U.S. for any single month. These surveillance activities should continue for a period of 3 years post-approval, with re-assessment of the duration, frequency of reporting and additional protocol methods to occur on an annual basis.

24.1.6. PMR 4392-6

Submit the final report with datasets for the ongoing trial, "A Phase 1, Open-Label, Non-Randomized Study To Investigate The Safety And PK Following Multiple Oral Doses Of PF-07321332 (Nirmatrelvir)/Ritonavir In Adult Participants With COVID-19 And Severe Renal Impairment Either On Hemodialysis Or Not On Hemodialysis" (Study C4671028; NCT05487040).

24.2. Postmarketing Commitments

The following postmarketing commitments (PMCs) will be issued at time of approval (note that wording changes may occur between those listed below and in the approval letter):

24.2.1. PMC 4392-7

Submit the final study report with datasets for the ongoing trial, "An Interventional Efficacy And Safety, Phase 2, Randomized, Double-Blind, 3-Arm Study To Investigate Nirmatrelvir/Ritonavir In Nonhospitalized Participants At Least 12 Years Of Age With Symptomatic COVID-19 Who Are Immunocompromised" (Study C4671034; NCT05438602).

24.2.2. PMC 4392-8

Submit the final study report with datasets for the ongoing trial, "A Phase 1, Open-Label Study To Evaluate The Pharmacokinetics, Safety, And Tolerability Of Orally Administered Nirmatrelvir/Ritonavir In Pregnant Women With Mild-To-Moderate COVID-19" (Study C4671035; NCT05386472).

24.2.3. PMC 4392-9

Submit the final study report with datasets for the ongoing trial, "A Phase I, Multiple Dose, Open-Label Pharmacokinetic Study Of Nirmatrelvir/Ritonavir In Healthy Lactating Women" (Study C4671039; NCT05441215).

24.2.4. PMC 4392-10

Conduct an observational study to evaluate pregnancy and infant outcomes following exposure to PAXLOVID during pregnancy.

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24.2.5. PMC 4392-11

Submit the final study report with datasets for the ongoing trial, "An Interventional, Efficacy And Safety, Phase 2, Randomized, Double-Blind, 2-Arm Study To Investigate A Repeat 5-Day Course Of Nirmatrelvir/Ritonavir Compared To Placebo/Ritonavir In Participants At Least 12 Years Of Age With Rebound Of COVID-19 Symptoms And Rapid Antigen Test Positivity" (Study C4671042; NCT05567952).

24.2.6. PMC 4392-12

Conduct a study to evaluate the activity of nirmatrelvir (±ritonavir) in combination with remdesivir against SARS-CoV-2 in cell culture.

24.2.7. PMC 4392-13

Conduct a study using cell culture assays to characterize the effect of nirmatrelvir/ritonavir on the anti-influenza virus activity of (a) oseltamivir and (b) baloxavir, and conversely the effect of (a) oseltamivir and (b) baloxavir on the anti-SARS-CoV-2 activity of nirmatrelvir/ritonavir

24.2.8. PMC 4392-14

Complete the proposed ecotoxicity studies that are currently in progress and update the environmental analysis report.

24.2.9. PMC 4392-15

Submit three-month long-term and accelerated stability data for three batches of nirmatrelvir tablets manufactured at the (b) (4)

25. Financial Disclosure

Table 241. Covered Clinical Studies: C4671002,C4671005, C4671006, C4671008, C4671010, C4671011, C4671012, C4671013, C4671014, C4671015, C4671019

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1955		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 26		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Abbreviation: CFR, Code of Federal Regulations; FDA, Food and Drug Administration

26. References

26.1. Literature

Aarnoutse, RE, KJ Grintjes, DS Telgt, M Stek, Jr., PW Hugen, P Reiss, PP Koopmans, YA Hekster, and DM Burger, 2002, The influence of efavirenz on the pharmacokinetics of a twice-daily combination of indinavir and low-dose ritonavir in healthy volunteers, Clin Pharmacol Ther, 71(1):57-67.

Aarnoutse, RE, J Kleinnijenhuis, PP Koopmans, DJ Touw, J Wieling, YA Hekster, and DM Burger, 2005, Effect of low-dose ritonavir (100 mg twice daily) on the activity of cytochrome P450 2D6 in healthy volunteers, Clin Pharmacol Ther, 78(6):664-674.

Abdelnabi, R, CS Foo, D Jochmans, L Vangeel, S De Jonghe, P Augustijns, R Mols, B Weynand, T Wattanakul, RM Hoglund, J Tarning, CE Mowbray, P Sjo, F Escudie, I Scandale, E Chatelain, and J Neyts, 2022, The oral protease inhibitor (PF-07321332) protects Syrian hamsters against infection with SARS-CoV-2 variants of concern, Nat Commun, 13(1):719.

Adjei, S, K Hong, NM Molinari, L Bull-Otterson, UA Ajani, AV Gundlapalli, AM Harris, J Hsu, SS Kadri, J Starnes, K Yeoman, and TK Boehmer, 2022, Mortality risk among patients hospitalized primarily for COVID-19 during the Omicron and Delta variant pandemic periods - United States, April 2020-June 2022, MMWR Morb Mortal Wkly Rep, 71(37):1182-1189.

Aggarwal, NR, KC Molina, LE Beaty, TD Bennett, NE Carlson, DA Mayer, JL Peers, S Russell, MK Wynia, and AA Ginde, 2023, Real-world use of nirmatrelvir and ritonavir in outpatients with COVID-19 during the era of omicron variants including BA.4 and BA.5 in Colorado, USA: a retrospective cohort study, The Lancet Infectious Diseases.

Anderson, AS, P Caubel, JM Rusnak, and E-HT Investigators, 2022, Nirmatrelvir-ritonavir and viral load rebound in COVID-19, N Engl J Med, 387(11):1047-1049.

Antonelli, G, D Focosi, O Turriziani, M Tuccori, R Brandi, S Fillo, C Ajassa, F Lista, and CM Mastroianni, 2022, Virological and clinical rebounds of COVID-19 soon after nirmatrelvir/ritonavir discontinuation, Clin Microbiol Infect, 28(12):1657-1658.

Arbel, R, Y Wolff Sagy, M Hoshen, E Battat, G Lavie, R Sergienko, M Friger, JG Waxman, N Dagan, R Balicer, Y Ben-Shlomo, A Peretz, S Yaron, D Serby, A Hammerman, and D Netzer, 2022, Nirmatrelvir use and severe Covid-19 outcomes during the Omicron surge, N Engl J Med, 387(9):790-798.

Aydillo, T, AS Gonzalez-Reiche, S Aslam, A van de Guchte, Z Khan, A Obla, J Dutta, H van Bakel, J Aberg, A Garcia-Sastre, G Shah, T Hohl, G Papanicolaou, MA Perales, K Sepkowitz, NE Babady, and M Kamboj, 2020, Shedding of Viable SARS-CoV-2 after Immunosuppressive Therapy for Cancer, N Engl J Med, 383(26):2586-2588.

Bajema, KL, XQ Wang, DM Hynes, M Rowneki, A Hickok, F Cunningham, A Bohnert, EJ Boyko, TJ Iwashyna, ML Maciejewski, EM Viglianti, E Streja, L Yan, M Aslan, GD Huang, and GN Ioannou, 2022, Early Adoption of Anti-SARS-CoV-2 Pharmacotherapies Among US Veterans With Mild to Moderate COVID-19, January and February 2022, JAMA Netw Open, 5(11):e2241434.

Baker, JM, JY Nakayama, M O'Hegarty, A McGowan, RA Teran, SM Bart, K Mosack, N Roberts, B Campos, A Paegle, J McGee, R Herrera, K English, C Barrios, A Davis, C Roloff, LE Sosa, J Brockmeyer, L Page, A Bauer, JJ Weiner, M Khubbar, S Bhattacharyya, HL Kirking, and JE Tate, 2022, SARS-CoV-2 B.1.1.529 (Omicron) variant transmission within households - four U.S. jurisdictions, November 2021-February 2022, MMWR Morb Mortal Wkly Rep, 71(9):341-346.

Bojkova, D, R Stack, T Rothenburger, JD Kandler, S Ciesek, MN Wass, M Michaelis, and J Cinatl, Jr., 2022a, Synergism of interferon-beta with antiviral drugs against SARS-CoV-2 variants, J Infect, 85(5):573-607.

Bojkova, D, M Widera, S Ciesek, MN Wass, M Michaelis, and J Cinatl, Jr., 2022b, Reduced interferon antagonism but similar drug sensitivity in Omicron variant compared to Delta variant of SARS-CoV-2 isolates, Cell Res, 32(3):319-321.

Boras, B, RM Jones, BJ Anson, D Arenson, L Aschenbrenner, MA Bakowski, N Beutler, J Binder, E Chen, H Eng, H Hammond, J Hammond, RE Haupt, R Hoffman, EP Kadar, R Kania, E Kimoto, MG Kirkpatrick, L Lanyon, EK Lendy, JR Lillis, J Logue, SA Luthra, C Ma, SW Mason, ME McGrath, S Noell, RS Obach, OB MN, R O'Connor, K Ogilvie, D Owen, M Pettersson, MR Reese, TF Rogers, R Rosales, MI Rossulek, JG Sathish, N Shirai, C Steppan, M

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Ticehurst, LW Updyke, S Weston, Y Zhu, KM White, A Garcia-Sastre, J Wang, AK Chatterjee, AD Mesecar, MB Frieman, AS Anderson, and C Allerton, 2021, Preclinical characterization of an intravenous coronavirus 3CL protease inhibitor for the potential treatment of COVID19, Nat Commun, 12(1):6055.

Boucau, J, R Uddin, C Marino, J Regan, JP Flynn, MC Choudhary, G Chen, AM Stuckwisch, J Mathews, MY Liew, A Singh, Z Reynolds, SL Iyer, GC Chamberlin, TD Vyas, JM Vyas, SE Turbett, JZ Li, JE Lemieux, AK Barczak, and MJ Siedner, 2022, Characterization of virologic rebound following nirmatrelvir-ritonavir treatment for COVID-19, Clin Infect Dis.

Bruno, G, M Giotta, S Perelli, G De Vita, N Bartolomeo, and GB Buccoliero, 2022a, Early Access to Oral Antivirals in High-Risk Outpatients: Good Weapons to Fight COVID-19, Viruses, 14(11).

Bruno, G, S Perelli, M Giotta, N Bartolomeo, G De Vita, and GB Buccoliero, 2022b, Efficacy and safety of oral antivirals in individuals aged 80 years or older with mild-to-moderate COVID-19: preliminary report from an Italian Prescriber Center, Infez Med, 30(4):547-554.

Caillard, S, I Benotmane, G Gautier Vargas, P Perrin, and S Fafi-Kremer, 2021, SARS-CoV-2 viral dynamics in immunocompromised patients, Am J Transplant, 21(4):1667-1669.

Carlin, AF, AE Clark, A Chaillon, AF Garretson, W Bray, M Porrachia, AT Santos, TM Rana, and DM Smith, 2022, Virologic and immunologic characterization of COVID-19 recrudescence after nirmatrelvir/ritonavir treatment, Clin Infect Dis.

Charness, ME, K Gupta, G Stack, J Strymish, E Adams, DC Lindy, H Mohri, and DD Ho, 2022, Rebound of SARS-CoV-2 infection after nirmatrelvir-ritonavir treatment, N Engl J Med, 387(11):1045-1047.

Dai, W, R Rao, A Sher, N Tania, CJ Musante, and R Allen, 2021, A Prototype QSP Model of the Immune Response to SARS-CoV-2 for Community Development, CPT Pharmacometrics Syst Pharmacol, 10(1):18-29.

Deo, R, MC Choudhary, C Moser, J Ritz, ES Daar, DA Wohl, AL Greninger, JJ Eron, JS Currier, MD Hughes, DM Smith, KW Chew, JZ Li, and A-AS Team, 2022, Viral and symptom rebound in untreated COVID-19 infection, medRxiv.

Dryden-Peterson, S, A Kim, AY Kim, EC Caniglia, IT Lennes, R Patel, L Gainer, L Dutton, E Donahue, RT Gandhi, LR Baden, and AE Woolley, 2023, Nirmatrelvir Plus Ritonavir for Early COVID-19 in a Large U.S. Health System : A Population-Based Cohort Study, Ann Intern Med, 176(1):77-84.

Duveau, DY and CJ Thomas, 2022, The Remarkable Selectivity of Nirmatrelvir, ACS Pharmacol Transl Sci, 5(6):445-447.

Epling, BP, JM Rocco, KL Boswell, E Laidlaw, F Galindo, A Kellogg, S Das, A Roder, E Ghedin, A Kreitman, RL Dewar, SEM Kelly, H Kalish, T Rehman, J Highbarger, A Rupert, G Kocher, MR Holbrook, A Lisco, M Manion, RA Koup, and I Sereti, 2022, Clinical, virologic,

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and immunologic evaluation of symptomatic coronavirus disease 2019 rebound following nirmatrelvir/ritonavir treatment, Clin Infect Dis.

Focosi, D, S McConnell, S Shoham, A Casadevall, F Maggi, and G Antonelli, 2023, Nirmatrelvir and COVID-19: development, pharmacokinetics, clinical efficacy, resistance, relapse, and pharmacoeconomics, Int J Antimicrob Agents, 61(2):106708.

Ford, ES, W Simmons, EN Karmarkar, LH Yoke, AB Braimah, JJ Orozco, CM Ghiuzeli, S Barnhill, CL Sack, JO Benditt, P Roychoudhury, AL Greninger, AE Shapiro, JL Hammond, JM Rusnak, M Dolsten, M Boeckh, C Liu, GS Cheng, and L Corey, 2022, Successful treatment of prolonged, severe COVID-19 lower respiratory tract disease in a B-cell ALL patient with an extended course of remdesivir and nirmatrelvir/ritonavir, Clin Infect Dis.

Ganatra, S, SS Dani, J Ahmad, A Kumar, J Shah, GM Abraham, DP McQuillen, RM Wachter, and PE Sax, 2022, Oral Nirmatrelvir and Ritonavir in Non-hospitalized Vaccinated Patients with Covid-19, Clin Infect Dis.

Gastine, S, J Pang, FAT Boshier, SJ Carter, DO Lonsdale, M Cortina-Borja, IFN Hung, J Breuer, F Kloprogge, and JF Standing, 2021, Systematic Review and Patient-Level Meta-Analysis of SARS-CoV-2 Viral Dynamics to Model Response to Antiviral Therapies, Clin Pharmacol Ther, 110(2):321-333.

Gentile, I, R Scotto, N Schiano Moriello, B Pinchera, R Villari, E Trucillo, L Ametrano, L Fusco, G Castaldo, AR Buonomo, and T Federico Ii Covid, 2022, Nirmatrelvir/Ritonavir and Molnupiravir in the Treatment of Mild/Moderate COVID-19: Results of a Real-Life Study, Vaccines (Basel), 10(10).

Gidari, A, S Sabbatini, E Schiaroli, S Bastianelli, S Pierucci, C Busti, L Comez, V Libera, A Macchiarulo, A Paciaroni, I Vicenti, M Zazzi, and D Francisci, 2022, The Combination of Molnupiravir with Nirmatrelvir or GC376 Has a Synergic Role in the Inhibition of SARS-CoV-2 Replication In Vitro, Microorganisms, 10(7).

Greasley, SE, S Noell, O Plotnikova, R Ferre, W Liu, B Bolanos, K Fennell, J Nicki, T Craig, Y Zhu, AE Stewart, and CM Steppan, 2022, Structural basis for the in vitro efficacy of nirmatrelvir against SARS-CoV-2 variants, J Biol Chem, 298(6):101972.

Gretebeck, LM and K Subbarao, 2015, Animal models for SARS and MERS coronaviruses, Curr Opin Virol, 13:123-129.

Hedvat, J, NW Lange, DM Salerno, EM DeFilippis, D Kovac, H Corbo, JK Chen, JY Choe, JH Lee, A Anamisis, DL Jennings, G Codispodo, T Shertel, RS Brown, Jr., and MR Pereira, 2022, COVID-19 therapeutics and outcomes among solid organ transplant recipients during the Omicron BA.1 era, Am J Transplant, 22(11):2682-2688.

Heilmann, E, F Costacurta, SA Moghadasi, C Ye, M Pavan, D Bassani, A Volland, C Ascher, AKH Weiss, D Bante, RS Harris, S Moro, B Rupp, L Martinez-Sobrido, and D von Laer, 2023, SARS-CoV-2 3CL(pro) mutations selected in a VSV-based system confer resistance to nirmatrelvir, ensitrelvir, and GC376, Sci Transl Med, 15(678):eabq7360.

Hoffmann, M, H Kleine-Weber, S Schroeder, N Kruger, T Herrler, S Erichsen, TS Schiergens, G Herrler, NH Wu, A Nitsche, MA Muller, C Drosten, and S Pohlmann, 2020, SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor, Cell, 181(2):271-280 e278.

Hong, E, LM Almond, PS Chung, AP Rao, and PM Beringer, 2022, Physiologically-Based Pharmacokinetic-Led Guidance for Patients With Cystic Fibrosis Taking Elexacaftor-Tezacaftor-Ivacaftor With Nirmatrelvir-Ritonavir for the Treatment of COVID-19, Clin Pharmacol Ther, 111(6):1324-1333.

Iketani, S, H Mohri, B Culbertson, SJ Hong, Y Duan, MI Luck, MK Annavajhala, Y Guo, Z Sheng, AC Uhlemann, SP Goff, Y Sabo, H Yang, A Chavez, and DD Ho, 2023, Multiple pathways for SARS-CoV-2 resistance to nirmatrelvir, Nature, 613(7944):558-564.

Imai, M, M Ito, M Kiso, S Yamayoshi, R Uraki, S Fukushi, S Watanabe, T Suzuki, K Maeda, Y Sakai-Tagawa, K Iwatsuki-Horimoto, PJ Halfmann, and Y Kawaoka, 2023, Efficacy of antiviral agents against Omicron subvariants BQ.1.1 and XBB, N Engl J Med, 388(1):89-91.

James, AD, C Marvalin, A Luneau, A Meissner, and G Camenisch, 2017, Comparison of (19)F NMR and (14)C Measurements for the Assessment of ADME of BYL719 (Alpelisib) in Humans, Drug Metab Dispos, 45(8):900-907.

Jochmans, D, C Liu, K Donckers, A Stoycheva, S Boland, SK Stevens, C De Vita, B Vanmechelen, P Maes, B Trueb, N Ebert, V Thiel, S De Jonghe, L Vangeel, D Bardiot, A Jekle, LM Blatt, L Beigelman, JA Symons, P Raboisson, P Chaltin, A Marchand, J Neyts, J Deval, and K Vandyck, 2023, The Substitutions L50F, E166A, and L167F in SARS-CoV-2 3CLpro Are Selected by a Protease Inhibitor In Vitro and Confer Resistance To Nirmatrelvir, mBio, 14(1):e0281522.

Kasserra, C, J Li, B March, and E O'Mara, 2011, Effect of vicriviroc with or without ritonavir on oral contraceptive pharmacokinetics: a randomized, open-label, parallel-group, fixed-sequence crossover trial in healthy women, Clin Ther, 33(10):1503-1514.

Killingley, B, AJ Mann, M Kalinova, A Boyers, N Goonawardane, J Zhou, K Lindsell, SS Hare, J Brown, R Frise, E Smith, C Hopkins, N Noulin, B Londt, T Wilkinson, S Harden, H McShane, M Baillet, A Gilbert, M Jacobs, C Charman, P Mande, JS Nguyen-Van-Tam, MG Semple, RC Read, NM Ferguson, PJ Openshaw, G Rapeport, WS Barclay, AP Catchpole, and C Chiu, 2022, Safety, tolerability and viral kinetics during SARS-CoV-2 human challenge in young adults, Nat Med, 28(5):1031-1041.

Kneller, DW, H Li, G Phillips, KL Weiss, Q Zhang, MA Arnould, CB Jonsson, S Surendranathan, J Parvathareddy, MP Blakeley, L Coates, JM Louis, PV Bonnesen, and A Kovalevsky, 2022, Covalent narlaprevir- and boceprevir-derived hybrid inhibitors of SARS-CoV-2 main protease, Nat Commun, 13(1):2268.

Kuemmel, C, Y Yang, X Zhang, J Florian, H Zhu, M Tegenge, SM Huang, Y Wang, T Morrison, and I Zineh, 2020, Consideration of a Credibility Assessment Framework in Model-

RETURN TO PACKAGE TABLE

Informed Drug Development: Potential Application to Physiologically-Based Pharmacokinetic Modeling and Simulation, CPT Pharmacometrics Syst Pharmacol, 9(1):21-28.

Kuwagata, M, Y Sakai, S Tanaka, H Takashima, R Katagiri, T Matsuoka, K Noritake, M Senuma, T Shimizu, H Hojo, K Ibi, S Kudo, T Oota, M Ube, Y Miwa, S Kajita, T Uesugi, K Yabe, T Tateishi, N Nakano, T Taniguchi, A Yamashita, T Hirano, Y Kirihata, Y Sakai, S Nishizawa, M Fujiwara, H Mineshima, M Horimoto, and M Ema, 2019, Historical control data on developmental toxicity studies in rats, Congenit Anom (Kyoto), 59(4):125-131.

la Porte, CJ, MJ de Graaff-Teulen, EP Colbers, DS Voncken, SM Ibanez, PP Koopmans, YA Hekster, and DM Burger, 2004, Effect of efavirenz treatment on the pharmacokinetics of nelfinavir boosted by ritonavir in healthy volunteers, Br J Clin Pharmacol, 58(6):632-640.

Lambrou, AS, P Shirk, MK Steele, P Paul, CR Paden, B Cadwell, HE Reese, Y Aoki, N Hassell, XY Zheng, S Talarico, JC Chen, MS Oberste, D Batra, LK McMullan, AL Halpin, SE Galloway, DR MacCannell, R Kondor, J Barnes, A MacNeil, BJ Silk, VG Dugan, HM Scobie, DE Wentworth, J Caravas, NA Kovacs, JG Gerhart, H Jia Ng, A Beck, R Chau, R Cintron, PW Cook, CA Gulvik, D Howard, Y Jang, K Knipe, KA Lacek, KA Moser, AC Paskey, BL Rambo-Martin, RR Nagilla, AC Retchless, MW Schmerer, S Seby, SS Shepard, RA Stanton, TJ Stark, A Uehara, Y Unoarumhi, ML Bentz, A Burgin, M Burroughs, ML Davis, MW Keller, LM Keong, SS Le, JS Lee, JC Madden Jr, S Nobles, DC Owuor, J Padilla, M Sheth, MM Wilson, S Strain, G Emerging Variants Bioinformatic Working, S Strain, and NSWG Emerging Variants, 2022, Genomic Surveillance for SARS-CoV-2 Variants: Predominance of the Delta (B.1.617.2) and Omicron (B.1.1.529) Variants - United States, June 2021-January 2022, MMWR Morb Mortal Wkly Rep, 71(6):206-211.

Lee, CY, MK Shah, D Hoyos, A Solovyov, M Douglas, Y Taur, P Maslak, NE Babady, B Greenbaum, M Kamboj, and SA Vardhana, 2022, Prolonged SARS-CoV-2 infection in patients with lymphoid malignancies, Cancer Discov, 12(1):62-73.

Leist, SR, KH Dinnon, 3rd, A Schafer, LV Tse, K Okuda, YJ Hou, A West, CE Edwards, W Sanders, EJ Fritch, KL Gully, T Scobey, AJ Brown, TP Sheahan, NJ Moorman, RC Boucher, LE Gralinski, SA Montgomery, and RS Baric, 2020, A Mouse-Adapted SARS-CoV-2 Induces Acute Lung Injury and Mortality in Standard Laboratory Mice, Cell, 183(4):1070-1085 e1012.

Lewnard, JA, JM McLaughlin, D Malden, V Hong, L Puzniak, BK Ackerson, BJ Lewin, JS Kim, SF Shaw, H Takhar, L Jodar, and SY Tartof, 2023, Effectiveness of nirmatrelvir-ritonavir against hospital admission or death: a cohort study in a large US healthcare system, medRxiv.

Li, P, Y Wang, M Lavrijsen, MM Lamers, AC de Vries, RJ Rottier, MJ Bruno, MP Peppelenbosch, BL Haagmans, and Q Pan, 2022, SARS-CoV-2 Omicron variant is highly sensitive to molnupiravir, nirmatrelvir, and the combination, Cell Res, 32(3):322-324.

Lucas, C, P Wong, J Klein, TBR Castro, J Silva, M Sundaram, MK Ellingson, T Mao, JE Oh, B Israelow, T Takahashi, M Tokuyama, P Lu, A Venkataraman, A Park, S Mohanty, H Wang, AL Wyllie, CBF Vogels, R Earnest, S Lapidus, IM Ott, AJ Moore, MC Muenker, JB Fournier, M Campbell, CD Odio, A Casanovas-Massana, IT Yale, R Herbst, AC Shaw, R Medzhitov, WL

Schulz, ND Grubaugh, C Dela Cruz, S Farhadian, AI Ko, SB Omer, and A Iwasaki, 2020, Longitudinal analyses reveal immunological misfiring in severe COVID-19, Nature, 584(7821):463-469.

Ma, C, MD Sacco, B Hurst, JA Townsend, Y Hu, T Szeto, X Zhang, B Tarbet, MT Marty, Y Chen, and J Wang, 2020, Boceprevir, GC-376, and calpain inhibitors II, XII inhibit SARS-CoV-2 viral replication by targeting the viral main protease, Cell Res, 30(8):678-692.

Mann, ER, M Menon, SB Knight, JE Konkel, C Jagger, TN Shaw, S Krishnan, M Rattray, A Ustianowski, ND Bakerly, P Dark, G Lord, A Simpson, T Felton, LP Ho, NR TRC, M Feldmann, Circo, JR Grainger, and T Hussell, 2020, Longitudinal immune profiling reveals key myeloid signatures associated with COVID-19, Sci Immunol, 5(51).

Mathias, AA, P German, BP Murray, L Wei, A Jain, S West, D Warren, J Hui, and BP Kearney, 2010, Pharmacokinetics and pharmacodynamics of GS-9350: a novel pharmacokinetic enhancer without anti-HIV activity, Clin Pharmacol Ther, 87(3):322-329.

Mathias, AA, S West, J Hui, and BP Kearney, 2009, Dose-response of ritonavir on hepatic CYP3A activity and elvitegravir oral exposure, Clin Pharmacol Ther, 85(1):64-70.

Matsuyama, S, N Nao, K Shirato, M Kawase, S Saito, I Takayama, N Nagata, T Sekizuka, H Katoh, F Kato, M Sakata, M Tahara, S Kutsuna, N Ohmagari, M Kuroda, T Suzuki, T Kageyama, and M Takeda, 2020, Enhanced isolation of SARS-CoV-2 by TMPRSS2-expressing cells, Proc Natl Acad Sci U S A, 117(13):7001-7003.

Mehandru, S and M Merad, 2022, Pathological sequelae of long-haul COVID, Nat Immunol, 23(2):194-202.

Mudd, PA, JC Crawford, JS Turner, A Souquette, D Reynolds, D Bender, JP Bosanquet, NJ Anand, DA Striker, RS Martin, ACM Boon, SL House, KE Remy, RS Hotchkiss, RM Presti, JA O'Halloran, WG Powderly, PG Thomas, and AH Ellebedy, 2020, Distinct inflammatory profiles distinguish COVID-19 from influenza with limited contributions from cytokine storm, Sci Adv, 6(50).

Najjar-Debbiny, R, N Gronich, G Weber, J Khoury, M Amar, N Stein, LH Goldstein, and W Saliba, 2023, Effectiveness of Paxlovid in Reducing Severe Coronavirus Disease 2019 and Mortality in High-Risk Patients, Clin Infect Dis, 76(3):e342-e349.

Ohashi, H, T Hishiki, D Akazawa, KS Kim, J Woo, K Shionoya, K Tsuchimoto, S Iwanami, S Moriyama, H Kinoshita, S Yamada, Y Kuroda, T Yamamoto, N Kishida, S Watanabe, H Hasegawa, H Ebihara, T Suzuki, K Maeda, S Fukushi, Y Takahashi, S Iwami, and K Watashi, 2022, Different efficacies of neutralizing antibodies and antiviral drugs on SARS-CoV-2 Omicron subvariants, BA.1 and BA.2, Antiviral Res, 205:105372.

Owen, DR, CMN Allerton, AS Anderson, L Aschenbrenner, M Avery, S Berritt, B Boras, RD Cardin, A Carlo, KJ Coffman, A Dantonio, L Di, H Eng, R Ferre, KS Gajiwala, SA Gibson, SE Greasley, BL Hurst, EP Kadar, AS Kalgutkar, JC Lee, J Lee, W Liu, SW Mason, S Noell, JJ Novak, RS Obach, K Ogilvie, NC Patel, M Pettersson, DK Rai, MR Reese, MF Sammons, JG

Sathish, RSP Singh, CM Steppan, AE Stewart, JB Tuttle, L Updyke, PR Verhoest, L Wei, Q Yang, and Y Zhu, 2021, An oral SARS-CoV-2 M(pro) inhibitor clinical candidate for the treatment of COVID-19, Science, 374(6575):1586-1593.

Pandit, JA, JM Radin, D Chiang, E Spencer, J Pawelek, M Diwan, L Roumani, and M Mina, 2022, The Paxlovid Rebound Study: A prospective cohort study to evaluate viral and symptom rebound differences between Paxlovid and untreated COVID-19 participants, medRxiv.

Park, H, YJ Park, HY Lee, M Yu, YJ Song, SE Lee, JJ Lee, ES Lee, and Y Kim, 2022a, The effectiveness of Paxlovid treatment in long-term care facilities in South Korea during the outbreak of the Omicron variant of SARS-CoV-2, Osong Public Health Res Perspect, 13(6):443-447.

Park, JJ, J Lee, YB Seo, and SH Na, 2022b, Nirmatrelvir/Ritonavir Prescription Rate and Outcomes in Coronavirus Disease 2019: A Single Center Study, Infect Chemother, 54(4):757-764.

Peluso, MJ and SG Deeks, 2022, Early clues regarding the pathogenesis of long-COVID, Trends Immunol, 43(4):268-270.

Qian, G, X Wang, NJ Patel, Y Kawano, X Fu, CE Cook, KMM Vanni, EN Kowalski, EP Banasiak, KJ Bade, S Srivatsan, ZK Williams, DJ Todd, ME Weinblatt, ZS Wallace, and JA Sparks, 2022, Outcomes with and without outpatient SARS-CoV-2 treatment for patients with COVID-19 and systemic autoimmune rheumatic diseases: A retrospective cohort study, medRxiv.

Ranganath, N, JC O'Horo, DW Challener, SM Tulledge-Scheitel, ML Pike, R Michael O'Brien, RR Razonable, and A Shah, 2022, Rebound phenomenon after nirmatrelvir/ritonavir treatment of coronavirus disease-2019 in high-risk persons, Clin Infect Dis.

Rao, R, CJ Musante, and R Allen, 2023, A quantitative systems pharmacology model of the pathophysiology and treatment of COVID-19 predicts optimal timing of pharmacological interventions, NPJ Syst Biol Appl, 9(1):13.

Rosenke, K, MC Lewis, F Feldmann, E Bohrnsen, B Schwarz, A Okumura, WF Bohler, J Callison, C Shaia, CM Bosio, J Lovaglio, G Saturday, MA Jarvis, and H Feldmann, 2023, Combined molnupiravir-nirmatrelvir treatment improves the inhibitory effect on SARS-CoV-2 in macaques, JCI Insight, 8(4).

Rubin, R, 2022, From positive to negative to positive again-the mystery of why COVID-19 rebounds in some patients who take Paxlovid, JAMA, 327(24):2380-2382.

Sacco, MD, C Ma, P Lagarias, A Gao, JA Townsend, X Meng, P Dube, X Zhang, Y Hu, N Kitamura, B Hurst, B Tarbet, MT Marty, A Kolocouris, Y Xiang, Y Chen, and J Wang, 2020, Structure and inhibition of the SARS-CoV-2 main protease reveal strategy for developing dual inhibitors against M(pro) and cathepsin L, Sci Adv, 6(50).

RETURN TO PACKAGE TABLE

Saito, A, T Tamura, J Zahradnik, S Deguchi, K Tabata, Y Anraku, I Kimura, J Ito, D Yamasoba, H Nasser, M Toyoda, K Nagata, K Uriu, Y Kosugi, S Fujita, M Shofa, M Monira Begum, R Shimizu, Y Oda, R Suzuki, H Ito, N Nao, L Wang, M Tsuda, K Yoshimatsu, J Kuramochi, S Kita, K Sasaki-Tabata, H Fukuhara, K Maenaka, Y Yamamoto, T Nagamoto, H Asakura, M Nagashima, K Sadamasu, K Yoshimura, T Ueno, G Schreiber, A Takaori-Kondo, C Genotype to Phenotype Japan, K Shirakawa, H Sawa, T Irie, T Hashiguchi, K Takayama, K Matsuno, S Tanaka, T Ikeda, T Fukuhara, and K Sato, 2022, Virological characteristics of the SARS-CoV-2 Omicron BA.2.75 variant, Cell Host Microbe, 30(11):1540-1555 e1515.

Schwartz, KL, J Wang, M Tadrous, BJ Langford, N Daneman, V Leung, T Gomes, L Friedman, P Daley, and KA Brown, 2022, Real-world effectiveness of nirmatrelvir/ritonavir use for COVID-19: A population-based cohort study in Ontario, Canada, medRxiv:2022.2011.2003.22281881.

Sekar, V, S Spinosa-Guzman, E De Paepe, T Stevens, F Tomaka, M De Pauw, and RM Hoetelmans, 2010, Pharmacokinetics of multiple-dose darunavir in combination with low-dose ritonavir in individuals with mild-to-moderate hepatic impairment, Clin Pharmacokinet, 49(5):343-350.

Seminari, E, A De Bona, G Gentilini, L Galli, G Schira, N Gianotti, C Uberti-Foppa, A Soldarini, F Dorigatti, A Lazzarin, and A Castagna, 2007, Amprenavir and ritonavir plasma concentrations in HIV-infected patients treated with fosamprenavir/ritonavir with various degrees of liver impairment, J Antimicrob Chemother, 60(4):831-836.

Shah, MM, B Joyce, ID Plumb, S Sahakian, LR Feldstein, E Barkley, M Paccione, J Deckert, D Sandmann, JL Gerhart, and MB Hagen, 2022, Paxlovid Associated with Decreased Hospitalization Rate Among Adults with COVID-19 - United States, April-September 2022, MMWR Morb Mortal Wkly Rep, 71(48):1531-1537.

Simonyan, V, K Chumakov, E Donaldson, K Karagiannis, PV Lam, H Dingerdissen, and A Voskanian, 2017, HIVE-heptagon: A sensible variant-calling algorithm with post-alignment quality controls, Genomics, 109(3-4):131-140.

Simonyan, V and R Mazumder, 2014, High-Performance Integrated Virtual Environment (HIVE) Tools and Applications for Big Data Analysis, Genes (Basel), 5(4):957-981.

Soon, GH, P Shen, EL Yong, P Pham, C Flexner, and L Lee, 2010, Pharmacokinetics of darunavir at 900 milligrams and ritonavir at 100 milligrams once daily when coadministered with efavirenz at 600 milligrams once daily in healthy volunteers, Antimicrob Agents Chemother, 54(7):2775-2780.

Stader, F, S Khoo, M Stoeckle, D Back, HH Hirsch, M Battegay, and C Marzolini, 2020, Stopping lopinavir/ritonavir in COVID-19 patients: duration of the drug interacting effect, J Antimicrob Chemother, 75(10):3084-3086.

Takashita, E, N Kinoshita, S Yamayoshi, Y Sakai-Tagawa, S Fujisaki, M Ito, K Iwatsuki-Horimoto, P Halfmann, S Watanabe, K Maeda, M Imai, H Mitsuya, N Ohmagari, M Takeda, H

Hasegawa, and Y Kawaoka, 2022a, Efficacy of antiviral agents against the SARS-CoV-2 Omicron subvariant BA.2, N Engl J Med, 386(15):1475-1477.

Takashita, E, S Yamayoshi, S Fukushi, T Suzuki, K Maeda, Y Sakai-Tagawa, M Ito, R Uraki, P Halfmann, S Watanabe, M Takeda, H Hasegawa, M Imai, and Y Kawaoka, 2022b, Efficacy of antiviral agents against the Omicron subvariant BA.2.75, N Engl J Med, 387(13):1236-1238.

Takashita, E, S Yamayoshi, V Simon, H van Bakel, EM Sordillo, A Pekosz, S Fukushi, T Suzuki, K Maeda, P Halfmann, Y Sakai-Tagawa, M Ito, S Watanabe, M Imai, H Hasegawa, and Y Kawaoka, 2022c, Efficacy of antibodies and antiviral drugs against Omicron BA.2.12.1, BA.4, and BA.5 subvariants, N Engl J Med, 387(5):468-470.

Tiseo, G, C Barbieri, V Galfo, S Occhineri, T Matucci, F Almerigogna, J Kalo, P Sponga, M Cesaretti, G Marchetti, A Forniti, C Caroselli, S Ferranti, M Pogliaghi, M Polidori, S Fabiani, S Verdenelli, E Tagliaferri, N Riccardi, LR Suardi, C Carmignani, S Batini, L Puccetti, R Iapoce, F Menichetti, and M Falcone, 2023, Efficacy and Safety of Nirmatrelvir/Ritonavir, Molnupiravir, and Remdesivir in a Real-World Cohort of Outpatients with COVID-19 at High Risk of Progression: The PISA Outpatient Clinic Experience, Infect Dis Ther, 12(1):257-271.

Trottier, CA, B Wong, R Kohli, C Boomsma, F Magro, S Kher, C Anderlind, and Y Golan, 2022, Dual antiviral therapy for persistent COVID-19 and associated organizing pneumonia in an immunocompromised host, Clin Infect Dis.

Uraki, R, M Kiso, S Iida, M Imai, E Takashita, M Kuroda, PJ Halfmann, S Loeber, T Maemura, S Yamayoshi, S Fujisaki, Z Wang, M Ito, M Ujie, K Iwatsuki-Horimoto, Y Furusawa, R Wright, Z Chong, S Ozono, A Yasuhara, H Ueki, Y Sakai-Tagawa, R Li, Y Liu, D Larson, M Koga, T Tsutsumi, E Adachi, M Saito, S Yamamoto, M Hagihara, K Mitamura, T Sato, M Hojo, SI Hattori, K Maeda, R Valdez, Is team, M Okuda, J Murakami, C Duong, S Godbole, DC Douek, K Maeda, S Watanabe, A Gordon, N Ohmagari, H Yotsuyanagi, MS Diamond, H Hasegawa, H Mitsuya, T Suzuki, and Y Kawaoka, 2022, Characterization and antiviral susceptibility of SARS-CoV-2 Omicron BA.2, Nature, 607(7917):119-127.

Vangeel, L, W Chiu, S De Jonghe, P Maes, B Slechten, J Raymenants, E André, P Leyssen, J Neyts, and D Jochmans, 2022, Remdesivir, molnupiravir and nirmatrelvir remain active against SARS-CoV-2 Omicron and other variants of concern, Antiviral Res, 198:105252.

Wai, AK, CY Chan, AW Cheung, K Wang, SC Chan, TT Lee, LY Luk, ET Yip, JW Ho, OW Tsui, KW Cheung, S Lee, CK Tong, T Yamamoto, TH Rainer, and EL Wong, 2023, Association of Molnupiravir and Nirmatrelvir-Ritonavir with preventable mortality, hospital admissions and related avoidable healthcare system cost among high-risk patients with mild to moderate COVID-19, Lancet Reg Health West Pac, 30:100602.

Wang, L, NA Berger, PB Davis, DC Kaelber, ND Volkow, and R Xu, 2022, COVID-19 rebound after Paxlovid and molnupiravir during January-June 2022, medRxiv.

Weinreich, DM, S Sivapalasingam, T Norton, S Ali, H Gao, R Bhore, BJ Musser, Y Soo, D Rofail, J Im, C Perry, C Pan, R Hosain, A Mahmood, JD Davis, KC Turner, AT Hooper, JD Hamilton, A Baum, CA Kyratsous, Y Kim, A Cook, W Kampman, A Kohli, Y Sachdeva, X

RETURN TO PACKAGE TABLE

Graber, B Kowal, T DiCioccio, N Stahl, L Lipsich, N Braunstein, G Herman, GD Yancopoulos, and I Trial, 2021, REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19, N Engl J Med, 384(3):238-251.

WHO, 2021, A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October 2021, accessed, https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1.

Willett, BJ, J Grove, OA MacLean, C Wilkie, G De Lorenzo, W Furnon, D Cantoni, S Scott, N Logan, S Ashraf, M Manali, A Szemiel, V Cowton, E Vink, WT Harvey, C Davis, P Asamaphan, K Smollett, L Tong, R Orton, J Hughes, P Holland, V Silva, DJ Pascall, K Puxty, A da Silva Filipe, G Yebra, S Shaaban, MTG Holden, RM Pinto, R Gunson, K Templeton, PR Murcia, AH Patel, P Klenerman, S Dunachie, P Consortium, C-GU Consortium, J Haughney, DL Robertson, M Palmarini, S Ray, and EC Thomson, 2022, SARS-CoV-2 Omicron is an immune escape variant with an altered cell entry pathway, Nat Microbiol, 7(8):1161-1179.

Wong, CKH, ICH Au, KTK Lau, EHY Lau, BJ Cowling, and GM Leung, 2022, Real-world effectiveness of molnupiravir and nirmatrelvir plus ritonavir against mortality, hospitalisation, and in-hospital outcomes among community-dwelling, ambulatory patients with confirmed SARS-CoV-2 infection during the omicron wave in Hong Kong: an observational study, Lancet, 400(10359):1213-1222.

Xie, X, A Muruato, KG Lokugamage, K Narayanan, X Zhang, J Zou, J Liu, C Schindewolf, NE Bopp, PV Aguilar, KS Plante, SC Weaver, S Makino, JW LeDuc, VD Menachery, and PY Shi, 2020a, An Infectious cDNA Clone of SARS-CoV-2, Cell Host Microbe, 27(5):841-848 e843.

Xie, X, AE Muruato, X Zhang, KG Lokugamage, CR Fontes-Garfias, J Zou, J Liu, P Ren, M Balakrishnan, T Cihlar, CK Tseng, S Makino, VD Menachery, JP Bilello, and PY Shi, 2020b, A nanoluciferase SARS-CoV-2 for rapid neutralization testing and screening of anti-infective drugs for COVID-19, Nat Commun, 11(1):5214.

Xie, Y, T Choi, and Z Al-Aly, 2022, Nirmatrelvir and the Risk of Post-Acute Sequelae of COVID-19, medRxiv.

Yang, KS, SZ Leeuwon, S Xu, and WR Liu, 2022, Evolutionary and Structural Insights about Potential SARS-CoV-2 Evasion of Nirmatrelvir, J Med Chem, 65(13):8686-8698.

Yip, TC, GC Lui, MS Lai, VW Wong, YK Tse, BH Ma, E Hui, MKW Leung, HL Chan, DS Hui, and GL Wong, 2023, Impact of the Use of Oral Antiviral Agents on the Risk of Hospitalization in Community Coronavirus Disease 2019 Patients (COVID-19), Clin Infect Dis, 76(3):e26-e33.

Zhao, MM, WL Yang, FY Yang, L Zhang, WJ Huang, W Hou, CF Fan, RH Jin, YM Feng, YC Wang, and JK Yang, 2021, Cathepsin L plays a key role in SARS-CoV-2 infection in humans and humanized mice and is a promising target for new drug development, Signal Transduct Target Ther, 6(1):134.

Zhao, Y, C Fang, Q Zhang, R Zhang, X Zhao, Y Duan, H Wang, Y Zhu, L Feng, J Zhao, M Shao, X Yang, L Zhang, C Peng, K Yang, D Ma, Z Rao, and H Yang, 2022, Crystal structure of

SARS-CoV-2 main protease in complex with protease inhibitor PF-07321332, Protein Cell, 13(9):689-693.

Zhou, X, SP Kelly, C Liang, L Li, R Shen, HK Leister-Tebbe, SG Terra, M Gaffney, and L Russo, 2022a, Real-World Effectiveness of Nirmatrelvir/Ritonavir in Preventing Hospitalization Among Patients With COVID-19 at High Risk for Severe Disease in the United States: A Nationwide Population-Based Cohort Study, medRxiv.

Zhou, Y, KA Gammeltoft, LA Ryberg, LV Pham, HD Tjornelund, A Binderup, CR Duarte Hernandez, C Fernandez-Antunez, A Offersgaard, U Fahnoe, GHJ Peters, S Ramirez, J Bukh, and JM Gottwein, 2022b, Nirmatrelvir-resistant SARS-CoV-2 variants with high fitness in an infectious cell culture system, Sci Adv, 8(51):eadd7197.

26.2. Reports

Abbott, 2021, Abbott RealTime SARS-CoV-2 assay, https://www.fda.gov/media/136258/download.

DARRTS ID: 5077785, 2022, Post-Emergency Use Authorization (EUA) Safety and Medication Error Summary, FDA, accessed, https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806992ad.

Emergency Use Authorization (EUA) for PAXLOVID: Center for Drug Evaluation and Research Review Memorandum - February 23, 2022 (FDA 2022a), https://www.fda.gov/media/159987/download.

Emergency Use Authorization (EUA) for PAXLOVID: Center for Drug Evaluation and Research Review Memorandum - September 26, 2022 (FDA 2022b), https://www.fda.gov/media/165148/download.

Pfizer, 2020a, PRELIMINARY STUDY OF THE BIOTRANSFORMATION OF PF-07321332, Report 084546, \\CDSESUB1\EVSPROD\nda217188\0001\m4\42-stud-rep\422-pk\4224-metab\084546\084546.pdf.

Pfizer, 2020b, PROTEIN BINDING OF PF-07321332 IN HUMAN, NON-HUMAN PRIMATE, AND RAT PLASMA, Report 010657, \\CDSESUB1\EVSPROD\nda217188\0001\m4\42-stud-rep\422-pk\4223-distrib\010657\010657.pdf.

Pfizer, 2021a, EVALUATION OF IN VITRO SELECTED RESISTANT MHV AGAINST PF-07321332, Report 035634, \\CDSESUB1\EVSPROD\nda217188\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\035634\035634.pdf.

Pfizer, 2021b, IN VITRO POTENCY OF PF-07321332 AGAINST ENTEROVIRUS 71 IN HUMAN RHABDOMYOSARCOMA CELLS AND HUMAN RHINOVIRUS 1B IN HELA CELLS, Report 041406, \\CDSESUB1\EVSPROD\nda217188\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\041406\041406.pdf.

Pfizer, 2021c, IN VITRO POTENCY OF PF-07321332 AGAINST HCOV-229E IN MRC5 CELLS, Report 092314, \\CDSESUB1\EVSPROD\nda217188\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\092314\092314.pdf.

Pfizer, 2021d, IN VITRO POTENCY OF PF-07321332 AGAINST MAMMALIAN AND VIRAL PROTEASES, Report 091415, \\CDSESUB1\EVSPROD\nda217188\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\091415\091415.pdf.

Pfizer, 2021e, IN VITRO POTENCY OF PF-07321332 AGAINST MERS IN VERO81 CELLS, Report 015423, \\CDSESUB1\EVSPROD\nda217188\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\015423\015423.pdf.

Pfizer, 2021f, IN VITRO POTENCY OF PF-07321332 AGAINST SARS-COV-1 IN VEROE6 CELLS, Report 104426, \\CDSESUB1\EVSPROD\nda217188\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\104426\104426.pdf.

Pfizer, 2021g, IN VITRO POTENCY OF PF-07321332 AGAINST SARS-COV-2 IN PRIMARY HUMAN AIRWAY EPITHELIAL CULTURES, Report 010204, \\CDSESUB1\EVSPROD\nda217188\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\010204\010204.pdf.

Pfizer, 2021h, IN VITRO POTENCY OF PF-07321332 AND ITS MAJOR OXIDATIVE METABOLITE PF-07329268 AGAINST SARS-COV-2 IN VEROE6 CELLS, Report 052017, \\CDSESUB1\EVSPROD\nda217188\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\052017\052017.pdf.

Pfizer, 2021i, IN VIVO EFFICACY OF PF-07321332 IN 129 MOUSE SARS-COV-2 MODELS, Report 022652, \\CDSESUB1\EVSPROD\nda217188\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\022652\022652.pdf.

Pfizer, 2021j, IN VIVO EFFICACY OF PF-07321332 IN BALB/C MOUSE-ADAPTED SARS-COV-2 MODELS, Report 105036, \\CDSESUB1\EVSPROD\nda217188\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\105036\105036.pdf.

Pfizer, 2022a, C4671005 Final Sequencing Report, \\CDSESUB1\evsprod\nda217188\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\treatment-of-mild-to-moderate-covid-19\5351-stud-rep-contr\c4671005\c4671005-final-viral-sequencing-report.pdf.

Pfizer, 2022b, C4671005 Final Virology Infectivity Report 12192022, \\CDSESUB1\EVSPROD\nda217188\0093\m1\us\resp-13-dec-2022-ir-clin-virology.pdf.

Pfizer, 2022c, EVALUATION OF IN VITRO SELECTED RESISTANT SARS-COV-2 AGAINST PF-07321332 (NIRMATRELVIR) IN A549-ACE2 CELLS, Report 065112, \\CDSESUB1\EVSPROD\nda217188\0038\m4\42-stud-rep\421-pharmacol\4211-prim-pd\065112\065112.pdf.

RETURN TO PACKAGE TABLE

Pfizer, 2022d, IN VITRO ANTIVIRAL ACTIVITY OF PF-07321332 AGAINST THE OMICRON VARIANT OF SARS-COV-2 IN VERO-TMPRSS2 AND HELA-ACE2 CELLS, Report 091706, \\CDSESUB1\EVSPROD\nda217188\0090\m4\42-stud-rep\421-pharmacol\4211-prim-pd\091706\091706.pdf.

Pfizer, 2022e, IN VITRO CELL-BASED EFFICACY OF PF-07321332 AGAINST MAJOR SARS-COV-2 VARIANTS, Report 104040, \\CDSESUB1\EVSPROD\nda217188\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\104040\104040.pdf.

Pfizer, 2022f, IN VITRO CELL-BASED EFFICACY OF PF-07321332 AGAINST SARS-COV-2 DELTA VARIANT CLINICAL ISOLATES, Report 012142, \\CDSESUB1\EVSPROD\nda217188\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\012142\012142.pdf.

Pfizer, 2022g, IN VITRO EVALUATION OF SELECTED RESISTANT SARS-COV-2 AGAINST PF-07321332 (NIRMATRELVIR) IN VERO E6 P-GP KNOCKOUT CELLS, Report 113117, \\CDSESUB1\EVSPROD\nda217188\0038\m4\42-stud-rep\421-pharmacol\4211-prim-pd\113117\113117.pdf.

Pfizer, 2022h, IN VITRO POTENCY OF PF-07321332 AGAINST SARS-COV-2 3CL PROTEASE ENZYME CONTAINING DIFFERENT MUTATIONS, Report 121015, \\CDSESUB1\EVSPROD\nda217188\0094\m4\42-stud-rep\421-pharmacol\4211-prim-pd\121015\121015.pdf.

Pfizer, 2022i, IN VITRO POTENCY OF PF-07321332 AGAINST SARS-COV-2 IN AN A549-ACE2 CELL LINE ALONE AND IN COMBINATION WITH RITONAVIR, Report 041209, \\CDSESUB1\EVSPROD\nda217188\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\041209\041209.pdf.

Pfizer, 2022j, IN VITRO POTENCY OF PF-07321332 AND METABOLITE PF-07329268 IN A SARS-COV-2 3CLPRO PROTEASE ASSAY, Report 090608, \\CDSESUB1\EVSPROD\nda217188\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\090608\090608.pdf.

Pfizer, 2022k, IN VITRO RT-qPCR-BASED EFFICACY OF PF-07321332 AGAINST MAJOR SARS-COV-2 VARIANTS, Report 042713, \\CDSESUB1\EVSPROD\nda217188\0038\m4\42-stud-rep\421-pharmacol\4211-prim-pd\042713\042713.pdf.

Pfizer, 2022l, IN VITRO VIRUS RNA REPLICATION EFFICIENCY OF THE RECOMBINANT SARS-COV-2 CONTAINING ENGINEERED MUTATIONS IN 3CL (MAIN) PROTEASE (M^{PRO}) PRELIMINARY REPORT WITH RESULTS TO DATE (V2.0), Report 024518, \\CDSESUB1\EVSPROD\nda217188\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\024518\024518.pdf.

Pfizer, 2022m, IN VIVO EFFICACY OF PF-07321332 AS A SINGLE AGENT OR IN COMBINATION WITH RITONAVIR IN BALB/C MOUSE-ADAPTED SARS-COV-2 MODEL, Report 092629, \\CDSESUB1\EVSPROD\nda217188\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\092629\092629.pdf.

RETURN TO PACKAGE TABLE

Pfizer, 2022n, Interim Sequencing and Infectivity Report 08312022, \\CDSESUB1\EVSPROD\nda217188\0022\m5\53-clin-stud-rep\535-rep-effic-safety-stud\treatment-of-mild-to-moderate-covid-19\5351-stud-rep-contr\c4671005\c4671005-interim-viral-sequenceing-rpt-aug22-pdf.pdf.

Pfizer, 2022o, PAXLOVID™ (nirmatrelvir [PF-07321332] tablets; ritonavir tablets): Response to FDA Information Request on P132 Substitutions, \\CDSESUB1\EVSPROD\nda217188\0036\m1\us\resp-fda-ir-16-sep-2022.pdf.

Pfizer, 2022p, PAXLOVID™ (nirmatrelvir [PF-07321332] tablets; ritonavir tablets): Response to FDA Information Request on Viral RNA from EPIC-SR Site 1197, Received 18 October 2022, \\CDSESUB1\EVSPROD\nda217188\0060\m1\us\resp-fda-ir-18oct2022.pdf.

Pfizer, 2022q, PAXLOVID™ (nirmatrelvir [PF-07321332] tablets; ritonavir tablets): Response to FDA Information Request Regarding Viral Sequence Clustering, Received 14 November 2022, \\CDSESUB1\EVSPROD\nda217188\0071\m1\us\resp-fda-ir-14-nov-2022-viral-seq.pdf.

Pfizer, 2022r, SEQUENCE CONSERVATION ANALYSES OF 3CLPRO RESIDUES INCLUDING PF-07321332 KEY CONTACT SITES ACROSS DIFFERENT SARS-COV-2 ISOLATES AND OTHER CORONAVIRUSES, Report 120222, \\CDSESUB1\EVSPROD\nda217188\0094\m4\42-stud-rep\421-pharmacol\4211-prim-pd\120222\120222.pdf.

Pfizer, 2022s, XRAY CO-CRYSTAL STRUCTURE OF PF-07321332 BOUND TO SARS-CoV-2 3CL PROTEASE, Report 054343, \\CDSESUB1\EVSPROD\nda217188\0038\m4\42-stud-rep\421-pharmacol\4211-prim-pd\054343\054343.pdf.

Pfizer, 2023b, IN VITRO POTENCY OF PF-07321332 AGAINST SARS-COV-2 3CL PROTEASE ENZYME CONTAINING DIFFERENT MUTATIONS, Report 121015 (v7), \\CDSESUB1\EVSPROD\nda217188\0141\m4\42-stud-rep\421-pharmacol\4211-prim-pd\121015\121015.pdf.

Pfizer, 2023c, IN VITRO RT-qPCR-BASED EFFICACY OF PF-07321332 AGAINST MAJOR SARS-COV-2 VARIANTS, Report 042713 (v8), \\CDSESUB1\EVSPROD\eua000105\0340\m4\42-stud-rep\421-pharmacol\4211-prim-pd\042713\042713.pdf.

Pfizer, 2023d, IN VITRO VIRUS RNA REPLICATION EFFICIENCY OF THE RECOMBINANT SARS-COV-2 CONTAINING ENGINEERED MUTATIONS IN 3CL (MAIN) PROTEASE (M^{PRO}), Report 024518 (v5), \\CDSESUB1\EVSPROD\eua000105\0342\m4\42-stud-rep\421-pharmacol\4211-prim-pd\024518\024518.pdf.

Pfizer, 2023e, PAXLOVID™ (nirmatrelvir [PF-07321332] tablets; ritonavir tablets): Response to FDA Comments on USPI, Received 21 March 2023, \\CDSESUB1\EVSPROD\nda217188\0146\m1\us\resp-fda-uspi-ir-20-mar-2023.pdf.

RETURN TO PACKAGE TABLE

26.3. Other

CDC, 2022a, Ending Isolation and Precautions for People with COVID-19: Interim Guidance, accessed February 8th, 2023, https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html.

CDC, 2022b, Post-COVID Conditions: Information for Healthcare Providers, accessed November 16, 2022, https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html.

CDC, 2023a, COVID Data Tracker, accessed May 8, 2023, https://covid.cdc.gov/covid-data-tracker/#datatracker-home.

CDC, 2023b, COVID Data Tracker: COVID-19 Vaccinations in the United States, accessed April 10, 2023, https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-count-pop12.

CDC, 2023c, COVID Data Tracker: Variant Proportions, accessed April 11, 2023, https://covid.cdc.gov/covid-data-tracker/#variant-proportions.

CDC, 2023d, Risk for COVID-19 Infection, Hospitalization, and Death By Age Group, accessed, https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-age.html.

CDC, 2023e, Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals, accessed, https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html.

ClinicalTrials.gov: NCT05438602, 2023, A Study to Learn About the Study Medicines (Nirmatrelvir Plus Ritonavir) in People Aged 12 Years or Older With COVID-19 and a Compromised Immune System, accessed, https://clinicaltrials.gov/ct2/show/NCT05438602.

ClinicalTrials.gov: NCT05567952, 2023, A Study to Learn About a Repeat 5-Day Treatment With the Study Medicines (Called Nirmatrelvir/Ritonavir) in People 12 Years Old or Older With Return of COVID-19 Symptoms and SARS-CoV-2 Positivity After Finishing Treatment With Nirmatrelvir/Ritonavir, accessed, https://clinicaltrials.gov/ct2/show/NCT05567952.

FDA, 2023, UPDATED INFORMATION: March 16, 2023: Antimicrobial Drugs Advisory Committee Meeting Announcement, accessed April 24, 2023, https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-information-march-16-2023-antimicrobial-drugs-advisory-committee-meeting-announcement.

Morgan M, Gwee A, Roberts J, Allard N, Turner T, 2022, I Have Mild COVID Should I take the Antiviral Paxlovid, The Conversation, accessed, https://theconversation.com/i-have-mild-covid-should-i-take-the-antiviral-paxlovid-183913.

NCBI, 2023, Basic Local Alignment Search Tool, National Institutes of Health (NIH), National Library of Medicine (NLM): National Center for Biotechnology Information (NCBI), accessed, https://blast.ncbi.nlm.nih.gov/Blast.cgi.

NCBI, 045512.2, Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1, complete genome, National Institutes of Health (NIH), National Library of Medicine (NLM): National Center for Biotechnology Information (NCBI), accessed.

NIH, 2022a, Clinical Spectrum of SARS-CoV-2 Infection, accessed February 8th, 2023, https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/.

NIH, 2022b, COVID-19 Treatment Guidelines: Anti-SARS-CoV-2 Monoclonal Antibodies, accessed February 8th, 2023, https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/anti-sars-cov-2-monoclonal-antibodies/.

NIH, 2022c, COVID-19 Treatment Guidelines: Molnupiravir, accessed February 8th, 2023, https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/molnupiravir/.

NIH, 2022d, COVID-19 Treatment Guidelines: Remdesivir, accessed February 8, 2023, https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/remdesivir/.

NIH, 2023, Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications, accessed, https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions/.

RETURN TO PACKAGE TABLE

Qiagen, 2023, Qiagen CLC Genomics, accessed, https://digitalinsights.qiagen.com/products-overview/discovery-insights-portfolio/qiagen-clc-genomics/.

RSC, ND, 2017, Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1, accessed, https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf.

Sheikh, K, 2023, Should You Take Paxlovid if You Are Mildly Ill, New York Times, accessed, https://www.seattletimes.com/nation-world/should-you-take-paxlovid-if-you-are-mildly-ill/.

26.4. Guidances

STANDARD SAFETY TABLES AND FIGURES: INTEGRATED GUIDE (August 2022), https://downloads.regulations.gov/FDA-2022-N-1961-0046/attachment_1.pdf.

Guidance for Industry *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023), https://www.fda.gov/media/72142/download.

Guidance for Industry *COVID-19: Developing Drugs and Biological Products for Treatment or Prevention* (May 2020), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/covid-19-developing-drugs-and-biological-products-treatment-or-prevention.

Guidance for Industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format* (October 2011), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/warnings-and-precautions-contraindications-and-boxed-warning-sections-labeling-human-prescription.

Pfizer, 2023a, FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR PAXLOVID, accessed, https://www.fda.gov/media/155050/download.

International Statistical Classification of Diseases and Related Health Problems *International Statistical Classification of Diseases and Related Health Problems 10th Revision* (WHO 2019), https://icd.who.int/browse10/2019/en.

26.5. Prescribing Information

AbbVie, 2010, Prescribing Information: NORVIR, accessed, https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/022417Orig1s025,020659Orig1s073,209512Orig1s008lbl.pdf.

Gilead Sciences, 2020, Prescribing Information: VEKLURY accessed, https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214787Orig1s000lbl.pdf.

Janssen Products, 2011, Prescribing Information: PREZISTA, accessed, https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/021976s06s068,202895s036lbl.pdf.

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27. Review Team

Table 242. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Myung-Joo Patricia Hong, MS
Nonclinical reviewer	Zheng "Jenny" Li, PhD, DABT
Nonclinical team leader	Chris Ellis, PhD
OCP reviewer(s)	Cristina Miglis, PharmD, MS Ye Xiong, PhD
OCP team leader(s)	Mario Sampson, PharmD Jiang Liu, PhD Ying-Hong Wang, PhD Manuela Grimstein, PhD
Clinical reviewers	Glen Huang, DO Stephanie Troy, MD
Clinical team leader	Sarah Connelly, MD
Clinical Virology reviewers	Patrick Harrington, PhD Jonathan Rawson, PhD
Clinical Virology TL	Jules O'Rear, PhD
Biometrics reviewer	Jie Cong, PhD
Supervisory Mathematical Statistician (DBIV), Biometrics Secondary Reviewer	Thamban Valappil, PhD
Cross-disciplinary team leader	Sarah Connelly, MD
Division director (pharm/tox)	Hanan Ghantous, PhD, DABT
Associate Director for Labeling	Stacey Min, PharmD
Associate Director for Therapeutic Review (OCP)	Vikram Arya, PhD, FCP
Supervisory Mathematical Statistician (DBIV), Biometrics Tertiary Reviewer	Scott Komo, DrPH
Division director (clinical)	Debra Birnkrant, MD
Office director (or designated signatory authority)	John Farley, MD

Abbreviations: DBIV, Division of Biometrics IV; OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics; TL, team lead

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Table 243. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	
RBPM	Erica Keafer, MS Musse Olani, PharmD
Drug Substance	Katherine Windsor, PhD Paresma Patel, PhD (TL)
Drug Product	Shalini Anand, PhD David Claffey, PhD
Process/Facility/Microbiology (OPMA)	Abdollah Koolivand, PhD Hang Guo, MS (TL)
Biopharmaceutics	Gerlie Gieser, PhD Elsbeth Chikhale, PhD (TL)
Environment Assessment	Xiaoqin Wu, PhD Janes Laurenson, PhD
CMC ATL	David Claffey, PhD
OPDP	Wendy Lubarsky, PharmD Sam Skariah, PharmD
OSI	Elena Boley, MD, MBA Phillip Kronstein, MD (TL)
DMPP	Susan Redwood, MPH, BSN, RN Barbara Fuller, PharmD (TL)
OSE/DMEPA	Melina Fanari, PharmD Madhuri Patel, PharmD (TL) Mishale Mistry, PharmD, MPH, Associate Director
OSE/OPE/DPV II	Kate McCartan, MD Rachna Kapoor, PharmD, MBA (TL)
OSE/OPE/DEPI II	Natasha Pratt, PhD John Rhee, PharmD, MS Sheheryar Muhammad, PharmD (TL)
OB/DB VII	Jiwei He, PhD Yong Ma, PhD (TL)
Other	
Medical Editor	Noah Benjamin Whiteman, BA Mei Lu Joseph Dorn, MPH (TL)
Clinical Data Scientist	Jun Zhu, PhD Jinzhong Liu, MD (TL)
CluePoints Analyst	Xiaofeng Wang, MS Paul Schuette, PhD (TL)
AC Designated Federal Officer	Joyce Frimpong, PharmD Yvette Waples, PharmD (TL)

Abbreviations: AC, advisory committee; ATL, Application Team Lead; CMC, chemistry, manufacturing, and controls; DB VII, Division of Biometrics VII; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DMPP, Division of Medical Policy Programs; DRISK, Division of Risk Management; OB, Office of Biostatistics; OPDP, Office of Prescription Drug Promotion; OPMA, Office of Pharmaceutical Manufacturing Assessment; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations; RBPM, regulatory business process manager; TL, team lead

27.1. Reviewer Signatures

See next page.

Table 244. Signatures of Reviewers

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Reviewer	Stephanie Troy Office of Infectious Diseases DAV	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 2.1, 2.2, 3.1, 6.3.1, 6.3.2, 6.3.4, 6.3.5, 6.3.7, 7.7, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Stephanie B. Troy -S Digitally signed by Stephanie B. Troy -S Date: 2023.05.22 10:22:42 -04'00'					

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Reviewer	Glen Huang Office of Infectious Diseases DAV	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections:.3, 4, 7.2, 7.3, 7.4, 7.5, 7.6, 8.3, 8.4, 17, 21, 22, 24	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Glen Huang -S Digitally signed by Glen Huang -S Date: 2023.05.22 10:25:05 -04'00'					
Clinical Virology Reviewer	Patrick Harrington Office of Infectious Diseases DAV	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 6, 18	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Patrick Harrington -S Digitally signed by Patrick Harrington -S Date: 2023.05.22 10:30:43 -04'00'					

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Virology Reviewer	Jonathan Rawson Office of Infectious Diseases DAV	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 5.1, 6, 18, 20	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Jonathan M. Raws - Digitally signed by Jonathan M. Rawson -S Date: 2023.05.22 10:39:41 -04'00'					
Clinical Virology Team Leader	Jules O'Rear Office of Infectious Diseases DAV	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 5.1, 6, 18, 20	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Julian J. O'rear -S Digitally signed by Julian J. O'rear -S Date: 2023.05.22 10:44:07 -04'00'					

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Pharmacology/ Toxicology Reviewer	Jenny Li Office of Infectious Diseases DPT-ID	☒ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 7.1, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Zheng Li -S Digitally signed by Zheng Li -S Date: 2023.05.22 11:56:54 -04'00'					
Pharmacology/ Toxicology Team Leader	Christopher Ellis Office of Infectious Diseases DPT-ID	☒ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 7.1, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Christopher E. Ellis -S Digitally signed by Christopher E. Ellis -S Date: 2023.05.22 11:52:25 -04'00'					

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Associate Director for Labeling	Stacey Min Office of Infectious Diseases DAV	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Stacey Min -S Digitally signed by Stacey Min -S Date: 2023.05.22 09:12:23 -04'00'					
Clinical Pharmacology Reviewer	Cristina Miglis Office of Clinical Pharmacology DIDP	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 5, 6, 8, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Cristina M. Miglis -S Digitally signed by Cristina M. Miglis -S Date: 2023.05.22 09:07:43 -04'00'					

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Pharmacology Secondary Reviewer	Mario Sampson Office of Clinical Pharmacology DIDP	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 5, 6, 8, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Mario Sampson -S Digitally signed by Mario Sampson -S Date: 2023.05.22 08:37:55 -05'00'					
Clinical Pharmacology Reviewer	Ye Xiong Office of Clinical Pharmacology DPM	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 14.5.1, 14.5.2, 14.5.3, 14.5.4	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Ye Xiong -S Digitally signed by Ye Xiong -S Date: 2023.05.22 09:54:39 -04'00'					

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Pharmacology Team Leader	Jiang Liu Office of Clinical Pharmacology DPM	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 14.5.1, 14.5.2, 14.5.3, 14.5.4	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Jiang Liu -S Digitally signed by Jiang Liu -S Date: 2023.05.22 19:22:26 -04'00'					
Clinical Pharmacology Team Leader	Yuching Yang Office of Clinical Pharmacology DPM	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 14.5.1, 14.5.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Yuching Yang -S Digitally signed by Yuching Yang -S Date: 2023.05.22 10:29:01 -04'00'					

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Pharmacology Team Leader	Manuela Grimstein Office of Clinical Pharmacology DPM	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 14.6	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Manuela D. Grimstein -S Digitally signed by Manuela D. Grimstein -S Date: 2023.05.22 11:14:25 -04'00'					
Clinical Pharmacology/ Pharmacometrics Primary Reviewer	Ying-Hong Wang Office of Clinical Pharmacology/ DPM	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 14.6	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒Yes ☐ No
Signature/date/time stamp: Ying-hong Wang -S Digitally signed by Ying-hong Wang -S Date: 2023.05.22 11:22:27 -04'00'					

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Pharmacology Tertiary Reviewer	Vikram Arya Office of Clinical Pharmacology DIDP	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 5, 6, 8, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Vikram Arya -S Digitally signed by Vikram Arya -S Date: 2023.05.22 08:21:51 -04'00'					
Biometrics Primary Reviewer	Jie Cong Office of Biostatistics DB IV	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 3.2, 6, 15, 16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Jie Cong -S Digitally signed by Jie Cong -S Date: 2023.05.22 10:38:58 -04'00'					

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Biometrics Secondary Reviewer	Thamban Valappil Office of Biostatistics DB IV	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 3.2, 6, 15, 16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Thamban I. Valappil -S Digitally signed by Thamban I. Valappil -S Date: 2023.05.22 10:44:32 -04'00'					
Biometrics Tertiary Reviewer	Scott Komo Office of Biostatistics DB IV	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 3.2, 6, 15, 16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Scott S. Komo -S Digitally signed by Scott S. Komo -S Date: 2023.05.22 10:53:26 -04'00'					

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Biometrics Primary Reviewer	Jiwei He Office of Biostatistics DB VII	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 16.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Jiwei He -S Digitally signed by Jiwei He -S Date: 2023.05.22 11:38:57 -04'00'					
Biometrics Team Leader	Yong Ma Office of Biostatistics DB VII	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 16.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Yong Ma -S Digitally signed by Yong Ma -S Date: 2023.05.22 11:55:00 -04'00'					

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Other Primary Reviewer	Natasha Pratt Office of Surveillance and Epidemiology Division of Epidemiology II	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 7.7, 16.5, 21	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Natasha C. Pratt -S Digitally signed by Natasha C. Pratt -S Date: 2023.05.22 10:48:03 -04'00'					
Other Primary Reviewer	John Rhee Office of Surveillance and Epidemiology Division of Epidemiology II	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 7.7.1	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: John T. Rhee -S Digitally signed by John T. Rhee -S Date: 2023.05.22 11:25:44 -04'00'					

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Other Team Leader	Sheheryar Muhammad Office of Surveillance and Epidemiology Division of Epidemiology II	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 7.7.1	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Sheheryar Muhammad -S Digitally signed by Sheheryar Muhammad -S Date: 2023.05.22 11:29:23 -04'00'					
Other Reviewer	Kate McCartan Office of Surveillance and Epidemiology DPV II	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 7.7.1	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Kate L. Mccartan -S Digitally signed by Kate L. Mccartan -S Date: 2023.05.22 12:14:47 -04'00'					

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Other Team Leader	Rachna Kapoor Office of Surveillance and Epidemiology DPV II	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 7.7.1	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Rachna Kapoor -S Digitally signed by Rachna Kapoor -S Date: 2023.05.22 12:21:28 -04'00'					
Product Quality Supervisor	David Claffey Office of Pharmaceutical Quality ONDP/DNDP1	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 9	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: David J. Claffey -S Digitally signed by David J. C - Date: 2023.05.22 13:44:05 -04'00'					

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Cross-Disciplinary Cross-Disciplinary Team Lead	Sarah Connelly Office of Infectious Diseases DAV	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections:	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Sarah M. Connelly -S Digitally signed by Sarah M. Connelly -S Date: 2023.05.22 09:47:39 -04'00'					
Regulatory Project Management Regulatory Project Manager	Myung-Joo P. Hong Other DROID	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 12	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Myung-joo P. Hong -S Digitally signed by Myung-joo P. Hong -S Date: 2023.05.23 10:16:40 -04'00'					

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Other Deputy Director (Safety)	Poonam Mishra Office of Infectious Diseases DAV	☒ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 24	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Poonam Mishra -S Digitally signed by Poonam Mishra -S Date: 2023.05.23 02:21:36 -04'00'					
Other Division Director	Hanan Ghantous Office of Infectious Diseases DPT-ID	☒ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 7.1, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Hanan N. Ghantous -S Digitally signed by Hanan N. Ghantous -S Date: 2023.05.22 11:56:12 -04'00'					

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Other Division Director	Debra Birnkrant Office of Infectious Diseases DAV	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections:	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Debra B. Birnkrant -S Digitally signed by Debra B. Birnkrant -S Date: 2023.05.22 11:27:11 -04'00'					

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/s/

SARAH M CONNELLY
05/24/2023 03:04:49 PM

DEBRA B BIRNKRANT
05/24/2023 03:06:51 PM

JOHN J FARLEY
05/24/2023 04:25:23 PM

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217188Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	217188
PDUFA Goal Date	May 28, 2023
OSE RCM #	2022-34
Reviewer Name(s)	Ingrid N. Chapman, Pharm.D., BCPS
Team Leader	Naomi Boston, Pharm.D.
Associate Director for REMS Design and Evaluation	Laura Zendel, Pharm.D., BCPS
Review Completion Date	May 25, 2023
Subject	Determination of the Need for a REMS
Established Name	nirmatrelvir and ritonavir
Trade Name	Paxlovid
Name of Applicant	Pfizer, Inc
Therapeutic Class	Antiviral agent and protease inhibitor
Formulation(s)	nirmatrelvir tablets co-packaged with ritonavir tablets 300 mg/100 mg and 150 mg/100 mg tablets for oral administration
Dosing Regimen	300 mg nirmatrelvir with 100 mg ritonavir with all 3 tablets taken together orally twice daily for 5 days In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), the dosage of Paxlovid is 150 mg nirmatrelvir and 100 mg ritonavir with both tablets taken together twice daily for 5 days

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity, Paxlovid (nirmatrelvir and ritonavir), is necessary to ensure the benefits outweigh its risks. Pfizer, Inc submitted a New Drug Application (NDA) 217288 for Paxlovid with the proposed indication: for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults (b) (4) who are at high risk for progression to severe COVID-19, including hospitalization or death. The FDA approved indication will be for the treatment of mild-to-moderate coronavirus 2019 (COVID-19) in adults who are at risk for progression to severe COVID-19, including hospitalization or death. The key safety concern determined to be associated with Paxlovid is the risk of serious adverse reactions due to drug-drug interactions (DDIs). The Applicant did not submit a proposed REMS or risk management plan with this application.

DRM and the Division of Antivirals (DAV) have determined that a REMS is not needed to ensure the benefits of Paxlovid outweigh its risks. The risk of serious adverse reactions due to DDIs, mainly due to the ritonavir component, will be addressed in labeling with a Boxed Warning. The Boxed Warning states to review all medications taken by the patient to assess potential drug-drug interactions with a strong CYP3A inhibitor like Paxlovid, and to determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring. Additionally, the label includes a table listing the clinically significant drug interactions, including contraindicated drugs for Paxlovid (not comprehensive) in Section 7.3, "Established and Other Potentially Signification Drug Interactions." This table includes a "Clinical Comments" column which provides guidance for the prescriber and patient to determine how to proceed with certain drug-drug combinations. Overall, the available safety data from the clinical trials demonstrate that Paxlovid is safe for its intended use and the risk of serious adverse reactions due to DDIs can be mitigated through labeling and further evaluated during routine pharmacovigilance.

1 Introduction

This review evaluates whether a REMS for the NME, Paxlovid (nirmatrelvir and ritonavir) is necessary to ensure the benefits outweigh its risks.[a] Pfizer, Inc submitted NDA 217188 for nirmatrelvir and ritonavir with the proposed indication: for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults (b) (4) who are at high risk for progression to severe COVID-19, including hospitalization or death.[1] This application is under review in the Division of Antivirals (DAV). The Applicant did not submit a proposed REMS or risk management plan with this application.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

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2 Background

2.1 PRODUCT INFORMATION

Paxlovid, an NME, includes nirmatrelvir (peptidomimetic inhibitor of the severe acute respiratory syndrome coronavirus 2 main protease inhibitor [SARS-CoV-2 M^{pro}]) co-packaged with ritonavir (HIV-1 protease inhibitor and CYP3A inhibitor). Inhibition of SARS-CoV-2 M^{pro} renders it incapable of processing the viral polyproteins pp1a and pp1ab, preventing viral replication. Ritonavir inhibits the Cytochrome P450 3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir.

The proposed indication for Paxlovid is for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults (b) (4) who are at high risk for progression to severe COVID-19, including hospitalization or death.[1,2]

The FDA approved indication will be:[2]
Paxlovid is indicated for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID 19, including hospitalization or death.

Paxlovid is available as nirmatrelvir 150 mg tablets and co-packaged with 100 mg tablets of ritonavir. The proposed dose of Paxlovid is 300 mg of nirmatrelvir (two 150 mg tablets) with 100 mg of ritonavir (one 100 mg tablet), with all 3 tablets taken by mouth together twice daily for 5 days. There is a dose reduction for moderate renal impairment (eGFR ≥ 30 to < 60 mL/min): 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet), with both tablets taken together twice daily for 5 days.

Ritonavir has been approved in the US since 1996 in various formulations including tablets and oral solution and is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. The oral powder formulation is indicated for the treatment of pediatric patients with HIV-1 infection.[3] Ritonavir is approved with a Boxed Warning for drug-drug interactions (DDIs) leading to potentially serious and/or life-threatening reactions. The proposed label for Paxlovid also includes a Boxed Warning for DDIs.[2]

Paxlovid is not currently approved in any jurisdiction, however, on December 22, 2021, the FDA issued an Emergency Use Authorization (EUA) for emergency use of PAXLOVID for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.[4]

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 217188 relevant to this review:

- **12/22/2020**: Pfizer, Inc submitted IND 153517 for PF-07321332 for the treatment of COVID-19.
- **10/21/2021**: Pfizer, Inc submitted an Emergency Use Authorization (EUA) request for Paxlovid for the treatment of mild-moderate COVID-19.

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- **12/22/2021**: The FDA issued an EUA for Paxlovid for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2, including hospitalization or death based on the totality of scientific evidence available to the Agency, including data from the clinical trial EPIC-HR (NCT04960202), a phase 2/3 randomized, double blind, placebo-controlled clinical trial.
- **02/17/2022**: Fast Track Designation was granted for Paxlovid for the treatment of COVID-19.
- **06/29/2022**: Pfizer, Inc submitted NDA 217188 for Paxlovid for the following proposed indication: for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults (b) (4) who are at high risk for progression to severe COVID-19, including hospitalization or death.
- **10/27/2022**: A Post Mid-Cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that the Agency does not anticipate a REMS will be needed.
- **12/16/2022**: The Applicant's submissions on November 23, 2022, and December 5, 2022, constituted a major amendment to NDA 217188. The goal date was extended by three months. The extended user fee goal date is May 28, 2023.
- **03/16/2023**: The Antimicrobial Drugs Advisory Committee (AMDAC) meeting convened to discuss Paxlovid. The majority of the committee voted "yes" (16/17) for to the question, "Is the overall benefit-risk assessment favorable for Paxlovid when used for the treatment of mild to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death?"

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

At the end of 2019, a novel coronavirus, SARS-CoV-2, was identified which resulted in a world-wide pandemic. SARS-CoV-2, commonly referred to as COVID-19, is a serious and potentially life-threatening illness, which can result in pneumonia, multiorgan failure, respiratory failure, and death.[5] Patients may experience the following symptoms: fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, and loss of taste and smell.[6] Some patients may also experience "long COVID" or "post-COVID conditions" which includes a broad range of symptoms (physical and mental) and symptom clusters that develop during or after COVID-19, continue for ≥2 months (i.e., three months from the onset of illness), have an impact on the patient's life, and are not explained by an alternative diagnosis.[7] As of March 10, 2023, there have been over 100 million cases of COVID-19 infection with approximately 1.1 million deaths attributable to COVID-19 in the United States.[8]

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Table 1:[6] Clinical Spectrum of COVID-19 Infection

COVID-19 Severity	Definition
Asymptomatic or Pre-symptomatic	Test positive using a virologic test but have no symptoms
Mild	Presence of symptoms without shortness of breath or abnormal chest imaging
Moderate	Presence of symptoms and evidence of lower respiratory tract disease by clinical examination or chest imaging accompanied by oxygen saturation ≥ 94% on room air
Severe	Oxygen saturation < 94% on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen of < 300 mmHg, a respiratory rate > 30 breaths/minute, or lung infiltrates > 50%
Critical	Respiratory failure, septic shock, and/or multiorgan dysfunction

3.2 Description of Current Treatment Options

Non-pharmacologic treatment of COVID-19 includes supportive care and convalescent plasma. Convalescent plasma is obtained from individuals, usually by apheresis, who have recovered from an infection and have generated an immune response against the infective pathogen. During the COVID-19 pandemic, over 250,000 units have been administered to patients via an expanded access program, emergency use authorizations, and clinical trials. The risk of serious adverse events associated with convalescent plasma for COVID-19 are low.[9] However, it is no longer widely available.

Remdesivir (Veklury), administered by intravenous infusion daily for 3 days, is the only FDA-approved treatment option for COVID-19. It is indicated for the treatment of COVID-19 in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) who are: hospitalized or not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.[10] However, access to remdesivir may be difficult for non-hospitalized patients as it requires a health care facility that can administer infusions and should be initiated within 7 days of symptom onset.

The FDA issued an Emergency Use Authorization (EUA) for both Paxlovid and Lagevrio (molnupiravir) on December 22, 2021, and December 23, 2021, respectively. Molnupiravir is a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis. It is authorized for the treatment of adults with a current diagnosis of mild-to-moderate coronavirus disease 2019 (COVID-19): who are at high risk for progression to severe COVID-19, including hospitalization or death; and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.[11] The National Institutes of Health guidelines offer molnupiravir as an alternative to those who cannot receive Paxlovid and remdesivir.[12] Anti-SARS-CoV-2 therapeutic monoclonal antibodies (mAbs) were previously available under EUA for the treatment of mild-to-moderate COVID-19 in certain individuals at high risk for progression to severe disease. However, no anti-SARS-CoV-2 mAbs are currently authorized for emergency use for COVID-19 treatment due to nonsusceptibility to the currently circulating SARS-CoV-2 Omicron subvariants.

There is an unmet medical need for safe, effective, and convenient outpatient COVID-19 treatment options, particularly ones with a target that is anticipated to be conserved across the different SARS-CoV-2 variants and subvariants.[13]

4 Benefit Assessment

4.1 EPIC-HR

EPIC-HR or C4671005 (NCT 04960202) is the pivotal, Phase 2/3, randomized, double-blind, placebo-controlled trial that provides the primary basis of efficacy and safety of nirmatrelvir/ritonavir for treatment in patients with mild-to-moderate COVID-19 who were at high risk for progression to severe COVID-19, including hospitalization or death.

Participants with a confirmed diagnosis of SARS-CoV-2 infection and with symptom onset within five days were randomized 1:1 to receive nirmatrelvir 300 mg co-administered with ritonavir 100 mg (N = 1,049) or placebo (N = 1,064) orally every 12 hours for five days (10 doses in total). The primary efficacy endpoint was the proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28 in the modified intent to treat (mITT) population. The first key secondary efficacy endpoint was proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28 in mITT1 population. The second key secondary efficacy endpoint was time to sustained alleviation of all targeted signs/symptoms through Day 28 in mITT.

The proposed label focuses on the MITT1 population. Results showed there was a 5.6% absolute reduction (95% confidence interval [CI]: -7.3% to -4.0%; p<0.0001) or 86% relative reduction (95% CI: 72%, 93%), compared to placebo, for the primary efficacy endpoint of COVID-19 related hospitalization or death from any cause through Day 28 in the mITT1 population. Refer to the tables below for details.

Table 2:[5] Proportion of Participants with COVID-19-Related-Hospitalization or Death from Any Cause Through Day 28, Trial EPIC-HR

mITT: All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤ 3 days of COVID-19 symptom onset		
	Paxlovid N=671	**Placebo N=647**
Participants with event, n (%)	5 (0.7)	44 (6.8)
COVID-19 hospitalization	5 (0.7)	44 (6.8)
Death	0	9 (1.4)
Estimated difference in proportion % (95% CI)*	-6.1 (-8.2, -4.1)	
Two-sided p-value	<0.0001	
mITT1: All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤ 5 days of COVID-19 symptom onset		
	Paxlovid N=977	**Placebo N=989**
Participants with event, n (%)	9 (0.9)	64 (6.5)
COVID-19 hospitalization	9 (0.9)	63 (6.4)
Death	0	12 (1.2)

Estimated difference in proportion % (95% CI)*	-5.6 (-7.3, -4.0)	
Two-sided p-value	<0.0001	
mITT2: All participants randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤ 5 days of COVID-19 symptom onset		
	Paxlovid N=1038	**Placebo N=1053**
Participants with event, n (%)	10 (1.0)	66 (6.3)
COVID-19 hospitalization	10 (1.0)	65 (6.2)
Death	0	12 (1.1)
Estimated difference in proportion % (95% CI)*	-5.4 (-7.0, -3.8)	
Two-sided p-value	<0.0001	
mAb = monoclonal antibody		

Table 3:[5] Time to Sustained Symptom Resolution through Day 28, Trial EPIC-HR in the mITT

	Paxlovid N=666	**Placebo N=645**
Participants with sustained symptom resolution, n (%)	445 (66.8)	388 (60.2)
Median time to sustained symptom resolution by Day 28 (95% CI)	16 (14, 17)	18 (17, 20)
Two-sided p-value	0.0026	

4.2 EPIC-SR

EPIC-SR (C4671002 – NCT 05011513) was a randomized, double-blind, global trial in which non-hospitalized adults who were either vaccinated against COVID-19 and at high risk for progression to severe disease or unvaccinated with no risk factors for progression to severe disease were randomized to receive 5 days of PAXLOVID versus placebo for the treatment of mild-to-moderate COVID-19. A total of 1,075 patients were randomized (1:1) to receive Paxlovid or placebo orally every 12 hours for 5 days; of these, 59% were fully vaccinated and high-risk.[2]

The primary endpoint in this trial, the difference in time to sustained alleviation of all targeted COVID-19 signs and symptoms through Day 28 among PAXLOVID versus placebo recipients, was not met. In an exploratory analysis of the subgroup of fully vaccinated subjects with at least 1 risk factor for progression to severe disease, a non-statistically significant numerical reduction relative to placebo for the secondary endpoint of COVID-19 related hospitalization or death from any cause through Day 28 was observed.[2]

The clinical review team concluded that the clinical trial results from EPIC-HR and EPIC-SR support the efficacy of Paxlovid for the treatment of mild-to-moderate COVID-19 in high-risk adults regardless of COVID-19 vaccination status or evidence of prior SARS-CoV-2 infection. Although the clinical trial data was limited to assess efficacy against the Omicron variant, the clinical reviewer concluded that Paxlovid is likely to retain clinical efficacy against the currently circulating Omicron subvariants.[13]

(b) (4)

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(b) (4)

5 Risk Assessment & Safe-Use Conditions

The safety of Paxlovid was established in two Phase 2/3 randomized, placebo-controlled trials in symptomatic adult subjects 18 years of age and older with a laboratory confirmed diagnosis of SARS-CoV-2 infection, EPIC-HR and EPIC-SR. In comparison, EPIC-HR included patients (Paxlovid – N = 1,038; Placebo – N = 1,053) who were at high risk for progression to severe disease while EPIC-SR enrolled patients (Paxlovid – N = 540; Placebo – N = 528) who were at standard risk for progression to severe disease (previously unvaccinated subjects at standard risk or fully vaccinated subjects with at least 1 risk factor for progression to severe disease).[5] Adverse reactions were those reported while patients were on study medication and through 28 days after the last dose of study treatment.

In EPIC-HR, the most common adverse reactions (≥ 1% incidence in the Paxlovid group and occurring at a greater frequency than in the placebo group) were dysgeusia (5% and <1%, respectively) and diarrhea (3% and 2%, respectively). In EPIC-SR, the adverse reactions observed were consistent with those observed in EPIC-HR.[2] Overall, no deaths occurred in patients who received Paxlovid.

The following adverse reactions have been identified during use of Paxlovid under EUA:[2]

- *Immune System Disorders:* Anaphylaxis, hypersensitivity reactions
- *Skin and Subcutaneous Tissue Disorders:* Toxic Epidermal Necrolysis, Stevens-Johnson syndrome
- *Nervous System Disorders:* Headache
- *Vascular Disorders:* Hypertension
- *Gastrointestinal Disorders:* Abdominal pain, nausea, vomiting
- *General Disorders and Administration Site Conditions:* Malaise

The key safety concern determined to be associated with Paxlovid is the risk of serious adverse reactions due to drug-drug interactions (DDIs).[b]

5.1 Drug-Drug Interactions

Ritonavir, a component of Paxlovid, exhibits strong Cytochrome P450 3A (CYP3A) inhibition and can result in significant elevations of concomitant medications that are metabolized by CYP3A. Both EPIC-HR and EPIC-SR excluded patients with current or expected use of any medications that have DDIs with Paxlovid; therefore, this risk could not be evaluated in those studies. However, analyses of post-EUA data shows:[13]

- Over 50% of Paxlovid-eligible patients (adults who are at high risk for development of severe COVID-19) are on medications with DDIs with Paxlovid.
- The majority of Paxlovid prescribers are adult primary care practitioners.

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

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- Serious adverse reactions, including death, have been reported in association with DDIs that are included in the current EUA Fact Sheet for Healthcare Providers. The most commonly reported concomitant medications resulting in serious adverse reactions were calcineurin inhibitors (e.g., tacrolimus, cyclosporine) and calcium channel blockers.

The clinical review team concluded based on the safety surveillance data this information should be highlighted in the prescribing information using a Boxed Warning.

The proposed Boxed Warning is as follows:[2]

WARNING: SIGNIFICANT DRUG INTERACTIONS WITH PAXLOVID

- PAXLOVID includes ritonavir, a strong CYP3A inhibitor, which may lead to greater exposure of certain concomitant medications, resulting in potentially severe, life-threatening, or fatal events *[see Contraindications (4), Warnings and Precautions (5.1), and Drug Interactions (7)].*
- Prior to prescribing PAXLOVID: 1) Review all medications taken by the patient to assess potential drug-drug interactions with a strong CYP3A inhibitor like PAXLOVID and 2) Determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring *[see Drug Interactions (7)].*
- Consider the benefit of PAXLOVID treatment in reducing hospitalization and death, and whether the risk of potential drug-drug interactions for an individual patient can be appropriately managed *[see Warnings and Precautions (5.1), Drug Interactions (7), and Clinical Studies (14)].*

A table listing of the clinically significant drug interactions, including contraindicated drugs for Paxlovid (not comprehensive) is provided in Section 7.3, "Established and Other Potentially Signification Drug Interactions," of the proposed label.[2] This table includes a "Clinical Comments" column which provides guidance for the healthcare provider and patient to determine how to proceed with certain drug-drug combinations.

5.2 Hypersensitivity Reactions

Anaphylaxis, serious skin reactions (including Toxic Epidermal Necrolysis and Stevens-Johnson syndrome), and other hypersensitivity reactions have been reported with Paxlovid.[2] In EPIC-HR, the frequency of hypersensitivity events were 0.4% in the Paxlovid group and 0.5% in the placebo group. In EPIC-SR, hypersensitivity events were 0.4% in the placebo group and none in the placebo group. There were no deaths or serious adverse events or deaths related to hypersensitivity events. There were no cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, or anaphylaxis reported in either EPIC-HR or EPIC-SR.[13]

The proposed label includes a Warning and Precaution for hypersensitivity reactions that states,[2] "If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue Paxlovid and initiate appropriate medications and/or supportive care."

6 Expected Postmarket Use

If approved, Paxlovid will primarily be used in the outpatient setting. The likely prescribers will be adult primary care providers. These providers may not be as familiar with managing ritonavir DDIs as

providers who specialize in HIV management. However, the proposed Paxlovid label states, "Prior to prescribing PAXLOVID, review all medications taken by the patient to assess potential drug-drug interactions and determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring." The label also refers prescribers to view the table of clinically significant drug interactions, including contraindicated drugs as a guide to drug therapy management. This information was also provided in the Fact Sheet for Healthcare Providers: EUA for Paxlovid.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Paxlovid beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The FDA review team has determined, based upon review of all available efficacy and safety data, the benefits of Paxlovid outweigh the risks for the treatment of mild-to-moderate COVID-19 in adults at high risk for progression to severe disease.[13]

COVID-19 is a serious and potentially life-threatening illness with a clinical spectrum that varies greatly. As of March 10, 2023, there have been over 100 million cases of COVID-19 infection with approximately 1.1 million deaths attributable to COVID-19 in the United States. There is an unmet medical need for safe, effective, and convenient outpatient COVID-19 treatment options, particularly ones with a target that is anticipated to be conserved across the different SARS-CoV-2 variants and subvariants.[13]

The key safety concern with Paxlovid is the risk of serious adverse reactions due to DDIs. While primary care provides may not be as familiar with managing DDIs with ritonavir as other specialists, many of the DDIs can be managed by dose adjustment, interruption, and/or additional monitoring of the concomitant medication. Prescribers need to consider the benefit of Paxlovid treatment in reducing hospitalization and death versus the risk of potential DDIs for an individual patient. This risk is described in Paxlovid's proposed labeling with a Boxed Warning to highlight this important risk.[13] The proposed label also includes a table of clinically significant drug interactions, including contraindicated drugs, as a guide to drug therapy management. Additionally, other CYP 3A4 inhibitors like clarithromycin and voriconazole have DDIs addressed in "Section 7 – Drug Interactions" of their respective labeling. Overall, the available safety data from the clinical trials demonstrate that Paxlovid is safe for its intended use and the risk of serious adverse reactions due to DDIs can be mitigated through labeling and further evaluated during routine pharmacovigilance.[13]

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for Paxlovid to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

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10 Appendices

10.1 References

1. Pfizer, Inc. Paxlovid (nirmatrelvir tablets and ritonavir). NDA 217188. Prescribing Information, proposed. June 29, 2022
2. Pfizer, Inc. Paxlovid (nirmatrelvir tablets and ritonavir). NDA 217188. Prescribing Information, final. May 25, 2023.
3. AbbVie, Inc. Norvir (ritonavir). NDA 022417. Prescribing Information. *Drugs@FDA*. December 15, 2022.
4. Emergency Use Authorizations for Drugs and Non-Vaccine Biological Products - EUAs for CDER Regulated Products. Paxlovid. Accessed May 11, 2023, https://www.fda.gov/drugs/emergency-preparedness-drugs/emergency-use-authorizations-drugs-and-non-vaccine-biological-products
5. Food and Drug Administration. Division of Antivirals/Office of Infectious Diseases. Antimicrobial Drugs Advisory Committee Meeting. Paxlovid (nirmatrelvir tablets and ritonavir). FDA Briefing Document. March 16, 2023. https://www.fda.gov/media/166197/download
6. National Institues of Health. COVID-19 Treatment Guidelines: Clinical Spectrum of SARS-CoV-2. . March 6, 2023. Accessed March 27, 2023. https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/
7. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Accessed October 5, 2022. https://www.covid19treatmentguidelines.nih.gov/
8. John Hopkins University of Medicince Coronovirus Resource Center. COVID-19 Dashboard. March 10, 2023. Accessed March 27, 2023. https://coronavirus.jhu.edu/map.html
9. Bloch E. COVID-19: Convalescent plasma and hyperimmune globulin. *UpToDate*. August 29, 2022. Accessed March 27, 2023. https://www.uptodate.com/contents/covid-19-convalescent-plasma-and-hyperimmune-globulin?search=convalescent%20plasma&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#
10. Gilead Sciences, Inc. Veklury (remdesivir). Prescribing Information. . *Drugs@FDA*. March 29, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/214787s018lbl.pdf
11. Merck. Fact Sheet for Healthcare Providers: Emergency Use Authorization for Lagevrio (molnupiravir). February 1, 2023. https://www.fda.gov/media/155054/download
12. Cohen P, Gebo K. COVID-19: Management of adults with acute illness in the outpatient setting. *UpToDate*. March 29, 2023. https://www.uptodate.com/contents/covid-19-management-of-adults-with-acute-illness-in-the-outpatient-setting?search=molnupiravir&source=search_result&selectedTitle=2~7&usage_type=default&display_rank=1#H1479728004
13. Food and Drug Administration. Paxlovid (nirmatrelvir and ritonavir). NDA 217188. Integrated Review. Reference ID: 5179402. May 24, 2023.

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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Review of Real-World Evidence on PAXLOVID effectiveness

Date:	May 18, 2023
Team Leader:	Natasha Pratt, Ph.D. Division of Epidemiology II
Division Director:	Monique Falconer, M.D. M.S. Division of Epidemiology II
Subject:	Review of Real-World Evidence on PAXLOVID effectiveness
Drug Name:	PAXLOVID (nirmatrelvir tablets; ritonavir tablets)
Application Type/Number:	NDA 217188
Applicant/sponsor:	Pfizer
OSE TTT #:	2022-679

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EXECUTIVE SUMMARY

Pfizer, the applicant, submitted the New Drug Application (NDA) for PAXLOVID **(nirmatrelvir tablets; ritonavir tablets)** in June 2022. The applicant is seeking an indication for COVID-19 treatment among high-risk patient regardless of their vaccination status, similar to the PAXLOVID indication for its Emergency Use Authorization (EUA). The clinical review team considers the clinical trial data submitted for the NDA sufficient to support the benefit of PAXLOVID as COVID-19 treatment in the Omicron era, regardless of vaccination status. The Division of Antivirals requested an assessment of the publicly available literature on observational real-world evidence (RWE) studies to determine whether the RWE contradicts the trial conclusions.

The literature search conducted by Division of Epidemiology II (DEPI II) on January 30, 2023, identified 22 RWE studies that evaluated PAXLOVID effectiveness in outpatient COVID-19 populations. Seventeen of the 22 published studies were excluded from in-depth DEPI II review as they included overlapping study populations with the reviewed RWE studies, were based on insufficient longitudinal data in the data sources and/or were unable to account for potential bias introduced by index time selection. The five remaining studies included in our in-depth review were cohort studies conducted in non-hospitalized COVID-19 patients during the Omicron era. Two studies were based on nation-wide or territory-wide electronic health records (EHR) of hospitals and outpatient clinics in Israel and China (Hong Kong); one study used province-wide integrated health care data from Quebec, Canada; two studies used EHR and administrative claims data from the U.S. Veterans Health Administration and an integrated healthcare system in a single U.S. state. All studies evaluated the risk of COVID-19-related hospitalization, or all-cause hospitalization between PAXLOVID-treated COVID-19 patients and those who were not treated with PAXLOVID.

The reviewed RWE studies consistently reported that PAXLOVID use is associated with a reduction in the risk of worsening COVID-19 outcomes in broader populations than those included in the pivotal trials - with respect to age, underlying “high-risk” comorbidities and COVID-19 vaccination status in Omicron era. However, the information available for the reviewed RWE studies is insufficient to determine their quality.

DEPI II determined that the results of the five reviewed studies did not contradict the findings of those trials. Given the lack of information to determine quality, DEPI II recommended against using the results of the available RWE studies to support or refute effectiveness of PAXLOVID treatment in non-hospitalized COVID-19 patients, especially among specific patient subgroups.

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1 INTRODUCTION

This review document Division of Epidemiology II's (DEPI II) assessment of the available real-world evidence (RWE) on the effectiveness of PAXLOVID (nirmatrelvir tablets; ritonavir tablets) to address a specific regulatory question from the Division of Antivirals (DAV), as part of the review of the PAXLOVID application for marketing approval.

1.1 BACKGROUND AND REGULATORY HISTORY

PAXLOVID is co-packaged oral tablets that includes nirmatrelvir, a SARS-CoV-2 main protease (M^{pro}: also referred to as 3CLpro or nsp5 protease) inhibitor, and ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor. On December 22, 2021, FDA authorized PAXLOVID for emergency use for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients with positive results of direct severe acute respiratory syndrome SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.[a]

On June 29, 2022, Pfizer, the applicant, submitted the New Drug Application for PAXLOVID. The applicant sought an indication for COVID-19 treatment among high-risk patient regardless of their vaccination status, similar to the indication for the PAXLOVID Emergency Use Authorization.

The applicant submitted two phase 2/3 placebo-controlled clinical trials-Study C4671005 (EPIC-HR) and study C4671002 (EPIC-SR) to support efficacy of PAXLOVID as COVID-19 treatment. These trials were conducted before the dominant circulating SARS-CoV-2 variant was Omicron.

- Although the completed EPIC-HR pivotal trial on efficacy in high-risk patients excluded vaccinated individuals, the relative risk reduction on COVID-19 related hospitalization or all cause death through Day 28 were similar between seropositive patients[b] versus seronegative patients in EPIC-HR trial (88%, p=0.02 vs. 86%, p=<0.0001).
- Fully vaccinated high-risk patients were eligible to enroll into the ongoing supportive EPIC-SR trial until December 19, 2021, since they are considered at low-risk for severe disease.[c] The submitted interim analyses data (with data cut on December 19, 2021) showed non-significant trend towards reduction in of COVID-19 related hospitalization or all cause death through Day 28 in the vaccinated patients (relative risk reduction= 57%, p=0.2).

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[a] EUA Factsheet: https://www fda.gov/media/155050/download

[b] "Seropositive" means that the trial participants had antibodies against SARS-CoV-2 antigens detected in their blood at baseline. Given that EPIC-HR excluded vaccinated patients, and patient with prior infection detected by a molecular test (antigen or nucleic acid), the seropositive patients were those with prior asymptomatic/undetected SARS-CoV-2 infection

[c] EPIC-SR stopped enrolling fully vaccinated "high-risk" patients for ethical reasons after PAXLOVID EUA was authorized in December 2021, since high-risk patient regardless of vaccination status could obtain PAXLOVID under EUA.

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The clinical review team considers that together the data submitted from EPIC-HR and EPIC-SR support the benefit of PAXLOVID as COVID-19 treatment in high-risk patients for hospitalization or death, regardless of vaccination status and whether in the Omicron era.

1.2 REGULATORY QUESTION

DAV consulted DEPI II to assess the publicly available literature on observational RWE studies of the use of PAXLOVID in vaccinated patients and/or in the Omicron era to answer the following question:

- Does the evidence from published observational RWE studies **contradict** the conclusion of benefit of PAXLOVID for the treatment of mild to moderate COVID-19 in patients who are at high risk for progression to severe COVID-19, including hospitalization or death, regardless of vaccination status and in the Omicron era?

2 REVIEW METHODS AND MATERIALS

We searched the WHO COVID-19-research database[d] and PubMed, using the search terms "PAXLOVID" and "epidemiology/RWE study" (Details in Appendix). We excluded articles that did not:

- report a study that evaluated PAXLOVID effectiveness.
- report observational studies (e.g., articles reported clinical trials, case reports, case series).
- report findings of analyses on PAXLOVID effectiveness, compared to non-PAXLOVID-treated COVID-19 patients.
- evaluate PAXLOVID effectiveness in an outpatient COVID-19 population.

We further applied the following criteria for selecting studies for in-depth review:

- Studies that fulfilled the following key data sources and design features:
    - **Longitudinal data**: used data source(s) that allows longitudinal capture of the key covariates across different healthcare settings:
        - Diagnosis/test of COVID-19 in an ambulatory setting.
        - Exposure to PAXLOVID as outpatient treatment.
        - Vaccination status prior to COVID-19 diagnosis/PAXLOVID exposure.
        - Clinical outcome (hospitalization or death) after COVID-19 diagnosis/PAXLOVID exposure.
        - Comorbid conditions and concurrent medication use at time of COVID-19 diagnosis/PAXLOVID use.
    - **"Nonuser" reference group**: Included "nonuser" as a reference group, since we do not have trial data to support effectiveness of PAXLOVID against an "active control" (i.e., other potential COVID-19 treatments).
    - **Index time selection**: Applied design feature that can account for the potential bias introduced by "index time" selection for the treated and

[d] https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/

untreated patients, given that PAXLOVID users were COVID-19 patients who remained hospitalization-free and survived from diagnosis to treatment, which can lead to bias in favor of finding PAXLOVID effectiveness.

3 REVIEW RESULTS

Our last literature search was conducted on January 30, 2023. Among the 297 English-language articles identified by our search terms, 22 were observational studies that evaluated PAXLOVID effectiveness in outpatient COVID-19 populations (see Appendix). Of those 22 studies, we excluded,

- three publications[1-3] of shorter study duration that used the same data source as another publication.[e]
- one publication[4] that only evaluated "post-acute sequelae of COVID-19"[f] occurring from 30 to 90 days after SARS-CoV-2 infection. This study was excluded due to the following study design concerns:
  - The validity of code-based algorithms to capture the individual post-acute COVID-19 sequelae were not reported.
  - Important confounders were neither reported nor accounted for in the analyses (e.g., use of medications that could influence the risk of clinical conditions classified as "post-acute COVID-19 sequelae").

We screened the remaining publications and further excluded 13 studies that did not meet all the key data source and design features criteria for "in-depth" review (Table 1)

Table 1 Screening of the identified observational RWE studies on outpatient PAXLOVID effectiveness

		Fulfilled key data source and design features for in-depth review		
	Study screened	**Longitudinal data source**	**"Non-user" reference group**	**Design to handle bias due to "index time selection"**
Excluded	Hedvat et al.[5]	No	Yes	No
	Dryden-Peterson et al.[6]	No	Yes	Yes
	Ganatra et al.[7]	No	Yes	No
	Zhou et al.[8]	No	Yes	Yes
	Aggarwal et al.[9]	No	Yes	No
	Bruno et al.(a)[10]	unclear	No	N/A
	Bruno et al.(b)[11]	unclear	No	N/A
	Gentile et al.[12]	unclear	No	N/A
	Park H et al.[13]	Yes	Yes	No
	Park J et al.[14]	Yes	Yes	No

[e] The publication by Najjar-Debbiny et al. was excluded due to an overlapping Israeli data source with Arbel et al. The publications by Yip et al. and Wai et al. were based on the same territory-wide population in Hong Kong as that by Wong et al.

[f] Post-acute death or hospitalization and individual sequela including ischemic heart disease, dysrhythmia, deep vein thrombosis, pulmonary embolism, fatigue, liver disease, acute kidney injury, muscle pain, diabetes, neurocognitive impairment, shortness of breath and cough.

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		Fulfilled key data source and design features for in-depth review		
	Study screened	**Longitudinal data source**	**"Non-user" reference group**	**Design to handle bias due to "index time selection"**
	Qian[15]	No	Yes	No
	Shah et al. [16]	No	Yes	unclear
	Tiseo et al.[17]	unclear	No	N/A
Included	Arbel et al.[18]	Yes	Yes	Yes
	Wong et al.[19]	Yes	Yes	Yes
	Bejama et al.[20]	Yes	Yes	Yes
	Schwartz et al.[21]	Yes	Yes	Yes
	Lewnard et al.[22]	Yes	Yes	Yes

Five studies were reviewed in-depth (Arbel, Wong Bejama, Schwartz and Lewnard). Of note, the publications by Bejama, Schwartz and Lewnard are non-peer-reviewed preprints.[g] We summarized the study designs, data sources and methods in Appendix Table 1.

Briefly, the five reviewed studies were cohort studies involving non-hospitalized patients with positive SARS-CoV-2 RT-PCR or antigen test results during the period of Omicron-variant dominance. One study in Israel and one study in China (Hong Kong) used nation-wide or territory-wide electronic health records of hospitals and outpatient clinics. One study in Quebec, Canada used a province-wide integrated health-care data. The final two studies used electronic health records and administrative claims data; one was based on the U.S. Veterans Health Administration and the other based on an integrated healthcare system of a single U.S. state. These five studies also included broader study populations than those included in the pivotal trials—with respect to age, underlying high-risk comorbidities, and COVID-19 vaccination status.

The five studies evaluated the risk of COVID-19-related hospitalization or all-cause hospitalization in PAXLOVID-treated COVID-19 patients compared to those not treated with PAXLOVID (nonusers). They also evaluated other clinical outcomes, such as mortality or in-hospital COVID-19 progression. The reviewed studies in general reported that PAXLOVID was effective or trended towards effectiveness regardless of COVID-19 vaccination status. (Appendix Table 2 and 3).

4 DISCUSSION

Compared to the studies excluded from in-depth review, the five reviewed RWE studies used more appropriate data sources, study design, or analytical approaches to account for the potential bias introduced by inappropriate handling of index time selection.

However, unlike applicant-sponsored efficacy trials that provide more information to assess study quality, none of the reviewed RWE studies published their protocol and analytical plan prior to the final study report. In at least one study (Lewnard), the analyses and results differed notably between two versions of the preprints. So, it was

[g] The manuscripts have not been peer-reviewed. Non-peer-reviewed preprints might not be accepted for publication by a peer-reviewed journal. If they are formally published in a peer-reviewed journal, there might be revisions of the methods or analyses to address the editor's or reviewers' comments.

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difficult to track whether these studies were conducted according to a prespecified protocol and analytical plan. Additionally, patient-level data in the observational studies were unavailable to verify the correct implementation of study design and statistical methods, which is a standard review process for trial data used to support treatment efficacy.

Despite insufficient information on reviewed studies due to what is reported in the public domain, we still identified methodological or analytical issues in the reviewed studies. Some of these issues had reasonably predictable impact on the study findings, while there were other review issues for which we would need more information than was provided to determine the potential impact on the study results. We discuss the review issues in Section 4.1 and 4.2.

4.1 REVIEW ISSUES WITH A REASONABLY PREDICTABLE IMPACT ON STUDY FINDINGS

Residual confounding by COVID-19 severity (All studies)

Three of the reviewed studies did not capture or adjust for baseline COVID-19 severity (Arbel, Wong, and Schwartz). The studies by Bajema and Lewnard accounted for the presence of COVID-19 symptoms at baseline; however, the validity of the operational definitions for COVID-19 symptoms was not reported. Residual confounding due to COVID-19 severity would likely to underestimate of PAXLOVID effectiveness, given that PAXLOVID was more likely to be given to symptomatic patients or patients with severe symptoms.

Residual confounding by "high-risk comorbidities" (Arbel and Wong studies)

Although the Arbel study captured information on medical conditions that increase a patient's risk for COVID-19 progression (high-risk comorbidities), not all were adjusted for in the analyses. The Wong study matched the treated and non-treated patients on a summary comorbidity risk score (i.e., Charlson Comorbidity Index), which did not guarantee the component medical conditions of the risk score would be balanced between treatment groups. Furthermore, the component medical conditions of the Charlson Comorbidity Index were not an exact match to the high-risk comorbidities for worse COVID-19 progression. For example, the Charlson Comorbidity Index does not account for all immunosuppressive diseases (e.g., bone marrow or organ transplantation), prolonged use of immune-weakening medications, chronic lung diseases (except for chronic obstructive pulmonary disease), neurodevelopmental disorders, sickle cell disease. Lastly, the Wong study did not report distribution of high-risk comorbidities for COVID-19 progression to inform if these important confounders were balanced between treatment groups.

Residual confounding due to unbalanced high-risk comorbidities would likely underestimate of PAXLOVID effectiveness, given that PAXLOVID treatment for COVID-19 patients with high-risk comorbidities was likely prioritized.

Outcome selection (Bejama and Lewnard studies)

Studies by Bajema and Lewnard used "all-cause hospitalization or death" as the primary outcome, which included events that are unrelated to PAXLOVID effect (i.e.,

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hospitalization or death due to causes other than COVID-19). If the proportion of outcome events unrelated to COVID-19 is nondifferential between treated and nontreated groups, it would bias findings toward null (underestimate of PAXLOVID effectiveness). The proportion of events unrelated to COVID-19 can be higher among PAXLOVID users, given that administration of PAXLOVID is prioritized to patients with comorbidities that may lead to a higher risk of hospitalization or death due to non-COVID-19 causes, which will also lead to underestimate of PAXLOVID effectiveness.

Study power to evaluate PAXLOVID effectiveness in subgroups (All studies)

Only one reviewed study reported a priori power analyses (Bajema et al.). All the reviewed studies were not powered to formally test treatment effect modification by patient characteristics, or to evaluate PAXLOVID effectiveness in any patient subgroup. Some studies suggested that PAXLOVID effectiveness may differ by age, for example, Arbel concluded that "no evidence of benefit was found in patients younger than 65 years of age." The study findings did not support a statistically significant reduction in COVID-19 hospitalization risk (hazard ratio=0.74, 95% CI=0.35 to 1.58) or death (hazard ratio=1.32, 95% CI=0.16 to 10.75) associated with PAXLOVID use among a younger population (40 to 65 years of age). However, it is likely that the study did not have sufficient power to evaluate PAXLOVID effectiveness in the younger population, evidenced by the wide 95% CIs of the effect estimates.

4.2 REVIEW ISSUES THAT REQUIRE MORE INFORMATION TO EVALUATE THE IMPACT ON STUDY RESULTS

Unvalidated outcome measures

COVID-19-Related Hospitalization (Arbel, Wong, and Schwartz Studies)

Three reviewed studies included "hospitalization due to COVID-19" as the endpoint, or part of the endpoints (Arbel, Wong, and Schwartz). However, none of the studies provided data to support the validity of the measure for "COVID-related hospitalization." Without a better understanding of how information on COVID-19 related hospitalization was recorded or derived, it is difficult to predict if the outcome misclassification would be differential and how it might influence the study findings.

Post-COVID-19 Conditions (Bajema Study)

The Bajema study also evaluated PAXLOVID's effectiveness on multiple potential post-COVID-19 conditions; however, they did not provide data to support the International Classification of Diseases, 10th Edition diagnosis codes that were used to capture these conditions. It is difficult to predict if the outcome misclassification would be differential and how it might influence the study findings.

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Residual confounding by other potential confounders

Information on the frequencies and the distribution of the potential confounders (discussed below) by treatment groups is needed to understand the magnitude and direction of potential biases on study findings.

Detailed Information on COVID-19 Vaccination (Arbel, Wong, and Lewnard Studies)

Total dose, timing of last dose, type or manufacturer of the COVID-19 vaccine could impact PAXLOVID effectiveness for COVID-19 outcomes. Not all reviewed studies captured or accounted for detailed information on COVID-19 vaccination in their analyses. The Arbel and Wong studies only reported and accounted for vaccination status as dichotomous variables ("presence of prior immunity or not" in Arbel study, "fully vaccinated or not" in the Wong study). The Lewnard study only adjusted for the number of total vaccine doses received in their analyses.

Other Outpatient COVID-19 Medication Use at Baseline (Lewnard Study)

Prior or concurrent use of other outpatient medications for COVID-19 at baseline can be a potential confounder as they can influence COVID-19-related clinical outcomes. The Lewnard study did not exclude patients who used other COVID-19 medications at baseline, while several treatment options were available in the United States during the timeframe of the study. The study also did not report the use of the other outpatient COVID-19 treatment at baseline, nor adjusted for baseline use of these medications in their analyses.

Other Medications Use (Bajema Study)

The Bajema study included analyses of PAXLOVID effectiveness on risk of long-term outcomes (i.e., hospital admission, nursing skilled nursing home facility admission, all-cause death, or post-COVID-19 conditions) that occurred 31 to 180 days after diagnosis. PAXLOVID was prioritized for patients with COVID-19 and certain comorbidities that are also components of the "post-COVID conditions", for example, cardiovascular disease, hypertension, asthma, chronic obstructive pulmonary disease, chronic kidney disease, cerebrovascular disease, diabetes, obesity. The use of other medications, especially those indicated for the components of the post-COVID-19 conditions, are important confounders that were not reported, nor accounted for in the study.

Handling of post-index time COVID-19 treatment

Information on the frequencies and the distribution of post-index time COVID-19 treatment changes (discussed below) by treatment groups is needed to understand the magnitude and direction of potential biases on study findings.

Other Outpatient COVID-19 Medication Use (All Studies)

In the analyses of PAXLOVID's effectiveness on hospitalization, use of other outpatient COVID-19 medications during follow-up could be on the causal pathway between PAXLOVID use and COVID-19 outcome—the need to use another treatment can be an early indication that PAXLOVID did not work well in preventing disease progression. Use of other COVID-19 treatments also have an impact on COVID-19 outcome, independently from PAXLOVID's effectiveness.

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Use of other outpatient COVID-19 medications was a censor criterion in the Wong study, but not in the Lewnard or Bajema studies, while the Arbel and Schwartz studies did not clearly state how they handled patients who initiated another outpatient COVID-19 treatment during follow-up. If the use of other outpatient COVID-19 medication is uncommon, these different approaches would likely all be acceptable; however, none of the three reviewed studies reported the extent of other COVID-19 medications used during follow-up.

Inpatient Medical Management (Arbel, Wong, Bajema, and Lewnard Studies)

Four of the reviewed studies (Arbel, Wong, Bajema, and Lewnard) also evaluated outpatient PAXLOVID's impact on in-patient outcomes, such as in-hospital disease progression, invasive mechanical ventilation use, intensive care unit admission and death, or post-acute COVID-19 symptoms. In these analyses, the medical treatment that patients received during hospitalization, such as inpatient COVID-19 treatment, could be in the causal pathway. None of these studies reported information on inpatient medical management during follow-up, nor accounted for its impact in the analyses.

Concern on Statistical Methods

Ambiguous Statistical Methods and Results (Lewnard Study)

The details of the analyses and the results are not clear. Without knowledge of the details, some of the results are difficult to review and interpret. The definition of the discordant pairs in the results tables (Table 2 and Table 3 of the publication) is not clear and the summaries of the discordant pairs do not seem to align with the effectiveness estimates. It is also unclear whether immortal time in treated subjects is handled properly when determining discordant pairs. In addition, about 42% of eligible PAXLOVID-treated patients were not included in the analyses, calling into question the generalizability of the results to that population..

Handling of Immortal Time Bias (Schwartz and Wong Studies)

The Schwartz study assigned random index dates to the unexposed group based on the time-to-dispense distribution from the exposed group. This approach did not consider factors that may impact the dispensing time for each subject (e.g., the presence of symptoms) and may not fully fix the immortal time bias problem.

The primary analyses of the Wong study set the index time at COVID-19 symptom onset or diagnosis, which introduced immortal time in the PAXLOVID-treated group and could overestimate PAXLOVID effectiveness. The investigators conducted post hoc sensitivity analyses that treated exposure status as a "time-varying" variable to account for immortal time bias. The findings of this sensitivity analysis that accounted for immortal time bias consistently support PAXLOVID effectiveness as the primary analyses in the overall study population. It is unclear if the conclusion would be the same for the subgroup analyses stratified by vaccination status, as the author did not report the findings of the sensitivity analyses by patient subgroup.

Handling of Missing Data (All Studies)

All the studies except for the Lewnard study did not report the degree of missing data for important baseline covariates. Most of the studies did not specify a method of handling missing data other than excluding subjects with missing covariates.

4.3 OVERALL ASSESSMENT OF THE AVAILABLE PAXLOVID RWE STUDIES

Seventeen of the twenty-two identified RWE studies reporting effectiveness of outpatient PAXLOVID use were excluded from in-depth review as they included overlapping study populations with the reviewed RWE studies, were based on insufficient longitudinal data in the data sources, and/or were unable to account for potential bias introduced by index time selection. The five remaining studies consistently reported that PAXLOVID use was associated with a reduced risk of worsening COVID-19 outcomes in broader populations than included in the pivotal trials—with respect to age, underlying "high-risk" comorbidities, and COVID-19 vaccination status in the Omicron era.

However, the information available for the reviewed observational studies was insufficient to determine their quality.

5 CONCLUSION

The pivotal trials data showed benefit of PAXLOVID for the treatment of mild to moderate COVID-19 in patients who are at high risk for progression to severe COVID-19, including hospitalization or death, regardless of vaccination status and in the Omicron era. The results of the five published studies reviewed did not contradict the findings of those trials. The findings from these studies alone cannot be used to support or refute effectiveness of PAXLOVID treatment in non-hospitalized COVID-19 patients, especially among specific patient subgroups.

6 RECOMMENDATIONS

Given the lack of information to determine quality, DEPI recommended against using the results of the available RWE studies to support or refute effectiveness of PAXLOVID treatment in non-hospitalized COVID-19 patients, especially among specific patient subgroups.

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7 REFERENCES

1. Najjar-Debbiny R, Gronich N, Weber G, et al. Effectiveness of Paxlovid in Reducing Severe COVID-19 and Mortality in High Risk Patients. *Clin infect dis*. 2022/06 2022;doi:10.1093/cid/ciac443 PMC -

2. Wai AK-CCCYCAW-LWKCSC-LLTT-LLLY-FYET-FHJ. Association of Molnupiravir and Nirmatrelvir-Ritonavir with preventable mortality, hospital admissions and related avoidable healthcare system cost among high-risk patients with mild to moderate COVID-19. *The Lancet regional health Western Pacific*. 2022/00 2022;

3. Yip TCF, Lui GCY, Lai MSM, et al. Impact of the use of oral antiviral agents on the risk of hospitalization in community COVID-19 patients. *Clin Infect Dis*. Aug 29 2022;doi:10.1093/cid/ciac687

4. Xie Y, Choi T, Al-Aly Z. Nirmatrelvir and the Risk of Post-Acute Sequelae of COVID-19 (preprint). 2022.

5. Hedvat J, Lange NW, Salerno DM, et al. COVID-19 therapeutics and outcomes among solid organ transplant recipients during the Omicron BA.1 era. *Am j transplant*. 2022/07 2022;doi:10.1111/ajt.17140 PMC -

6. Dryden-Peterson S, Kim A, Kim AY, et al. Nirmatrelvir plus ritonavir for early COVID-19 and hospitalization in a large US health system. *medRxiv*. Jun 17 2022;doi:10.1101/2022.06.14.22276393

7. Ganatra S, Dani SS, Ahmad J, et al. Oral Nirmatrelvir and Ritonavir in Non-hospitalized Vaccinated Patients with Covid-19. *Clin Infect Dis*. Aug 20 2022;doi:10.1093/cid/ciac673

8. Xiaofeng Z. Real-World Effectiveness of Nirmatrelvir/Ritonavir in Preventing Hospitalization Among Patients With COVID-19 at High Risk for Severe Disease in the United States: A Nationwide Population-Based Cohort Study (preprint). 2022.

9. Aggarwal N, R. , Kyle M, Laurel B, Tellen DB, Nichole C, Adit AG. Real-world Use of Nirmatrelvir-Ritonavir in COVID-19 Outpatients During the Emergence of Omicron Variants BA.2/BA2.12.1. 2022.

10. Bruno G, Giotta M, Perelli S, De Vita G, Bartolomeo N, Buccoliero GB. Early Access to Oral Antivirals in High-Risk Outpatients: Good Weapons to Fight COVID-19. *Viruses*. 2022/11 2022;14(11)doi:10.3390/v14112514

11. Bruno G, Perelli S, Giotta M, Bartolomeo N, De Vita G, Buccoliero GB. Efficacy and safety of oral antivirals in individuals aged 80 years or older with mild-to-moderate COVID-19: preliminary report from an Italian Prescriber Center. *Infezioni in Medicina*. 2022/00 2022;30(4):547-554. doi:10.53854/liim-3004-9

12. Gentile I, Scotto R, Schiano Moriello N, et al. Nirmatrelvir/Ritonavir and Molnupiravir in the Treatment of Mild/Moderate COVID-19: Results of a Real-Life Study. 2022/10 2022;10(10)doi:10.3390/vaccines10101731

13. Park H, Park YJ, Lee HY, et al. The effectiveness of Paxlovid treatment in long-term care facilities in South Korea during the outbreak of the Omicron variant of SARS-CoV-2. *Osong Public Health Res Perspect*. Dec 2022;13(6):443-447. doi:10.24171/j.phrp.2022.0262

14. Park JJ, Lee J, Seo YB, Na SH. Nirmatrelvir/Ritonavir Prescription Rate and Outcomes in Coronavirus Disease 2019: A Single Center Study. *Infect Chemother*. 2022/00 2022;doi:10.3947/ic.2022.0123

15. Qian G, Wang X, Patel NJ, et al. Outcomes with and without outpatient SARS-CoV-2 treatment for patients with COVID-19 and systemic autoimmune rheumatic diseases: A retrospective cohort study. *medRxiv*. Oct 30 2022;doi:10.1101/2022.10.27.22281629

16. Shah MM, Joyce B, Plumb ID, et al. Paxlovid Associated with Decreased Hospitalization Rate Among Adults with COVID-19 - United States, April-September 2022. *MMWR - Morbidity & Mortality Weekly Report*. 2022/00 2022;71(48):1531-1537. doi:10.15585/mmwr.mm7148e2

17. Tiseo G, Barbieri C, Galfo V, et al. Efficacy and Safety of Nirmatrelvir/Ritonavir, Molnupiravir, and Remdesivir in a Real-World Cohort of Outpatients with COVID-19 at High Risk of Progression: The PISA Outpatient Clinic Experience. *Infect Dis Ther*. Jan 2023;12(1):257-271. doi:10.1007/s40121-022-00729-2

18. Arbel R, Wolff Sagy Y, Hoshen M, et al. Nirmatrelvir Use and Severe Covid-19 Outcomes during the Omicron Surge. *N Engl J Med*. Aug 24 2022;doi:10.1056/NEJMoa2204919

19. Wong CKH, Au ICH, Lau KTK, Lau EHY, Cowling BJ, Leung GM. Real-world effectiveness of molnupiravir and nirmatrelvir plus ritonavir against mortality, hospitalisation, and in-hospital outcomes among community-dwelling, ambulatory patients with confirmed SARS-CoV-2 infection during the omicron wave in Hong Kong: an observational study. *The Lancet*. 2022/00 2022;400(10359):1213-1222. doi:10.1016/s0140-6736(22)01586-0

20. Bajema KL, Berry K, Streja E, et al. Effectiveness of COVID-19 treatment with nirmatrelvir-ritonavir or molnupiravir among U.S. Veterans: target trial emulation studies with one-month and six-month outcomes. *medRxiv*. Dec 16 2022;doi:10.1101/2022.12.05.22283134

21. Schwartz K, Wang J, Tadrous M, et al. Real-world effectiveness of nirmatrelvir/ritonavir use for COVID-19: A population-based cohort study in Ontario, Canada (preprint). 2022.

22. Lewnard JA, McLaughlin JM, Malden D, et al. Effectiveness of nirmatrelvir-ritonavir against hospital admission or death: a cohort study in a large US healthcare system. *medRxiv*. Jan 10 2023;doi:10.1101/2022.10.02.22280623

APPENDICES

Search process (Steps and number of articles left)

1. English language article with "PAXLOVID OR nirmatrelvir" AND keywords of "epidemiology or RWE study," excluding animal, cellular, pharmacokinetic/pharmacodynamics, identified 297 articles (search terms are required in Title, Abstract, or Subject)
2. Restrict to studies evaluate PAXLOVID effectiveness 44
3. Exclude duplicate publications 26
4. Exclude study conducted in hospitalized COVID-19 patient 22

Search terms

- Key words for epidemiology or RWE study
  epidemiology OR observational OR non-randomized OR cohort OR sample OR adjustment OR "propensity score" OR "inverse probability weighting" OR "integrated health care system" OR multivariate OR multivariable OR population-based OR case-control OR database OR bayesian OR abstracted OR "convenience sample" OR "electronic health record" OR "systematic review" OR cohort OR case-control OR database OR datalink OR "claims data" OR "drug utilization" OR "electronic health records" OR "electronic medical records" OR biobank OR "pooled analysis" OR crossover OR registry OR registries OR meta-analysis OR retrospective OR prospective OR "cross sectional" OR cross-sectional OR "prevalence study" OR "longitudinal study" OR "before-after study" OR "administrative database" OR "insurance claim" OR matched-cohort OR population-based OR "insurance database" OR "claims database" OR "pharmaceutical claims" OR "case control" OR "meta analysis" OR self-controlled OR "self controlled" OR comparative OR emr OR prevalence OR incidence OR rate OR "administrative claim" OR "Real-World" OR "Real World" OR "RWE"
- Animal cellular, pharmacokinetic/pharmacodynamics studies
  animals OR animal OR mice OR mus OR mouse OR murine OR woodmouse OR rats OR rat OR murinae OR muridae OR cottonrat OR cottonrats OR hamster OR hamsters OR cricetinae OR rodentia OR rodent OR rodents OR pigs OR pig OR swine OR swines OR piglets OR piglet OR boar OR boars OR "sus scrofa" OR ferrets OR ferret OR polecat OR polecats OR "mustela putorius" OR "guinea pigs" OR "guinea pig" OR cavia OR callithrix OR marmoset OR marmosets OR cebuella OR hapale OR octodon OR chinchilla OR chinchillas OR gerbillinae OR gerbil OR gerbils OR jird OR jirds OR merione OR meriones OR rabbits OR rabbit OR hares OR hare OR diptera OR flies OR fly OR dipteral OR drosphila OR drosophilidae OR cats OR cat OR carus OR felis OR nematoda OR nematode OR nematoda OR nematode OR nematodes OR sipunculida OR dogs OR dog OR canine OR canines OR canis OR sheep OR sheeps OR mouflon OR mouflons OR ovis OR goats OR goat OR capra OR capras OR rupicapra OR chamois OR haplorhini OR monkey OR monkeys OR anthropoidea OR anthropoids OR saguinus OR tamarin OR tamarins OR leontopithecus OR hominidae OR ape OR apes OR pan OR paniscus OR "pan paniscus" OR bonobo OR bonobos OR troglodytes OR "pan troglodytes" OR gibbon OR gibbons OR siamang OR siamangs OR nomascus OR symphalangus OR chimpanzee OR chimpanzees OR prosimians OR "bush baby" OR prosimian OR bush

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babies OR galagos OR galago OR pongidae OR gorilla OR gorillas OR pongo OR pygmaeus OR "pongo pygmaeus" OR orangutans OR pygmaeus OR lemur OR lemurs OR lemuridae OR horse OR horses OR pongo OR equus OR cow OR calf OR bull OR chicken OR chickens OR gallus OR quail OR bird OR birds OR quails OR poultry OR poultries OR fowl OR fowls OR reptile OR reptilia OR reptiles OR snakes OR snake OR lizard OR lizards OR alligator OR alligators OR crocodile OR crocodiles OR turtle OR turtles OR amphibian OR amphibians OR amphibia OR frog OR frogs OR bombina OR salientia OR toad OR toads OR "epidalea calamita" OR salamander OR salamanders OR eel OR eels OR fish OR fishes OR pisces OR catfish OR catfishes OR siluriformes OR arius OR heteropneustes OR sheatfish OR perch OR perches OR percidae OR perca OR trout OR trouts OR char OR chars OR salvelinus OR "fathead minnow" OR minnow OR cyprinidae OR carps OR carp OR zebrafish OR zebrafishes OR goldfish OR goldfishes OR guppy OR guppies OR chub OR chubs OR tinca OR barbels OR barbus OR pimephales OR promelas OR "poecilia reticulata" OR mullet OR mullets OR seahorse OR seahorses OR mugil curema OR atlantic cod OR shark OR sharks OR catshark OR anguilla OR salmonid OR salmonids OR whitefish OR whitefishes OR salmon OR salmons OR sole OR solea OR "sea lamprey" OR lamprey OR lampreys OR pumpkinseed OR sunfish OR sunfishes OR tilapia OR tilapias OR turbot OR turbots OR flatfish OR flatfishes OR sciuridae OR squirrel OR squirrels OR chipmunk OR chipmunks OR suslik OR susliks OR vole OR voles OR lemming OR lemmings OR muskrat OR muskrats OR lemmus OR otter OR otters OR marten OR martens OR martes OR weasel OR badger OR badgers OR ermine OR mink OR minks OR sable OR sables OR gulo OR gulos OR wolverine OR wolverines OR minks OR mustela OR llama OR llamas OR alpaca OR alpacas OR camelid OR camelids OR guanaco OR guanacos OR chiroptera OR chiropteras OR bat OR bats OR fox OR foxes OR iguana OR iguanas OR xenopus laevis OR parakeet OR parakeets OR parrot OR parrots OR donkey OR donkeys OR mule OR mules OR zebra OR zebras OR shrew OR shrews OR bison OR bisons OR buffalo OR buffaloes OR deer OR deers OR bear OR bears OR panda OR pandas OR "wild hog" OR "wild boar" OR fitchew OR fitch OR beaver OR beavers OR jerboa OR jerboas OR capybara OR capybaras OR cell OR "cell line" OR cellular OR tissue OR "in vitro" OR spectroscopic OR spectrometer OR spectrophotometry OR "transformation products" OR synthesized OR "gene variants" OR polymorphism OR plant OR pharmacokinetics OR pharmacokinetic OR pharmacodynamic OR pharmacodynamics

Table 1 Data source, design, and methods of the submitted EPIC HR and EPIC SR trials and reviewed RWE studies

Product, therapeutic area, indication	Paxlovid (nirmatrelvir/ ritonavir), Antiviral, treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults (b) (4) who are at high risk for progression to severe COVID-19, including hospitalization or death			
Regulatory purpose	Marketing approval			
Existing evidence	The main efficacy evidence submitted for Paxlovid as COVID-19 treatment is based on two phase 2/3 placebo-controlled clinical trials- Study C4671005 (EPIC-HR) and study C4671002 (EPIC-SR).			
Regulatory need and gap	The clinical review team considers that the submitted data from EPIC-HR and EPIC-SR together support the benefit of Paxlovid as COVID-19 treatment in high-risk patients for hospitalization or death, regardless of vaccination status and in the Omicron era. Review of available RWE studies was conducted to evaluate if any RWE study findings contradicts with trial findings.			
Study	**EPIC-HR (Pivotal trial)**	**EPIC-SR (Supportive trial)**	**Arbel (RWE)**	**Wong (RWE)**
Objective	To compare efficacy of Paxlovid to placebo for the treatment of symptomatic COVID-19 in non-hospitalized adult participants with COVID-19 who are at increased risk of progression to severe disease	To compare efficacy of Paxlovid to placebo for the treatment of symptomatic COVID-19 in non-hospitalized adult participants with COVID-19 who are at low risk of progression to severe disease	To assess the effectiveness of Paxlovid in preventing severe Covid-19 outcomes during the omicron surge in a population with widespread SARS-CoV-2 immunity.	To assess the clinical effectiveness of Paxlovid among community-dwelling COVID-19 outpatients in Hong Kong during the Omicron BA.2.2 wave in January to June 2022[1]
Country	Multi-countries (41% US, 30% Europe, 9% India, 20% rest of the World)	Multi-countries (43% US, 28% Europe, 29% rest of the World)	Israel	China (Hong Kong)
Data source	Primary collected data	Primary collected data	EHR of an integrated payor-provider healthcare system covered 52% of Israeli population	Territory-wide EHR (did not provide clear description on the data source)
Design	Randomized (1:1), doble blink, placebo-controlled study	Randomized (1:1), doble blink, placebo-controlled study	Cohort study	Cohort study[2]
Population/setting	Non-hospitalized, symptomatic, adult patients with COVID-19 who were at increased risk of progression to severe illness	Non-hospitalized, symptomatic, adult patients with COVID-19 who were at low risk of progression to severe illness	Non-hospitalized COVID-19 patients (40+ yrs), at high risk for progression to severe disease and deemed eligible to received Paxlovid	Non-hospitalized COVID-19 patients (18+ yrs)

[1] The study also evaluated the effectiveness of molnupiravir as outpatient treatment of COVID-19, which is out of the review scope.
[2] Study included a sensitivity analysis using case-control design. Our evaluation focused on the primary analyses using cohort design.

Time period •Total duration Date of first enrollment, date of last completed	07/16/2021 to 04/26/2022	08/25/2021-12/19/2021	01/09-03/31/22 Patients diagnosed between 01/09 and 02/24/22, with a min of 35 days follow-up	02/26- 07/03/2022 Patients diagnosed between 02/26 and 06/26/22, did not require min follow-up time
Exposure	Paxlovid, PO q12h for 5 days	Paxlovid, PO q12h for 5 days	Paxlovid use in 5 days vs. non-use Paxlovid use was ascertained by medical staff*	Paxlovid use in 5 days vs. non-use Unclear how the study ascertained data on Paxlovid use (the data source was stated to have both prescribing and dispensing records)
Reference group	Placebo (non-users)	Placebo (non-users)	Non-users	Non-users
Primary Outcome	Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28	Time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28	Hospitalization due to COVID-19 Unclear how the reason for hospitalization was determined	1) All-cause mortality, 2) hospitalization due to COVID-19 3) a composite outcome of in-hospital disease progression (in-hospital mortality, invasive mechanical ventilation [IMV], or intensive care unit [ICU] admission), and (4) individual in-hospital outcomes (in-hospital death, IMV initiation, and ICU admission) Unclear how the reason for hospitalization was determined
Secondary	Time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28	Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28	Death due to COVID-19 Unclear how cause of death was determined	
Index time	At enrollment	At enrollment	Positive SARs-COV-2 test date, with time-varying exposure status	Symptom onset or diagnosis, whichever is earlier Post-hoc sensitivity analyses of treating oral Paxlovid use as a time-varying covariate in the Cox regression models (did not provide details on this analyses)

Censor	Follow-up up to 24 weeks	Follow-up up to 24 weeks	Follow-up stopped at hospitalization or death from any causes, 35 days after diagnosis, end of study	Follow-up stopped at death, outcome event occurrence, receiving molnupiravir or end of study (07/03/2022) (median follow-up=99 days (IQR=92-104))
Covariates reported	**Demographic:** Age, sex, race/ethnicity, geographic region **Clinical risk factors:** BMI, duration from first COVID-19 diagnosis, duration since first COVID-19 symptom, number of risk factors of interest, comorbidities (cardiovascular disorder, chronic kidney disease, chronic lung disease, cigarette smoker, diabetes, hypotension, immunosuppression, cancer, neurodevelopmental disorder, sickle cell disease, HIV infection, device dependence), mAb treatment, serology status, viral load	**Demographic:** Age, sex, race/ethnicity, geographic region **Clinical risk factors:** BMI, duration from first COVID-19 diagnosis, duration since first COVID-19 symptom, number of risk factors of interest, comorbidities (cardiovascular disorder, chronic kidney disease, chronic lung disease, cigarette smoker, diabetes, hypotension, cancer, neurodevelopmental disorder, sickle cell disease, HIV infection, device dependence), vaccination status, serology status, viral load, baseline severity	**Demographic:** Age, sex, population section (general Jewish, Ultra-Orthodox Jewish, Arab), Score for socioeconomic status **Clinical risk factors:** Obesity, HTN, diabetes, history of smoking, immunosuppression, neurologic disease, current cancer, Asthma, history of stroke, chronic hepatic disease, COPD, chronic heart failure, CKD, recent hospitalization **SARS-CoV-2 Immunity status** No previous immunity vs previous immunity induced by vaccination, infection or both	**Demographic:** Age, sex **Clinical risk factors:** Carlson's comorbidity index (did not report the individual component of the score) **Vaccination status:** Fully vaccinated or not
Key unmeasured covariates of concern	Not applicable (due to randomization)	Not applicable (due to randomization)	Symptoms and severity of COVID-19 at baseline Use of other COVID-19 treatment at follow-up, in-patient COVID-19 management when hospitalized, detailed vaccination information	Symptoms and severity of COVID-19 at baseline Use of other COVID-19 treatment at follow-up, in-patient COVID-19 management when hospitalized, detailed vaccination information

Statistical Analysis	Randomization was stratified by geographic region, by whether participants had received mAb treatment Analyses were conducted in all participants who take at least 1 dose of study intervention, who at baseline did not receive mAb and were treated within 3 days of symptom onset. Participants will be analyzed according to the study intervention they were randomized (ITT approach). The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study will be estimated for each treatment group using the Kaplan-Meier method.	Randomization was stratified by geographic region, by vaccination status and by COVID-19 symptom onset (≤3 or >3-5 days) Analyses were conducted in all participants who take at least 1 dose of study intervention, Participants will be analyzed according to the study intervention they were randomized (ITT approach). Time to sustained alleviation of all targeted COVID-19 signs/symptoms were summarized with Kaplan-Meier curves. Log-rank test will be used to compare the difference in outcome between treatment groups	Hazard ratios (HR) with 95% confidence intervals (CI) of outcome was estimated with the multivariate Cox proportional-hazards regression model with time-dependent exposure status. The analyses were conducted in subgroups defined by age (40-64 yrs vs 65+) and immune status (**patients with or without previous immunity, acquired by vaccination, prior infection, or both**) The stratified analyses for each subgroup adjusted for different covariates, selected based on a two-step testing criteria[3]	HR with 95% CI of each outcome between Paxlovid users and their propensity score matched non-users were estimated using Cox regression models. The propensity score model included age, sex, date of confirmed SARS-CoV-2 infection, Charlson Comorbidity Index, and vaccination status
Methods to evaluate effectiveness by vaccination status	Not applicable	Not applicable	Primary analyses were stratified by age and immune status	Stratified analyses evaluated impact of vaccination status (**fully vaccinated vs not fully vaccinated**)
Sample Size and power	3,000 participants for 90% power to show a difference of 3.5% in the proportion of participants hospitalized/dying that did not receive mAb and were treated within 3 days after symptom onset.	1980 participants for 90% power to detect 2 days difference in the median days to sustained alleviation of all targeted COVID-19-associated symptoms	Did not report a priori sample size/power calculation	Did not report a priori sample size/power calculation

[3] First, a univariate Kaplan–Meier analysis with a log-rank test was applied to evaluate the associations between each independent candidate variable and the time-dependent primary outcome. Then, a comparison of the survival curves and Schoenfeld's global test was used to test the proportional-hazards assumption for those variables. Variates that met these two testing criteria served as the inputs for the multivariate regression analysis

Table 1 Data source, design, and methods of the submitted EPIC HR and EPIC SR trials and reviewed RWE studies (cont.)

Product, therapeutic area, indication	Paxlovid (nirmatrelvir/ ritonavir), Antiviral, treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults (b) (4) who are at high risk for progression to severe COVID-19, including hospitalization or death				
Regulatory purpose	Marketing approval				
Existing evidence	The main efficacy evidence submitted for Paxlovid as COVID-19 treatment is based on two phase 2/3 placebo-controlled clinical trials-Study C4671005 (EPIC-HR) and study C4671002 (EPIC-SR).				
Regulatory need and gap	The clinical review team considers that the submitted data from EPIC-HR and EPIC-SR together support the benefit of Paxlovid as COVID-19 treatment in high-risk patients for hospitalization or death, regardless of vaccination status and in the Omicron era. Review of available RWE studies was conducted to evaluate if any RWE study findings contradicts with trial findings.				
Study	**EPIC-HR (Pivotal trial)**	**EPIC-SR (Supportive trial)**	**Bejama (RWE)**	**Shwartz (RWE)**	**Lewnard (RWE)**
Objective	To compare efficacy of Paxlovid to placebo for the treatment of symptomatic COVID-19 in non-hospitalized adult participants with COVID-19 who are at increased risk of progression to severe disease	To compare efficacy of Paxlovid to placebo for the treatment of symptomatic COVID-19 in non-hospitalized adult participants with COVID-19 who are at low risk of progression to severe disease	To determine the effectiveness of nirmatrelvir-ritonavir and molnupiravir for the outpatient treatment of COVID-19[4]	To evaluate the real-world effectiveness of nirmatrelvir/ritonavir on health outcomes including hospitalization and death from COVID-19 while Omicron and its subvariants predominate.	To measure the effectiveness of nirmatrelvir-ritonavir in preventing severe outcomes of SARS-CoV-2 infection among cases ascertained via outpatient testing within a large, integrated US healthcare system
Country	Multi-countries (41% US, 30% Europe, 9% India, 20% rest of the World)	Multi-countries (43% US, 28% Europe, 29% rest of the World)	US	Canada (Ontario)	US
Data source	Primary collected data	Primary collected data	Administrative claims data and EHR from the Veterans Health Administration	Province-wide prescription dispensing data, SARS-CoV-2 PCR test data, COVID-19 vaccination data, insurance plan data, disease specific databases	Kaiser Permanente Southern California, and comprehensive healthcare system providing integrated care. Vaccination capture through California Immunization Registry
Design	Randomized (1:1), doble blink, placebo-controlled study	Randomized (1:1), doble blink, placebo-controlled study	Cohort study	Cohort study	Cohort study
Population/setting	Non-hospitalized, symptomatic, adult patients with COVID-19 who were at increased risk of progression to severe illness	Non-hospitalized, symptomatic, adult patients with COVID-19 who were at low risk of progression to severe illness	Non-hospitalized patients (18+ yr) who newly tested positive for COVID-19 and had at least one risk factor for progression to severe COVID-19	Non-hospitalized patients tested positive for COVID-19 (18+ yrs)	Non-hospitalized patients (12+ yr) who newly tested positive for COVID-19

[4] The study also evaluated the effectiveness of molnupiravir as outpatient treatment of COVID-19, which is out of the review scope.

Time period •Total duration Date of first enrollment, date of last completed	07/16/2021 to 04/26/2022	08/25/2021-12/19/2021	01/01/2022-08/31/2022 Patients with positive test between 01/01/2022 and 02/28/22, with up to 6 months follow-up	04/04- 9/30/2022 Patients with positive PCR test between 04/04 and 08/31/22	04/08/2022-10/20/2022 Patients with positive test between 04/08 and 10/07/2022, up to 60 days follow-up
Exposure	Paxlovid, PO q12h for 5 days	Paxlovid, PO q12h for 5 days	Paxlovid use in 10 days vs. non-use Paxlovid use was identified from dispensing records	Paxlovid use vs. non-use Paxlovid use was identified from dispensing records	Paxlovid use (in 5 days, or at any time) vs. non-use Paxlovid use was identified from dispensing records
Reference group	Placebo (non-users)	Placebo (non-users)	Non-users	Non-users	Non-users
Primary Outcome	Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28	Time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28	All cause hospitalization or death in 30 days.	Hospitalization for COVID or death in 1-30 days COVID-19 hospitalization was determined by local public health units, unclear about the criteria	All-cause hospitalization or death in 30 days
Secondary	Time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28	Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28	Intensive care unit (ICU) admission and mechanical ventilation occurring during hospitalizations through day 30. Acute or long-term care admission, death, post-COVID condition from day 31-180	Death in 1-30 days	ICU admission, mechanical ventilation, or death within 60 days
Index time	At enrollment	At enrollment	**Paxlovid users:** Treatment initiation **Non-users:** Assigned an index date with the same duration between test date and treatment initiation date of their matched treated patients	**Paxlovid users**: Treatment initiation **Non-users:** Assigned index date that matched the distribution of the time from positive test-to-dispensing in Paxlovid users	**Positive SARS-CoV-2 test date** with time-varying exposure status
Censor	Follow-up up to 24 weeks	Follow-up up to 24 weeks	Follow-up stopped at outcome events, 30 days after index for short-term outcomes, or 31-180 days after index for post-COVID conditions	Did not specified follow-up/censor criteria	Follow-up stopped at outcome events, loss of insurance coverage, end of follow-up (30 days or 60 days) or end of study (10/20/2022)

Covariates captured	**Demographic:** Age, sex, race/ethnicity, geographic region **Clinical risk factors:** BMI, duration from first COVID-19 diagnosis, duration since first COVID-19 symptom, number of risk factors of interest, comorbidities (cardiovascular disorder, chronic kidney disease, chronic lung disease, cigarette smoker, diabetes, hypotension, immunosuppression, cancer, neurodevelopmental disorder, sickle cell disease, HIV infection, device dependence), mAb treatment, serology status, viral load	**Demographic:** Age, sex, race/ethnicity, geographic region **Clinical risk factors:** BMI, duration from first COVID-19 diagnosis, duration since first COVID-19 symptom, number of risk factors of interest, comorbidities (cardiovascular disorder, chronic kidney disease, chronic lung disease, cigarette smoker, diabetes, hypotension, cancer, neurodevelopmental disorder, sickle cell disease, HIV infection, device dependence), vaccination status, serology status, viral load, baseline severity	**Demographic:** Age, sex, race/ethnicity, rurality, VA integrated Service Network (VISN), area deprivation index **Clinical risk factors:** Calendar week of positive test, presence of symptom in preceding 30 days, NIH risk tier of prioritization for anti-SARS-CoV-2 therapies, smoking, alcohol dependence, substance dependence, number of comorbidities, care assessment need (CAN) score for mortality, obesity (BMI 30+), chronic kidney disease, diabetes, immunosuppressive medications or cancer therapies, cancer, cardiovascular diseases, chronic lung disease, dementia, cerebrovascular disease, chronic liver disease, mental health conditions, number of prior healthcare encounters, days from test to treatment **SARS-CoV-2 Immunity status** Vaccination status and time since last dose	**Demographic:** Age, sex **Clinical risk factors:** Previous COVID-19 infection, Ontario Science Table (OST) risk group (standard or high risk), comorbidities (chronic respiratory disease, chronic heart disease, diabetes, immune compromised conditions, hypertension, dementia, autoimmune disease, chronic kidney disease, advanced liver disease), long-term care resident, **Vaccination status:** Number of dose (0,1,2,3+), time from last vaccine dose (14-89 days, 90-179 days, 180-269 days, 270+ days)	**Demographics:** Age, sex, race/ ethnicity, neighborhood deprivation index **Clinical risk factors:** Time from COVID-19 symptoms onset[5] to testing, Outpatient care received within 1 day prior to COVID-19 testing, prior SARS-CoV-2 infection, Charlson comorbidity index, BMI, cigarette smoking, prior year health care use, receipt of other respiratory vaccines[6] **Vaccination status:** Number of doses (0,1,2,3,4) received

[5] The date of SARS-CoV-2 symptom onset was defined as the earliest date that cases reported acute fever, cough, headache, fatigue, dyspnea, chills, sore throat, myalgia, anosmia, diarrhea, vomiting/nausea, or abdominal pain within 14 days before or after their index test date. If new-onset symptoms were not recorded within this period, we categorized cases as "not experiencing acute COVID-19 symptoms" in association with their infection

[6] Other vaccine including: 2021-22 season influenza vaccination, pneumococcal polysaccharide vaccine, and pneumococcal conjugate vaccine.

Key unmeasured covariates of concern	Not applicable (due to randomization)	Not applicable (due to randomization)	Severity of COVID-19 at baseline Use of other COVID-19 treatment at follow-up, in-patient COVID-19 management when hospitalized	Symptoms and severity of COVID-19 at baseline Use of other COVID-19 treatment at follow-up, in-patient COVID-19 management when hospitalized	Use of other COVID-19 treatment at follow-up, in-patient COVID-19 management when hospitalized

Statistical Analysis	Randomization was stratified by geographic region, by whether participants had received mAb treatment Analyses were conducted in all participants who take at least 1 dose of study intervention, who at baseline did not receive mAb and were treated within 3 days of symptom onset. Participants will be analyzed according to the study intervention they were randomized (ITT approach). The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study will be estimated for each treatment group using the Kaplan-Meier method.	Randomization was stratified by geographic region, by vaccination status and by COVID-19 symptom onset (≤3 or >3-5 days) Analyses were conducted in all participants who take at least 1 dose of study intervention, Participants will be analyzed according to the study intervention they were randomized (ITT approach). Time to sustained alleviation of all targeted COVID-19 signs/symptoms were summarized with Kaplan-Meier curves. Log-rank test will be used to compare the difference in outcome between treatment groups	Users and non-users were first exact-matched as of their assigned index date on: NIH tier, VISN, and calendar time (±7 days of positive test). Then matched on propensity score (PS) calculated based on demographic, geographic, healthcare utilization, and clinical factors. Up to 4 non-users with the closest PS within 0.2 standard deviations of the mean were matched to each user. For 30-day outcomes of hospitalization or death, risk rates, risk differences, risk ratios (and 95% CIs) were calculated. Time-to-event analyses treating death as a competing risk was used for incidence of long-term outcomes extending from 31-180 days. Subgroup analyses by age, vaccination status and presence of symptoms was conducted. All analyses were importance-weighted to account for variable-ratio matching. A robust sandwich-type variance estimator was used to account for clustering within the matched group due to ties in the PS, clustering within subjects due to matching with replacement, and clustering	Weighted odds ratios with 95% CI of each outcome between IPTW weighted Paxlovid users and non-users were estimated using logistics regression models. The IPTW was calculated from propensity score model included age, sex, number of SARS-CoV-2 vaccine dose, previous infection, time from last vaccine dose, individual comorbidities, long-term care residence and OST risk group Pre-specified stratified analyses were conducted based on age, vaccination status, potential DDIS for those over 70 years of age, comorbidities, long-term care residents, OST risk group and time period (April-June 2022 vs July to August 2022)	For each endpoint, treatment effectiveness was calculated as (1 − adjusted hazards ratio [aHR]) × 100%, for the aHR comparing outcomes among users and non-users. aHR and 95% (CI) was estimated by Cox proportional hazards models, using the Andersen-Gill extension update time-varying exposures. Cluster-robust standard errors were used to account for multiple observations from cases whose treatment status changed during follow-up. We verified the proportional hazards assumption by Schoenfeld residuals. Regression strata (matches) among cases were defined based on week of testing, age, sex, receipt of any clinical care in association with testing (across ED, urgent care, outpatient, or telehealth settings), days from symptom onset, or absence of acute symptoms, healthcare utilization, COVID-19 vaccine doses received; Charlson comorbidity index, and body mass index category. Analyses further controlled for race/ethnicity, smoking status, neighborhood deprivation index quintile,

			in the cross-classification of the matched and within subject clusters. We verified that the proportional hazards assumption was met using log-log plots and Schoenfeld residuals.		and receipt of other vaccines. Analyses were repeated in subgroups who received ≥2 or ≥3 COVID-19 vaccine doses. Multiple imputations were used to handle missing value on smoking status, BMI and census-tract neighborhood deprivation index measures
Methods to evaluate effectiveness by vaccination status	Not applicable	Not applicable	Stratified analyses evaluated impact of vaccination status (**unvaccinated versus any primary or booster vaccination**)	Stratified analyses evaluated impact of vaccination status (**0, 1-2, 3+ doses**)	Conduct sensitivity analyses restricted to patients who received **2+ or 3+ doses of COVID-19 vaccine**
Sample Size and power	3,000 participants for 90% power to show a difference of 3.5% in the proportion of participants hospitalized/dying that did not receive mAb and were treated within 3 days after symptom onset.	1980 participants for 90% power to detect 2 days difference in the median days to sustained alleviation of all targeted COVID-19-associated symptoms	A sample size of 2,650 persons (530 Paxlovid users, 2,120 non-users) was determined to have 80% power to detect a 2% difference in 30-day hospitalization or death, given a 1:4 match and assuming a 3% incidence of 30-day hospitalization or death among non-users	Did not report a priori sample size/power calculation	Did not report a priori sample size/power calculation

Table 1-1 Inclusion and exclusion criteria for the submitted EPIC HR and EPIC SR trials and reviewed RWE studies

EPIC HR	EPIC SR	Arbel	Wong
Inclusion criteria			
Age 18+		40+	18+
Confirmed SARS-CoV-2 infection (RT-PCR) within 5 days prior to randomization (non PCR test are allowed as long as test results can be available)		Confirmed SARS-CoV-2 infection (RT-PCR or antigen test), received outpatient COVID-19 diagnosis Excluded use more than 5 days	Confirmed outpatient COVID-19 diagnosis
Initial onset of COVID-19 signs/symptoms within 5 days prior to the day of randomization and at least 1 of the specified COVID-19 signs/symptoms present on the day of randomization		Not required	Not required
Has at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19	Did not required	Assessed as being at "high risk" for progression to severe disease, based on a risk score	Not required
Agreement to use contraceptives	Same	Not required	Not required
Exclusion			
History of hospitalization for the medical treatment of COVID-19		Hospitalized before the positive SARS-CoV-2 test or Paxlovid use	History of hospitalizations
Current need for hospitalization or anticipated need for hospitalization within 48 hours after randomization in the clinical opinion of the site investigator		Hospitalized on the same day of the positive SARS-CoV-2 test	Diagnosed at the time of hospitalization, death on the same day of diagnosis, and Paxlovid users who initiated the treatment during hospitalization
Prior to current disease episode, any confirmed SARS-CoV-2 infection, as determined by a molecular test (antigen or nucleic acid) from any specimen collected		Did not exclude	Did not exclude
Known medical history of active liver disease (other than nonalcoholic hepatic steatosis), including chronic or active hep B or C, primary biliary cirrhosis, Child-Pugh Class B or C or acute liver failure		Hepatic disease is a component of risk score	Did not exclude
Receiving dialysis or have known moderate to severe renal impairment (eGFR <45 within 6 months of screening, using the serum creatinine-based CKD-EPI formula)	Receiving dialysis or have known renal impairment	eGFR <60	Did not exclude

EPIC HR	EPIC SR	Arbel	Wong
Known human immunodeficiency virus (HIV) infection with a viral load greater than 400 copies/mL or taking prohibited medications for HIV treatment (within past 6 months of screening)		HIV carrier is a component of risk score despite viral load. Study excluded all patients taking contraindicated medication to Paxlovid	Did not exclude
Suspected or confirmed concurrent active systemic infection other than COVID-19 that may interfere evaluation of response to the treatment		Did not exclude	Did not exclude
History of hypersensitivity or other contraindication to any of the components of the study intervention as determined by the investigator		Did not exclude	Did not exclude
Current or expected use of any medications or substances that are highly dependent on CYP3A4 for clearance, and for which elevated plasma concentrations may be associated with serious and/or life-threatening events during treatment or for 4 days after the last dose		Patients treated with contraindicated medication with Paxlovid (referenced FDA Fact Sheet)	Did not exclude
Concomitant use of any medications of substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to first dose and during study treatment		Patients treated with contraindicated medication with Paxlovid (referenced FDA Fact Sheet)	Did not exclude
Has received or is expected to receive convalescent COVID-19 plasma	Has received or is expected to receive mAb, convalescent COVID-19 plasma	Has received molnupiravir or Evusheld	Has received molnupiravir
Has received or is expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit	Has received or is expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit ***Did not exclude fully vaccinated patients prior to December 19, 2021** (Fully vaccinated participants with underlying med conditions associated with an increased risk of COVID-19 must not receive a booster before Day 34 visit.)	Did not exclude unvaccinated patients. Vaccinated status is a component of risk score	Did not exclude patient based on vaccination status
Participating in another interventional clinical study with an investigational compound or device, including those for COVID-19 through the long-term follow-up visit		Did not exclude	Did not exclude
Previous administration with any investigational drug or vaccine within 30 days or 5 half-lives preceding the first dose of study innervation		Did not exclude	Did not exclude
Known prior participation in this trial or other trial involving Paxlovid		Did not exclude	Did not exclude

EPIC HR	EPIC SR	Arbel	Wong
Oxygen saturation of <92% on room air within 24 hours prior to randomization, or on their standard home oxygen supplementation for those who regularly receive chronic supplementary oxygen for an underlying lung condition		Did not exclude	Did not exclude
Abnormal tests in past 6 months AST or ALT level 2.5+X ULN Total bilirubin 2+X ULN eGFR <45, **using serum creatinine-based CKD-EPI** Absolute neutrophil count < 1000	Abnormal tests in past 6 months AST or ALT level 2.5+X ULN Total bilirubin 2+X ULN eGFR <45 Absolute neutrophil count < 1000	Did not exclude	Did not exclude
Females who are pregnant or breastfeeding		Did not exclude	Did not exclude
Any comorbidity requiring hospitalization and/or surgery within 7 days prior to study entry or that is considered life threatening within 30 days prior to study entry as determined by the investigator		Did not exclude	Did not exclude
Other medical or psychiatric condition including recent (in the past year) or active suicidal ideation or lab abnormality that may increase the risk of study participation, or in the investigator's judgement, make the participant inappropriate for the study		Did not exclude	Did not exclude
	Having criteria for high-risk **Participants with high-risk condition who are fully vaccinated against SARS-CoV-2 are eligible until December 19, 2021** (since they are considered at low risk for severe disease)		
		Patients who were residents in long-term care facilities	Patients who were residents in long-term care facilities

Table 1-1 Inclusion and exclusion criteria for the submitted EPIC HR and EPIC SR trials and reviewed RWE studies (cont.)

EPIC HR	EPIC SR	Bejama	Schewartz	Lewnard
Inclusion criteria				
Age 18+		18+	18+	12+
Confirmed SARS-CoV-2 infection (RT-PCR) within 5 days prior to randomization (non PCR test are allowed as long as test results can be available)		Confirmed SARS-CoV-2 infection (NAAT or antigen test)	Confirmed SARS-CoV-2 infection (PCR test)	Confirmed SARS-CoV-2 infection, diagnosed in outpatient setting
Initial onset of COVID-19 signs/symptoms within 5 days prior to the day of randomization and at least 1 of the specified COVID-19 signs/symptoms present on the day of randomization		Not required	Not required	Not required
Has at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19	Did not required	**Required**	Not required	Not required
Agreement to use contraceptives	Same	Not required	Not required	Not required
Exclusion				
History of hospitalization for the medical treatment of COVID-19		Hospitalized within 7 days before the test-positive date or Paxlovid treatment date	Hospitalized prior to positive test	Hospitalized within 0-7 days before COVID-19 test
Current need for hospitalization or anticipated need for hospitalization within 48 hours after randomization in the clinical opinion of the site investigator		Hospitalized on the same day of the positive SARS-CoV-2 test or Paxlovid treatment	Hospitalized on the same day of positive test	COVID-19 diagnosis during hospitalization
Prior to current disease episode, any confirmed SARS-CoV-2 infection, as determined by a molecular test (antigen or nucleic acid) from any specimen collected		Excluded	Did not exclude	Prior COVID-19 diagnosis 1-90 days prior to COVID-19 test
Known medical history of active liver disease (other than nonalcoholic hepatic steatosis), including chronic or active hep B or C, primary biliary cirrhosis, Child-Pugh Class B or C or acute liver failure		Patients with advanced hepatic disease	Did not exclude	Did not exclude
Receiving dialysis or have known moderate to severe renal impairment (eGFR <45 within 6 months of screening, using the serum creatinine-based CKD-EPI formula)	Receiving dialysis or have known renal impairment	Patients with advanced renal disease	Did not exclude	Did not exclude
Known human immunodeficiency virus (HIV) infection with a viral load greater than 400 copies/mL or taking prohibited medications for HIV treatment (within past 6 months of screening)		Did not exclude	Did not exclude	Did not exclude

EPIC HR	EPIC SR	Bejama	Schewartz	Lewnard
Suspected or confirmed concurrent active systemic infection other than COVID-19 that may interfere evaluation of response to the treatment		Did not exclude	Did not exclude	Did not exclude
History of hypersensitivity or other contraindication to any of the components of the study intervention as determined by the investigator		Did not exclude	Did not exclude	Did not exclude
Current or expected use of any medications or substances that are highly dependent on CYP3A4 for clearance, and for which elevated plasma concentrations may be associated with serious and/or life-threatening events during treatment or for 4 days after the last dose		Patients treated with contraindicated medication with Paxlovid	Did not exclude	Did not exclude
Concomitant use of any medications of substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to first dose and during study treatment		Patients treated with contraindicated medication with Paxlovid	Did not exclude	Did not exclude
Has received or is expected to receive convalescent COVID-19 plasma	Has received or is expected to receive mAb, convalescent COVID-19 plasma	Has received any outpatient COVID-19 treatment	Has received molnupiravir	Did not exclude
Has received or is expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit	Has received or is expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit ***Did not exclude fully vaccinated patients prior to December 19, 2021** (Fully vaccinated participants with underlying med conditions associated with an increased risk of COVID-19 must not receive a booster before Day 34 visit.)	Did not exclude unvaccinated patients.	Did not exclude patient based on vaccination status	Did not exclude patient based on vaccination status
Participating in another interventional clinical study with an investigational compound or device, including those for COVID-19 through the long-term follow-up visit		Did not exclude	Did not exclude	Did not exclude
Previous administration with any investigational drug or vaccine within 30 days or 5 half-lives preceding the first dose of study innervation		Did not exclude	Did not exclude	Did not exclude
Known prior participation in this trial or other trial involving Paxlovid		Did not exclude	Did not exclude	Did not exclude

EPIC HR	EPIC SR	Bejama	Schewartz	Lewnard
Oxygen saturation of <92% on room air within 24 hours prior to randomization, or on their standard home oxygen supplementation for those who regularly receive chronic supplementary oxygen for an underlying lung condition		Did not exclude	Did not exclude	Did not exclude
Abnormal tests in past 6 months AST or ALT level 2.5+X ULN Total bilirubin 2+X ULN eGFR <45, **using serum creatinine-based CKD-EPI** Absolute neutrophil count < 1000	Abnormal tests in past 6 months AST or ALT level 2.5+X ULN Total bilirubin 2+X ULN eGFR <45 Absolute neutrophil count < 1000	Did not exclude	Did not exclude	
Females who are pregnant or breastfeeding		Did not exclude	Did not exclude	Did not exclude
Any comorbidity requiring hospitalization and/or surgery within 7 days prior to study entry or that is considered life threatening within 30 days prior to study entry as determined by the investigator		Did not exclude	Did not exclude	Did not exclude
Other medical or psychiatric condition including recent (in the past year) or active suicidal ideation or lab abnormality that may increase the risk of study participation, or in the investigator's judgement, make the participant inappropriate for the study		Did not exclude	Did not exclude	Did not exclude
	Having criteria for high-risk **Participants with high-risk condition who are fully vaccinated against SARS-CoV-2 are eligible until December 19, 2021** (since they are considered at low risk for severe disease)			
		Patients who were residents in long-term care facilities No VA primary care encounters in the 18 months prior to positive test	Patients who were residents of Ontario or have invalid date of birth, patient tested from centers that dispense Paxlovid as exposure status cannot be verified in dispensing records. Patients whose dispensing date is prior to test date	

Table 1-2 High risk definition in the submitted EPIC HR and EPIC SR trials and RWE study

EPIC HR	EPIC SR	Arbel (Components for COVID-19 risk score)
≥60 years of age	≥65 years of age	Deduct points if < 60yrs, add 2 points if 70+yrs

EPIC HR	EPIC SR	Arbel (Components for COVID-19 risk score)
BMI >25	BMI >30	Add 1 point if BMI>30
Current smoker (cigarette smoking within the past 30 days) and history of at least 100 lifetime cigarettes		Adds 1 point if >10 packs cigarette/day
Chronic Kidney Disease **(exclude those who on dialysis or moderate to severe renal impairment)**	Chronic Kidney Disease	Adds 1 point for renal disease
Diabetes		Adds 1 point for diabetes
Immunosuppressive disease (e.g. bone marrow or organ transplantation or primary immune delicacies) OR prolonged use of immune-weakening meds (has received CS equivalate to prednisone 20+mg daily for at least 14 consecutive days within 30 days prior, treatment with biologics (infliximab, ustekinumab, etc) immunomodulators (methotrexate, 6MP, azathioprine, etc) or cancer chemotherapy within 90days prior to study entry, HIV infection with CD4+ cell count <200 **and viral load <400**	Immunosuppressive disease (e.g. bone marrow or organ transplantation or primary immune delicacies) OR prolonged use of immune-weakening meds (has received CS equivalate to prednisone 20+mg daily for at least 14 consecutive days within 30 days prior, treatment with biologics (infliximab, ustekinumab, etc) immunomodulators (methotrexate, 6MP, azathioprine, etc) or cancer chemotherapy within 90days prior to study entry, HIV infection with CD4+ cell count <200	Adds 7 points for immunosuppression Adds 1 point for organ transplant, bone marrow transplant or previous splenectomy or AIDS patient/HIV carrier, treatment at least twice with immunosuppressants in the last year or steroid treatment at least twice in the last year
CVD, defined as history of MI, stroke ,TIA, HF, angina with prescribed NO, CABG, PCI, carotid endarterectomy and aortic bypass. Known diagnosis of HTN		Adds 1 point for heart disease, vascular disease or cerebrovascular disease
Chronic lung disease (if asthma, required daily prescribed therapy)		Adds 1 points for COPD
Sickle cell disease		Not included
Neurodevelopmental disorders (eg, cerebral palsy, Down's syndrome) or other conditions that confer medical complexity (eg, genetic or metabolic syndromes and severe congenital anomalies)		Adds 1 point for neurological disease
Active cancer other than localized skin cancer, including those requiring treatment (including palliative treatment), as long as the treatment is not among the prohibited meds		Adds 1 point for active malignancy
Medical-related technological dependence not related to COVID-19 (eg, tracheostomy, gastrostomy, or positive pressure ventilation)		Not included
Did not include hepatic disease as "high-risk" criteria		Adds 1 point for hepatic disease

Table 1-2 High risk definition in the submitted EPIC HR and EPIC SR trials and RWE study (cont.)

EPIC HR	EPIC SR	Bejama
≥60 years of age	≥65 years of age	≥65 years of age
BMI >25	BMI >30	BMI > 25
Current smoker (cigarette smoking within the past 30 days) and history of at least 100 lifetime cigarettes		Current or formal Tobacco use

EPIC HR	EPIC SR	Bejama
Chronic Kidney Disease **(exclude those who on dialysis or moderate to severe renal impairment)**	Chronic Kidney Disease	Chronic kidney disease including dialysis
Diabetes		Diabetes
Immunosuppressive disease (e.g. bone marrow or organ transplantation or primary immune delicacies) OR prolonged use of immune-weakening meds (has received CS equivalate to prednisone 20+mg daily for at least 14 consecutive days within 30 days prior, treatment with biologics (infliximab, ustekinumab, etc) immunomodulators (methotrexate, 6MP, azathioprine, etc) or cancer chemotherapy within 90days prior to study entry, HIV infection with CD4+ cell count <200 **and viral load <400**	Immunosuppressive disease (e.g. bone marrow or organ transplantation or primary immune delicacies) OR prolonged use of immune-weakening meds (has received CS equivalate to prednisone 20+mg daily for at least 14 consecutive days within 30 days prior, treatment with biologics (infliximab, ustekinumab, etc) immunomodulators (methotrexate, 6MP, azathioprine, etc) or cancer chemotherapy within 90days prior to study entry, HIV infection with CD4+ cell count <200	Immunosuppressive meds or cancer therapies HIV
CVD, defined as history of MI, stroke ,TIA, HF, angina with prescribed NO, CABG, PCI, carotid endarterectomy and aortic bypass. Known diagnosis of HTN		CVD including cardiomyopathy, chronic rheumatic heart disease, congestive heart failure, coronary artery disease, hypertension, myocardial infarction, peripheral artery disease, pulmonary heart disease Stroke or cerebrovascular disease
Chronic lung disease (if asthma, required daily prescribed therapy)		Chronic lung disease including asthma, chronic obstructive pulmonary disease, emphysema, pulmonary fibrosis
Sickle cell disease		Sickle cell disease
Neurodevelopmental disorders (eg, cerebral palsy, Down's syndrome) or other conditions that confer medical complexity (eg, genetic or metabolic syndromes and severe congenital anomalies)		-
Active cancer other than localized skin cancer, including those requiring treatment (including palliative treatment), as long as the treatment is not among the prohibited meds		-
Medical-related technological dependence not related to COVID-19 (eg, tracheostomy, gastrostomy, or positive pressure ventilation)		-
-		Chronic liver disease including chronic hepatitis and cirrhosis
-		Chronic neurologic conditions including epilepsy, multiple sclerosis and Parkinson's disease
-		Dementia
-		Mental health conditions including bipolar disorder, major depressive disorder, PTSD and schizophrenia
-		Pregnancy
-		Substance use, alcohol dependence, non-alcohol substance dependence
-		Thalassemia

Table 2 Main findings on hospitalization in reviewed RWE studies

	Outcome	Paxlovid user			Non-users			Effect estimates (95% Confidence interval)
		N	Event N	Event rate*	N	Event N	Event rate*	
Arbel age 40-64	Hospitalization due to COVID-19	1,418	7	15.2 0.5%	65,015	327	15.8 0.5%	0.74 (0.35 to 1.58)
With previous immunity		n/a	n/a	n/a	n/a	n/a	n/a	1.13 (0.50 to 2.58)
Without previous immunity		n/a	n/a	n/a	n/a	n/a	n/a	0.23 (0.03 to 1.67)
Arbel age ≥ 65	Hospitalization due to COVID-19	2,484	11	14.7 0.4%	40,337	766	58.9 1.9%	0.27 (0.15 to 0.49)
With previous immunity		n/a	n/a	n/a	n/a	n/a	n/a	0.32 (0.17 to 0.63)
Without previous immunity		n/a	n/a	n/a	n/a	n/a	n/a	0.15 (0.04 to 0.60)
Wong (**86% >60**)	COVID-19 Hospitalization	5,542	n/a	48.5	54,672	n/a	61	0.76 (0.67 to 0.86) *0.85 (0.75 to 0.97)-post-hoc sensitivity analyses*
Fully Vaccinated		1,850	n/a	20.4	18,138	n/a	28.3	0.71 (0.51 to 1.01)
Not fully-vaccinated		3,692	n/a	60.6	36,534	n/a	76	0.76 (0.66 to 0.87)
Age 18- 60		784	n/a	25.4	8071	n/a	46.9	0.5 (0.31 to 0.81)
Age >60		4758	n/a	51.5	46601	n/a	63.8	0.8 (0.69 to 0.91)
	Outcome	**Paxlovid user**			**Non-users**			**Effect estimates (95% Confidence interval)**
		N	**Event N**	**%**	**N**	**Event N**	**%**	
Lewnard (54% age 60+)	Hospital admission or death in 30 days	7,274	51	0.7	126,152	695	0.5	HR=0.46 (0.23-0.93)
≥3 COVID-19 vaccine doses		5,866	n/a	n/a	75,837	n/a	n/a	0.34 (0.15-0.76)
≥2 COVID-19 vaccine doses		6,831	n/a	n/a	107,377	n/a	n/a	0.45 (0.21-0.93)
							0-5 days	HR=0.20 (0.06-0.66)
								0.08 (0.01-0.48)
								0.17 (0.04-0.70)
	Hospital admission		46	0.6		641	0.5	
Bejama (median age 65)	Hospitalization or death in 30 days	1,587	45	2.8	1,587	84.8	5.3%	RR=0.53 (0.39-0.72)
Primary/booster vaccination		1,126	25	2.2	1,108	50.8	4.6%	0.48 (0.32-0.73)
Unvaccinated		461	20	4.3	479	34	7.1%	0.61 (0.38-0.97)
18-64		743	15	2	733	18.3	2.5%	0.81 (0.46-1.42)
≥65		844	30	3.6	853	66.4	7.8%	0.46 (0.31-0.66)
	Hospitalization in 30 days	1,587	43	2.7	1,587	65.2	4.1	0.66 (0.48-0.91)
Shewartz (73.5% age 70+)	Hospitalization or death in 30 days	8,876	n/a	2.1	168,669	n/a	3.7%	OR=0.56 (0.47- 0.67)
Vaccine doses 3+		7,524	n/a	2.2	127,906	n/a	3.5%	0.62 (0.51-0.75)
Vaccine doses 1-2		885	n/a	1.1	30,329	n/a	4.4%	0.25 (0.12-0.50)

unvaccinated		467	n/a	3	10,434	n/a	6.6%	0.44 (0.23-0.84)
<70		2,443	n/a	0.3	129,647	n/a	0.8%	0.34 (0.15-0.79)
≥70		6,433	n/a	2.8	39,022	n/a	5%	0.55 (0.45-0.66)

*per 100,000 person-days, HR=Hazard ratio, RR=risk ratio, OR=odds ratio;

Table 3 Main findings on all-cause mortality in reviewed RWE studies

	Outcome	Paxlovid user			Non-users			Hazard ratio (95% Confidence interval)
		N	Event N	Event rate*	N	Event N	Event rate*	
Arbel 40-64 yr	Death	1,418	1	n/a	65,015	16	n/a	1.32 (0.16-10.75)
With previous immunity		n/a	n/a	n/a	n/a	n/a	n/a	n/a
Without previous immunity		n/a	n/a	n/a	n/a	n/a	n/a	n/a
Arbel ≥65 yr	Death	2,484	2	n/a	40,337	158	n/a	0.21 (0.05-0.82)
With previous immunity		n/a	n/a	n/a	n/a	n/a	n/a	n/a
Without previous immunity		n/a	n/a	n/a	n/a	n/a	n/a	n/a
Wong (86% >60 yr)	Death	5,542	n/a	4.2	54,672	n/a	11.6	0.34 (0.22 to 0.52) *0.35 (0.23 to 0.54)*
Fully Vaccinated		1,850	n/a	0.6	18,138	n/a	2.3	n/a
Not fully-vaccinated		3,692	n/a	7.1	36,534	n/a	15.1	0.44 (0.30 to 0.66)
Age 18- 60		784	n/a	0.0	8071	n/a	1.2	n/a
Age >60		4758	n/a	5.2	46601	n/a	10.5	0.48 (0.32 to 0.74)
Bejama	Death	1,875	5	0.3%	1,875	23.6	1.5%	0.21 (0.09-0.52)
Schwartz	Death	8,876	n/a	1.6%	168,669	n/a	3.3%	0.49 (0.40-0.60)
3 doses		7,524	n/a	1.7%	127,906	n/a	3.1%	0.54 (0.42-0.67)
1-2 doses		885	n/a	0.9%	30,329	n/a	3.8%	0.23 (0.11-0.51)
No vaccine		467	n/a	1.9%	10,434	n/a	5.5%	0.34 (0.16-0.74)
Age <70		2,443	n/a	0.1%	129,647	n/a	0.6%	0.13 (0.03-0.57)
Age >=70		6,433	n/a	2.2%	39,022	n/a	4.5%	0.48 (0.39-0.59)

*per 100,000 person-days

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NATASHA PRATT
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05/18/2023 12:23:46 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 8, 2023

To: Myong-Joo Patricia Hong, Regulatory Project Manager
Division of Antivirals (DAV)

From: Wendy Lubarsky, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Sam Skariah, Team Leader, OPDP
CC: Andrew Haffer, Director, DAPR1, OPDP

Subject: OPDP Labeling Comments for PAXLOVID (nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use

NDA: 217188

Background:

In response to DAV's consult request dated June 30, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for the original NDA submission for Paxlovid.

PI/PPI:
OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on May 2, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI, and comments were sent under separate cover on May 8, 2023.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on May 5, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Wendy Lubarsky at (240) 402-7721 or wendy.lubarsky@fda.hhs.gov .

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WENDY R LUBARSKY
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 8, 2023
To:	Myung-Joo Patricia Hong, M.S. Senior Regulatory Project Manager **Division of Antivirals (DAV)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Wendy Lubarsky, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	PAXLOVID (nirmatrelvir tablets; ritonavir tablets)
Dosage Form and Route:	co-packaged for oral use
Application Type/Number:	NDA 217188
Applicant:	Pfizer, Inc.

1 INTRODUCTION

On June 29, 2022, Pfizer, Inc., submitted for the Agency's review an original New Drug Application (NDA) 217188 for PAXLOVID (nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use indicated for the treatment of mild-to-moderate COVID-19 in adults (b) (4) who are at high risk for progression to severe COVID-19, including hospitalization or death.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antivirals (DAV) on June 30, 2022, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for PAXLOVID (nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use.

2 MATERIAL REVIEWED

- Draft PAXLOVID (nirmatrelvir tablets; ritonavir tablets) co-packaged for oral use PPI received on June 29, 2022, and received by DMPP and OPDP on May 2, 2023.
- Draft PAXLOVID (nirmatrelvir tablets; ritonavir tablets) co-packaged for oral use Prescribing Information (PI) received on June 29, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 2, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

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4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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BARBARA A FULLER
05/08/2023 11:24:12 AM

LASHAWN M GRIFFITHS
05/08/2023 11:29:17 AM

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 2, 2023
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 217188
Product Name and Strength:	Paxlovid (Nirmatrelvir 300 mg[a]; Ritonavir 100 mg) and (Nirmatrelvir 150 mg; Ritonavir 100 mg) dose packs
Applicant/Sponsor Name:	Pfizer Inc.
OSE RCM #:	2022-33-3
DMEPA 1 Safety Evaluator:	Melina Fanari, R.Ph.
Acting DMEPA 1 Team Leader:	Madhuri R. Patel, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on April 28, 2023 for Paxlovid. The previously reviewed container labels were also included in the submission.[b] The Division of Antivirals (DAV) requested that we review the revised carton labeling for Paxlovid (Appendix A) to determine if they are acceptable from a medication error perspective.

2 CONCLUSION

The carton labeling was revised to include the following alert to patients:

"Find out about medicines that should not be taken with Paxlovid."

Our evaluation of the proposed changes did not identify any areas of vulnerability to medication error. We have no additional recommendations at this time.

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[a] packaged as two 150 mg Nirmatrelvir tables.
[b] Fanari, Melina. Label and Labeling Review for Paxlovid (NDA 217188). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 Dec 12. RCM No.: 2022-33-1.

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/s/

MELINA N FANARI
05/02/2023 12:21:35 PM

MADHURI R PATEL
05/02/2023 01:26:19 PM

Clinical Inspection Summary

Date	31 Jan 2023
From	Elena Boley, M.D., M.B.A. Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Myung-Joo Patricia Hong, M.S., SRPM Glen Huang, M.D., Clinical Reviewer Stephanie Troy, M.D., Clinical Team Leader Sarah Connelly, M.D., Cross-Discipline Team Leader
NDA #	NDA 217188
Applicant	Pfizer, Inc.
Drug	PAXLOVID (nirmatrelvir [PF-07321332] 150 mg co-packaged with ritonavir 100 mg)
NME	Yes
Proposed Indication	Treatment of mild-to-moderate COVID-19 in adults (b) (4) [redacted] who are at high risk for progression to severe COVID-19, including hospitalization or death.
Consultation Request Date	16 Aug 2022
Summary Goal Date	8 Feb 2023
Action Goal Date	20 Apr 2023
PDUFA Date	28 May 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Igbinadolor, Hernandez, Martinez, Mitreva, Simova, Medzhidiev, Haytova as well as the sponsor, Pfizer, Inc., were inspected in support of NDA 217188. With the exception of the inspection of Dr. Medzhidiev, which covered only Protocol C4671002 (EPIC-SR), all of these inspections covered the pivotal study, Protocol C4671005 (EPIC-HR).

(b) (7)(A) [redacted]

Dr. Hernandez (site #1470 in Florida for EPIC-HR) was inspected due to a complaint. For this site, we recommend a sensitivity analysis not based primarily on the results of inspection, which were not able to confirm a whistleblower's complaint, but instead on the sponsor's report of Good Clinical Practice non-compliance following their own investigation. The sponsor subsequently decided, per the NDA submission, to perform sensitivity analyses without the data for the subjects (n=2) enrolled at site #1470 who withdrew consent. Because the 36 subjects who were transferred to site #1276 at the time of site termination had already reached the primary efficacy analysis timepoint, it seemed appropriate to perform a sensitivity analysis without the data from all 38 subjects.

At the sites of Drs. Martinez, Medzhidiev, and Haytova, use of birthyear or commonly used e-diary PIN code(s) was found. For these three inspections, instructions or suggestions for subjects to create PIN codes using specific numbers or easily identifiable numbers (birthyear) were provided by the site. Nevertheless, the inspections found no evidence that anyone other than the subject entered data into the e-diaries.

Overall, the inspections found that the primary efficacy endpoint data for EPIC-HR were verifiable. Except for significant protocol deviations at the Martinez and Hernandez sites, the study appears to have been conducted adequately, and the data generated from the other sites appear reliable in support of the proposed indication. As mentioned above, we recommend sensitivity analyses for the data from the Martinez and Hernandez sites.

II. BACKGROUND

NDA 217188 was submitted in support of the use of PAXLOVID (nitmatrelvir/ritonavir) tablets for oral administration for the treatment of treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults (b) (4) [redacted] ho are at high risk for progression to severe COVID-19, including hospitalization or death. The pivotal study supporting the application was the following:

- Protocol C4671005: "An interventional efficacy, safety, Phase 2/3, double-blind study to investigate oral nirmatrelvir/ritonavir compared with placebo in nonhospitalized symptomatic high risk adults with COVID-19 (EPIC-HR)"

This study was a Phase 2/3, multinational, multicenter, randomized, double-blind, placebo-controlled trial in nonhospitalized symptomatic adult participants with COVID-19 who were at increased risk of progressing to severe illness. The primary efficacy objective was to compare the efficacy of nirmatrelvir/ritonavir to placebo for the treatment of COVID-19 in this population. The secondary efficacy objective was to compare nirmatrelvir/ritonavir to placebo for the duration and severity of signs and symptoms in this population.

Eligible subjects were males or females, aged 18 to 80 years of age, who had laboratory confirmed (see protocol for more details) SARS-CoV-2 infection from a specimen collected

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within five days prior to randomization and whose initial onset of signs/symptoms attributable to COVID-19 occurred within five days prior to the day of randomization with at least one of the specified signs/symptoms attributable to COVID-19 present on the day of randomization. Enrolled participants had at least one characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19 (age 60 years, body mass index >25, smoker, immunocompromised, history of chronic lung disease, hypertension, cardiovascular disease, diabetes mellitus, chronic kidney disease, sickle cell disease, neurodevelopmental disorders, active cancer, medical-related technological dependence). Participants were excluded if they received or were expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit.

The study was comprised of three periods: a screening and randomization period, a study intervention period, and a follow-up period. The total duration of the study was 24 weeks.

After screening, subjects were randomized in a 1:1 fashion (stratified by geographic region and whether participants had received/were expected to receive COVID-19 therapeutic mAb treatment [yes/no])). Subjects then began the study intervention period, during which they received either nirmatrelvir 300 mg (i.e., two tablets of 150 mg or three tablets of 100 mg for participants in the sentinel cohort) and ritonavir 100 mg (i.e., one capsule of 100 mg) q12h by mouth for five days, or a matching placebo for nirmatrelvir (two tablets [three tablets for the sentinel cohort]) and placebo for ritonavir (one capsule) q12h by mouth for five days.

The ***primary efficacy endpoint*** was the proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28.

The review division was also particularly interested in the ***secondary efficacy endpoint*** of viral titers measured via RT-PCR in nasal swabs over time.

Details relevant to Study C4671005

Study C4671005 was conducted at 343 centers that screened subjects in 19 countries/regions worldwide (Argentina, Brazil, Bulgaria, Colombia, Czech Republic, Hungary, India, Japan, Republic of Korea, Malaysia, Mexico, Poland, Russian Federation, South Africa, Spain, Thailand, Turkey, Ukraine, and US); 191 of the centers randomized at least one subject. The first subject was enrolled on July 16, 2021, and the last subject completed final visit on April 26, 2022. Of the 2246 subjects that were randomized, 2092 subjects (93.1%) completed the study. The original protocol was dated June 18, 2021, there were four protocol amendments, and the final protocol was dated November 20, 2021.

Protocol C4671002

The supportive study is entitled:

- Protocol C4671002: "An interventional efficacy and safety, Phase 2/3, double-blind, 2-arm study to investigate orally administered PF-07321332/Ritonavir compared with placebo in nonhospitalized symptomatic adult participants with COVID-19 who are at low risk of progressing to severe illness (EPIC-SR)"

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This Phase 2/3, multinational, multicenter, randomized, double-blind, placebo-controlled study in nonhospitalized symptomatic adult participants with COVID-19 who were at low risk of progressing to severe illness. The primary efficacy objective was to compare the efficacy of nirmatrelvir/ritonavir to placebo for the treatment of symptomatic COVID-19 in this population. The secondary efficacy objective was to compare nirmatrelvir/ritonavir versus placebo for COVID-19 related hospitalization and all-cause mortality in this population.

Eligible participants were male or females, aged ≥18 years of age (or the minimum country-specific age of consent if >18) with a laboratory confirmed diagnosis (see protocol for more details) of SARS-CoV-2 infection from a specimen collected within five days prior to randomization and whose initial onset of signs/symptoms attributable to COVID-19 occurred within five days prior to the day of randomization with at least one of the specified signs/symptoms attributable to COVID-19 present on the day of randomization. Participants were excluded if they had at least one of the following characteristics indicating an underlying medical condition associated with an increased risk of developing severe illness from COVID-19: ≥65 years of age; body mass index ≥30 kg/m^2; smoker; chronic lung disease; hypertension; cardiovascular disease; diabetes mellitus; chronic kidney disease; sickle cell disease; neurodevelopmental disorders; active cancer; and immunosuppressive disease (see protocol for full list with details).

The study was comprised of three periods: a screening and randomization period, a study intervention period, and a follow-up period. The total duration of the study was 24 weeks.

After screening, subjects were randomized in a 1:1 fashion (stratified by geographic region, by vaccination status, and by COVID-19 symptom onset [≤3 days vs >3 to 5 days]). Subjects then began the study intervention period, during which they received either nirmatrelvir 300 mg (i.e., two tablets of 150 mg) and ritonavir 100 mg (i.e., one capsule of 100 mg) q12h by mouth for five days., or a matching placebo for nirmatrelvir (two tablets) and placebo for ritonavir (one capsule) q12h by mouth for five days.

The ***primary efficacy endpoint*** was the time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28.

Details relevant to Study C4671002

Study C4671002 was conducted at 343 centers that screened subjects in 18 countries/regions worldwide (Argentina, Brazil, Bulgaria, Colombia, Czech Republic, Hungary, Japan, Republic of Korea, Malaysia, Mexico, Poland, Russian Federation, South Africa, Spain, Thailand, Turkey, Ukraine, and US); 173 of the centers randomized at least one subject. The first subject was enrolled on August 25, 2021. The data cutoff point for the interim analysis was December 19, 2021. At that time, 1153 (92%) of the 1251 randomized subjects had completed the study. Enrollment restarted on March 16, 2022, and the last subject completed their final visit on July 25, 2022. The original protocol was dated June 18, 2021, there were six protocol amendments, and the final protocol was dated June 9, 2022.

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Rationale for Site Selection

Initially, five clinical investigator (CI) sites were selected for inspection. Of the 5 sites, 4 sites (#1274, #1108, #1158, and #1097, all sites in Study C4671005) were chosen for routine inspection primarily based on the regional distribution of subjects, the numbers of enrolled subjects, and site-specific efficacy results (based on a composite of endpoints). Two (2) of these 4 clinical sites (sites #1158 and #1097 in Bulgaria) were selected for inspection because there were insufficient domestic data (i.e., subjects from the US comprised only 40% of the safety population in Study C4671005), and 30% of subjects were at sites in Eastern Europe. The fifth site, site 1470 (Study C4671005) in Florida, was chosen to be inspected due to a complaint.

The Division of Antivirals' (DAV's) review detected data anomalies (viral load and e-diary symptom data) at site 1274 in Study C4671005 (previously selected for routine inspection) as well as three additional sites: sites #1281, #1157, and #1197 (all in Study C4671002). These three sites were added to the inspections. In addition, because the clinical investigator Nezabravka Petrova Haytova in Bulgaria participated in both Study C4671002 (site #1197) and Study C4671005 (site #1193), Study C4671005 was added to the inspection of Dr. Haytova.

III. RESULTS (by site):

1. **Awawu Igbinadolor, M.D.**
   Site #1108
   Protocol: C4671005 (EPIC-HR)
   343 Venus Street
   Monroe, NC 28112
   PDUFA Inspection Dates: September 19-22, 2022

At this site for Protocol EPIC-HR, 25 subjects were screened, 24 were randomized, and 18 subjects completed the study. One subject (subject # (b) (6)) was randomized but never treated because it was learned that he had met exclusion criterion #14 (he had received the SARS-CoV-2 vaccine). Of the 5 subjects who did not complete the study, 3 subjects withdrew consent (subjects # (b) (6) and # (b) (6) were assigned to the placebo group and subject (b) (6) was assigned to the Paxlovid group). The two remaining subjects, both assigned to the placebo group, died prior to study completion.

The inspection evaluated the study records for the 24 randomized subjects. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; institutional review board (IRB) submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records; primary efficacy endpoint data; adverse event reporting; protocol deviations; drug accountability logs; monitor logs and follow-up letters; and other regulatory documentation (e.g., Form FDA 1572s).

There was no evidence of under-reporting of adverse events, with the exception of two instances of low potassium (K= 3.0 mEq/L for subject (b) (6) and K= 3.3 mEq/L for subject # (b) (6)) identified during routine clinical laboratory testing. In both cases, the CI had noted the low potassium on the lab results and had recommended that the subject be treated with potassium supplementation.

Reviewer's comment: These two protocol deviations are minor and isolated. Although these clinical laboratory test abnormalities should have been reported as AEs, the NDA submission contained this data in the clinical laboratory datasets and so they were included in the safety analyses for this application.

During the inspection, the paper medical and other source records were reviewed, and the occurrence of COVID-19 related hospitalizations and death from any cause was verified against the data line listings provided by the sponsor for all 24 randomized subjects. No discrepancies were noted. Viral RNA level measurements for this site were verified at the sponsor inspection.

2. **Humberto Hernandez, M.D.**
   Site #1470
   Protocol: C4671005 (EPIC-HR)
   14001 NW 4th Street, Suite C
   Sunrise, FL 33325
   PDUFA Inspection Dates: September 22, 23, 26, 27, and 30, 2022 and October 3-7 and 11-13, 2022

At this site for Protocol EPIC-HR, 39 subjects were screened, 38 were randomized, and zero subjects completed the study. Thirty-six (36) subjects were transferred to another site (site #1276) to complete the study after the study was terminated by the IRB (1/13/2022) for serious noncompliance and the site was closed by the sponsor (2/19/2022). Of the 4 subjects who did not complete the study, 2 subjects (subjects (b) (6) and # (b) (6) discontinued after experiencing a serious adverse event (SAE), and 2 subjects (subjects (b) (6) and (b) (6)) withdrew consent.

Reviewer's comment: At the time of their transfer to site #1276, the transferred subjects had already reached the primary efficacy analysis timepoint. For this reason, we determined that verification of the primary efficacy endpoint data for the transferred subjects could be conducted during the inspection of Dr. Hernandez.

The inspection evaluated the study records for 38 randomized subjects. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; institutional review board (IRB) submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records; primary efficacy endpoint data; adverse event reporting; protocol deviations; drug accountability logs; monitor logs and follow-up letters; and other regulatory documentation (e.g., Form FDA 1572s).

Adverse events were reviewed for 23 randomized subjects. One (1) adverse event for each of 9

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subjects was not recorded in the EDC. These included 2 events of metallic taste, 5 events of abnormal lab results (elevated ALT [n=2]; increased PTT, increased D-dimer, and increased CPK [n=1 each]), and a single event each of hypertension and elevated TSH/low T3 (hypothyroidism). The occurrence of COVID-19 related hospitalizations and death from any cause were verified against the data line listings provided by the sponsor for 23 of 38 randomized subjects. Viral RNA level measurements for this site were verified at the sponsor inspection.

Reviewer's comment: Although these clinical laboratory test abnormalities should have been reported as AEs, all but one (metallic taste, a known side effect of Paxlovid) were contained in the NDA submission in the clinical laboratory datasets and vital sign datasets and so these data were included in the safety analyses.

An FDA Form 483 was issued stating that 5 of 23 subjects did not meet an inclusion criterion, or met an exclusion criterion, but were screened, enrolled, randomized, and received investigational product. Specifically, subject (b) (6) had a chronic lung disease but was not taking daily prescription therapy as required (a protocol deviation was recorded and submitted to the IRB); subjects # (b) (6) and (b) (6) were enrolled >5 days after the onset of their COVID-19 signs/symptoms; and subjects # (b) (6) and (b) (6) both had received or were expected to receive a dose of SARS-CoV-2 vaccine before the Day 34 visit.

Reviewer's comment: At the time the protocol deviations for subjects (b) (6) were noted by the study monitors, the subjects had completed the study treatment. No notation regarding vaccination-related protocol deviations for subjects (b) (6) and (b) (6) appears in the monitoring records. With the exception of subject (b) (6) each of these subjects was appropriately not included in the per protocol analysis set. Subject (b) (6) 's data should have been removed by the sponsor from the per-protocol analysis set, a single extra subject is very unlikely to make a difference for the per-protocol analysis.

3. **Carlos Martinez, M.D.**
   Site #1274
   Protocol: C4671005 (EPIC-HR)
   Site #1281
   Protocol: C4671005 (EPIC-SR)
   10912 Southwest 184th Street
   Cutler Bay, FL 33157
   PDUFA Inspection Dates: October 17, 2022, to November 1, 2022

At this site for Protocol EPIC-HR, 101 subjects were screened, 95 were randomized, and 94 subjects completed the study. At this site for Protocol EPIC-SR, 50 subjects were screened, 46 were randomized, and 46 subjects completed the study.

The inspection evaluated the study records for the 95 randomized subjects for Protocol EPIC-HR and all 46 subjects for Protocol EPIC-SR. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; institutional review

board (IRB) submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records; primary efficacy endpoint data; adverse event reporting; protocol deviations; drug accountability logs; monitor logs and follow-up letters; and other regulatory documentation (e.g., Form FDA 1572s).

Adverse events were reviewed for both studies. There was no evidence of under-reporting of adverse events, with the exception of a single AE of headache (subject # (b) (6) in Study EPIC-HR).

Reviewer's comment: This single AE should have been reported to the sponsor. However, headache is proposed to be included in the label for Paxlovid.

Regarding adverse events, the inspection found that an SAE (subject (b) (6) in Study EPIC-HR) was reported more than 24 hours after the site became aware of their occurrence. The protocol required that any subject with an eGFR <45 ml/min/1.73m^2 be discontinued from the study intervention dosing. The eGFR measured on Day 1 (b) (6) was 32 ml/min/1.73m^2. The CI signed the result as reviewed on (b) (6), but the initial SAE report was not submitted to the sponsor until six days later (b) (6). The subject was not discontinued from the study intervention dosing and completed all five days of the study treatment.

Reviewer's comment: In general, the failure to report SAEs within the 24-hour time frame as required by the protocol puts subjects at increased risk. In this case, Dr. Martinez did not discontinue the study drug for this subject. As a result, subject (b) (6) was unnecessarily exposed to potential increased risk.

During the EPIC-HR inspection, the paper medical and other source records were reviewed, and the occurrence of COVID-19 related hospitalizations and death from any cause was verified against the data line listings provided by the sponsor for all 95 randomized subjects. No discrepancies were noted. Viral RNA level measurements for this site were verified at the sponsor inspection.

A comparison of the PIN codes used by each subject to the PIN codes used by other subjects was performed for all randomized subjects in both studies. An FDA Form 483 was issued stating that during the conduct of EPIC-HR and EPIC-SR, multiple subjects were instructed to change their e-diary PIN code (used for recording their daily dosing and symptoms data) to one provided by the study staff.

Reviewer's comment: The inspection found no information to suggest that anyone other than the subjects entered e-diary data into their e-diaries. However, we recommend sensitivity analyses with regard to this site.

(b) (7)(A)

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(b) (7)(A)

4. **Roza Mitreva, M.D.**
   Site #1158
   Protocol: C4671005 (EPIC-HR)
   49 Macedonia St.
   Samokov 2000 BULGARIA
   PDUFA Inspection Dates: October 24-28, 2022

At this site for Protocol EPIC-HR, 56 subjects were screened, 56 were randomized, and 50 subjects completed the study. Of the 6 subjects who did not complete the study, 5 subjects discontinued due to personal reasons, and one subject died. Of the 5, 3 were assigned to the Paxlovid group and 2 were assigned to the placebo group.

The inspection evaluated the study records for the 56 randomized subjects. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; independent ethics committee approvals; subject eligibility criteria; informed consent process and forms; source records, including medical records; primary efficacy endpoint data; adverse event reporting; protocol deviations; drug accountability logs; monitor logs and follow-up letters; and other regulatory documentation.

Serious adverse events were reviewed for all subjects and nonserious adverse events were reviewed for over half of the subjects. There was no evidence of under-reporting of adverse events. During the inspection, the paper medical and other source records were reviewed, and the occurrence of COVID-19 related hospitalizations and death from any cause was verified against the data line listings provided by the sponsor for all 56 randomized subjects. No discrepancies were noted. Viral RNA level measurements for this site were verified at the sponsor inspection.

A notable number of laboratory reports indicated that samples sent for clinical laboratory testing were “unable to process” or “out of stability.” The site staff was not aware of these issues until well after samples were received by the laboratory. Pfizer became aware of this issue and arranged for high-enrolling sites to have daily sample pickup for shipment to the central laboratory.

Reviewer’s comment: Although a number of laboratory tests were not completed, because this lab data did not contribute to the primary efficacy endpoint, this did not impact the efficacy results of the study. However, missing lab results did limit the robustness of the safety data for subjects at this site.

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5. **Iana Simova, M.D.**
   Site #1097
   Protocol: C4671005 (EPIC-HR)
   2, Pier Curie Str.
   Pleven 5800 BULGARIA
   PDUFA Inspection Dates: October 31, 2022, to November 4, 2022

At this site for Protocol EPIC-HR, 41 subjects were screened, 41 were randomized, and 36 subjects completed the study. Of the 5 subjects who did not complete the study, 2 subjects discontinued for personal reasons, 1 subject was randomized but did not receive treatment due to enrollment closure, and 2 subjects died. Both of the subjects who discontinued were assigned to the Paxlovid group.

The inspection evaluated the study records for the 41 randomized subjects. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; independent ethics committee approvals; subject eligibility criteria; informed consent process and forms; source records, including medical records; primary efficacy endpoint data; adverse event reporting; protocol deviations; drug accountability logs; monitor logs and follow-up letters; and other regulatory documentation.

Serious adverse events were reviewed for all subjects and nonserious adverse events were reviewed for over half of the subjects. There was no evidence of under-reporting of adverse events. During the inspection, the paper medical and other source records were reviewed, and the occurrence of COVID-19 related hospitalizations and death from any cause was verified against the data line listings provided by the sponsor for all 41 randomized subjects. No discrepancies were noted.

A modest number of laboratory reports indicated that samples sent for clinical laboratory testing were “unable to process” or “out of stability.” The site was not aware of these issues until well after samples were received by the laboratory. Pfizer became aware of this issue and arranged for high-enrolling sites to have daily sample pickup for shipment to the central laboratory.

Reviewer’s comment: Although a modest number of laboratory tests were not completed, because this lab data did not contribute to the primary efficacy endpoint, this did not impact the efficacy results of the study. However, missing lab results did limit the robustness of the safety data for subjects at this site.

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6. **Asen G. Medzhidiev**
   Site #1157
   Protocol: C4671002 (EPIC-SR)
   UMHATEM N. I. Pirogov EAD, Department of Ear & Throat Diseases
   Bulevard Gen Totleben 21, Sofiya, Oblast Sofiya Grad,
   1606 Bulgaria
   PDUFA Inspection Dates: December 12-16, 2022

At this site for Protocol EPIC-SR, 49 subjects were screened, 48 were randomized, and 46 subjects completed the study. Two subjects did not complete the study. Of the 2 subjects who did not complete the study, 1 (subject # (b) (6)) never started treatment due to "insufficient medication" and the other withdrew consent (subject # (b) (6)). Both were assigned to the placebo group.

The inspection evaluated the study records for 16 of the 49 randomized subjects. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; independent ethics committee approvals; subject eligibility criteria; informed consent process and forms; source records, including medical records; primary efficacy endpoint data; adverse event reporting; protocol deviations; drug administration records; monitor logs and follow-up letters; and other regulatory documentation.

Adverse events were reviewed for 16 randomized subjects. There was no evidence of under-reporting of adverse events. During the inspection, the paper medical and other source records were reviewed, and, although not a primary efficacy endpoint, the occurrence of COVID-19 related hospitalizations and death from any cause was verified against the data line listings provided by the sponsor for 16 of randomized subjects. No discrepancies were noted.

PIN code comparisons to subject birth years and to other subject's PIN codes were performed for all randomized subjects. An FDA Form 483, Inspectional Observations, was issued stating that during the conduct of EPIC-SR, the clinical investigator did not ensure that each participant created a new device PIN code that remained confidential to the participant only. Instead, participants were instructed to use PIN codes that were easy to remember, such as their birth dates, which were readily available to the site. Records revealed that 46 of 49 enrolled participants used their birth year as their new PIN code.

Reviewer's comment: The inspection found no information to suggest that anyone other than the subjects entered e-diary data into their e-diaries.

7. **Nezabravka Petrova Haytova**
   Site #1193
   Protocol: C4671005 (EPIC-HR)
   Site #1197
   Protocol: C4671002 (EPIC-SR)
   Specialized Hospital for Active Treatment of
   Pneumo-Phthisiatric Diseases Vratsa EOOD,
   Department of Pneumology

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93 General Leonov str. Vratsa,
VRATSA, 3000 BULGARIA
PDUFA Inspection Dates: December 12-16, 2022

At this site for Protocol EPIC-HR, 59 subjects were screened and randomized, and 58 subjects completed the study. A single subject who decided to drop out, subject (b) (6) was assigned to the placebo group.

At this site for Protocol EPIC-SR, 33 subjects were screened, 33 were randomized, and 32 subjects completed the study. Subject (b) (6), assigned to the Paxlovid group, withdrew consent. The inspection evaluated the study records for all 59 randomized subjects for Protocol EPIC-HR and all 33 randomized subjects for Protocol EPIC-SR. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; independent ethics committee approvals; subject eligibility criteria; informed consent process and forms; source records, including medical records; primary efficacy endpoint data; adverse event reporting, protocol deviations; drug administration records; monitor logs and follow-up letters; and other regulatory documentation.

During the EPIC-HR inspection, the paper medical and other source records were reviewed, and the occurrence of COVID-19 related hospitalizations and death from any cause was verified against the data line listings provided by the sponsor for all 59 of randomized subjects. No discrepancies were noted.

After study EPIC-SR closure, the sponsor provided the site with a USB flash drive with copies of the final versions of the e-diary source data. During the inspection, the e-diary data was reviewed, and the time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28 was verified against the data line listings provided by the sponsor for all 33 randomized subjects. No discrepancies were noted.

Adverse events were reviewed for both studies. There was no evidence of under-reporting of adverse events.

PIN code comparisons to subject birth years and to other subject's PIN codes were performed for all randomized subjects from both protocols. An FDA Form 483 was issued stating that during the conduct of EPIC-HR and EPIC-SR, the clinical investigator did not follow the Site User Guide. Specifically, the Site User Guide for the electronic patient reported outcome (ePRO) application used in the study to collect electronic diaries states "The participant should not share their PIN code with anyone, not even with study staff. The new PIN code must remain confidential, with only the participant knowing the PIN code." However, when assisting subjects to download and activate the application, the investigator's site staff provided suggestions in a manner that caused the subjects in the studies to create nonconfidential PIN codes. The investigator's site staff gave examples of easily memorable numbers to use for a PIN code, including birth year and specific numbers such as "2323."

Reviewer's comment: The inspection found no information to suggest that anyone other than the subjects entered e-diary data into their e-diaries.

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8. Pfizer, Inc.
Protocol: C4671005 (EPIC-HR)
Protocol: C4671002 (EPIC-SR) – limited coverage of this protocol
445 Eastern Point Road,
Groton, CT 06340
PDUFA Inspection Dates: October 12-28, 2022

This inspection covered the sponsor practices primarily related to Protocol EPIC-HR with limited coverage of Protocol EPIC-SR and focused on the five clinical investigator sites from Study EPIC-HR (sites #1274, #1108, #1470, #1158, and #1097) that had been selected for inspection.

The inspection reviewed the following activities and found them to be adequate:

- Clinical investigator selection (identification and monitoring was provided by (b) (4), who contracted (b) (4) to supplement the site visits and clinical monitoring)
- Site monitoring, as per the monitoring plan, and the sponsor's procedure
- Contractual agreements with (b) (4)
- Vendor data transfer methods to the sponsor
- Monitoring of the vendors to ensure the study was being conducted in accordance with the study protocol, contractual agreement, and sponsor's procedures
- Communication methods and frequency between the sponsor, vendor, and clinical sites
- Completion of monitoring reports and management of findings
- Quality assurance audits
- Custody and retention of records
- Maintenance of financial disclosure forms
- Maintenance of adequate records showing receipt and shipment of the investigational product
- Confirmation of receipt condition and storage conditions of the investigational product

Due to limited time, safety and adverse event reporting was reviewed only briefly. The inspection found that the following related to the data monitoring committee were sufficient: the charter, written procedure, membership qualification, board composition, meeting minutes, blinding, and the process of collection, evaluation, analyses, and reporting of adverse events.

General discussion with management included the following issues: inadequate supply of e-diary devices, inadequate supply of nasal swabs, and concerns about attributing data to specific subjects because a majority of the subjects at Martinez's site for both studies were found to be using the PIN code "1274" for their e-diaries. Of note, the sponsor performed an audit related to the PIN code issue at Dr. Martinez's site. They concluded that (b) (4), which was responsible for the e-diaries, did not have systems in place to prevent and detect the use of common PIN codes among participants.

Reviewer comment: Please see the summary of Dr. Martinez's site above for more detail regarding this issue.

Regarding the inadequate supply of e-diary devices: the sponsor did not track the supply of e-diaries at clinical sites to ensure each site had adequate supplies, and the clinical sites were not required to confirm adequate supply of e-diaries. Therefore, it was concluded that the sponsor oversight of e-diary supplies was inadequate.

Regarding the inadequate supply of nasal swabs, sponsor oversight was similarly not sufficient. As with the e-diary supply problem, the sponsor did not track the supply of nasal swabs at the clinical sites to ensure each site had adequate supplies. Furthermore, the response to the inadequate supply of I SWAB PLUS swabs ultimately led to the approval of locally sourced swabs for use and, ultimately, to the exclusion of this data from the data set because viral RNA data obtained using locally sourced swabs were not permitted per the statistical analysis plan.

{See appended electronic signature page}

Elena Boley, M.D., M.B.A.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
Central Doc. Rm. NDA 217188
DAV/Senior Project Manager/Myung-Joo Patricia Hong
DAV/Clinical Reviewer/Glen Huang

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DAV/Clinical Team Leader/Stephanie Troy
DAV/Cross-Discipline Team Leader/Sarah Connelly
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/Branch Chief/Jenn Sellers
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Reviewer/Elena Boley
OSI/GCPAB/Program Analyst/Yolanda Patague

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JENN W SELLERS
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 9, 2023
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 217188
Product Name and Strength:	Paxlovid (Nirmatrelvir 300 mg[a]; Ritonavir 100 mg) and (Nirmatrelvir 150 mg; Ritonavir 100 mg) dose packs
Applicant/Sponsor Name:	Pfizer Inc.
OSE RCM #:	2022-33-2
DMEPA 1 Safety Evaluator:	Melina Fanari, R.Ph.
Acting DMEPA 1 Team Leader:	Madhuri R. Patel, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on December 20, 2022 for Paxlovid. The Division of Antivirals (DAV) requested that we review the revised container labels and carton labeling for Paxlovid (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] packaged as two 150 mg Nirmatrelvir tables.
[b] Fanari, Melina. Label and Labeling Review for Paxlovid (NDA 217188). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 Dec 12. RCM No.: 2022-33-1.

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	December 12, 2022
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 217188
Product Name, Dosage Form, and Strength:	Paxlovid (Nirmatrelvir 300 mg[a]; Ritonavir 100 mg) and (Nirmatrelvir 150 mg; Ritonavir 100 mg) dose packs
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Pfizer Inc.
FDA Received Date:	June 29, 2022 and November 9, 2022
TTT ID #:	2022-33-1
DMEPA 1 Safety Evaluator:	Melina Fanari, R.Ph.
Acting DMEPA 1 Team Leader:	Madhuri R. Patel, PharmD
DMEPA 1 Associate Director for Nomenclature and Labeling:	Mishale Mistry, PharmD, MPH

[a] packaged as two 150 mg Nirmatrelvir tables.

1 REASON FOR REVIEW

As part of the approval process for Paxlovid (Nirmatrelvir; Ritonavir) tablets (NDA 217188), the Division of Antivirals (DAV) requested that we review the proposed Paxlovid prescribing information, patient prescribing information, container labels and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Paxlovid is currently authorized for use under EUA 105 for the treatment of symptomatic COVID-19 in pediatric and adult patients who are at high risk for progression to severe COVID-19. Under EUA 105, there have been multiple revisions to product labeling to address ongoing wrong dose medication errors occurring during patient self-administration.[b] As a result, FDA requested for Pfizer to revise the product design and/or packaging configuration (e.g., single dose blister cards) under NDA 217188[c] to address the ongoing wrong dose medication errors and support all dosing regimens in the product labeling. Pfizer proposed a new packaging presentation in their November 9, 2022 submission. Our review of the revised packaging presentation of Paxlovid, the prescribing information (PI), patient prescribing information (PPI),

[b] Fanari, M. Label and Labeling Review for Paxlovid (NDA 217188). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 Aug 3. RCM No.: 2021-2174-4

[c] Fanari, M. Label and Labeling Review for Paxlovid (NDA 217188). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 Aug 29 RCM No.: 2022-33

container labels and carton labeling identified areas that may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error. We collaborated with DAV to update the PI (section 2, 3, 16 and 17) and PPI to reflect the revised single dose blister packaging presentation and administration instructions and provide comments in Section 5 for Pfizer.

4 RECOMMENDATIONS FOR PFIZER

Table 1. Identified Issues and Recommendations for Pfizer (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels (150 mg;100 mg and 300 mg;100 mg)			
1.	Arrows needed to identify tablets needed.	Clearly define the location of tablets.	Insert arrows from the dose statements (Take these 2 tablets together, Take these 3 tablets together) to clearly indicate which tablets to take on the blister card.
2.	Redundancy in use of established name (in 2 locations, (b) (4)	Remove clutter and redundancy of information, which may lead to confusion.	Revise the strength presentation as follows (b) (4) **PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets),** co-packaged for oral use 150 mg;100 mg or **PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets),** co-packaged for oral use 300 mg;100 mg

Table 1. Identified Issues and Recommendations for Pfizer (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Carton Labeling (150 mg;100 mg and 300 mg;100 mg)			
1.	Dose statement is unclear and lacks prominence.	Mitigate wrong dose errors.	Revise the dose statements as follows: 150 mg;100 mg Dose Pack Take both tablets from one blister card together, twice daily (in morning and at bedtime) for 5 days. Or 300 mg;100 mg Dose Pack Take all 3 tablets from one blister card together, twice daily (in morning and at bedtime) for 5 days. In addition, increase the prominence of the dose statement with the use of different colors, boxing, or some other means and ensure the dose statement follows the product strength throughout the carton labeling.
2.	"Each carton contains" statements (with bullets) are too prominent.	Relocate to a less prominent area to increase prominence for dosing information.	Relocate the "Each carton contains" statements to the bottom of the principal display panel, after the strength statements and dose statements.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Paxlovid received on June 29, 2022 and November 9, 2022 from Pfizer Inc.

Table 2. Relevant Product Information for Paxlovid	
Initial Approval Date	N/A; EUA authorized 12/2022
Active Ingredient	nirmatrelvir copackaged with ritonavir
Indication	Treatment of adult (b) (4) who are at high risk for progression to severe COVID-19.
Route of Administration	oral
Dosage Form	tablet
Strength	150 mg nirmatrelvir and 100 mg ritonavir 300 mg nirmatrelvir and 100 mg ritonavir
Dose and Frequency	300 mg nirmatrelvir (2 tablets of 150 mg) and 100 mg ritonavir (one 100 mg tablet) or 150 mg nirmatrelvir (one 150 mg tablet) and 100 mg ritonavir (one 100 mg tablet) twice daily for 5 days
How Supplied	150 mg;100 mg-Cartons of 20 tablets in 10 blister cards. Each blister card contains 2 tablets 300 mg;100 mg-Cartons of 30 tablets in 10 blister cards. Each blister card contains 3 tablets
Storage	Store at room temperature 20°C to 25°C (68°F to 77°F)

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APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 17, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, Paxlovid and EUA 105. Our search did not identify any previous relevant reviews and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Paxlovid labels and labeling submitted by Pfizer Inc..

- Container label received on November 9, 2022
- Carton labeling received on November 9, 2022
- Prescribing Information (Image not shown) received on June 29, 2022, available from \\CDSESUB1\evsprod\NDA217188\0001\m1\us

G.2 Label and Labeling Images

Container Labels

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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12/12/2022 01:19:30 PM

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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 217188
Submission Number	6
Submission Date	7/29/2022
Date Consult Received	8/1/2022
Drug Name	Paxlovid (nirmatrelvir and ritonavir)
Indication	Treatment of mild to moderate COVID-19
Therapeutic Dose	Nirmatrelvir/ritonavir 300/100 mg BID for 5 days
Clinical Division	DAP
Protocol Review	Link

Note: Any text in the review with a light background should be considered to be copied from the sponsor's document.

This review responds to your consult dated 8/1/2022 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review for IND-153517 dated 01/27/2022 (link), 11/18/2021 (link), and 10/14/2021 (link) in DARRTS;
- Sponsor's QT evaluation report (SN0005; link);
- Sponsor's CQT analysis report for study #C4671001 (SN0005; link);
- Appendices to CQT analysis report for study #C4671001 (SN005; link);
- Sponsor's protocol #C4671001 (SN0001; link);
- Sponsor's clinical study report for #C4671001 (SN0001; link);
- Sponsor's clinical pharmacology summary (SN0001; link);
- Sponsor's proposed label (SN0001; link);
- Investigator's brochure Version 5.0 (SN0005; link); and
- Highlights of clinical pharmacology and cardiac safety (SN0005; link).

1 SUMMARY

Nirmatrelvir/ritonavir did not prolong the QTcF interval which is based on both the concentration-QTc analysis of study #C4671001 and negative findings in the nonclinical studies (hERG and in vivo QT). This clinical and nonclinical integrated risk assessment can be used as a substitute for a thorough QTc study under ICH E14 Q&A 5.1.

The clinical study #C4671001 included a cross-over study with placebo and nirmatrelvir 2250 mg (divided into three doses) and ritonavir 100 mg (Part 5). The dose provided 1.5-fold high clinical exposure (severe renal impairment with 150 / 100 mg, see section 3.1.2). The high clinical exposure scenario considers severe renal impairment as the proposed label did not include contraindication and assumes that the dose administered would be the same as patients with moderate renal impairment. Because the study did not

provide sufficiently high exposures to support waiving the requirement for a separate positive control, a negative integrated nonclinical risk assessment (hERG and in vivo QT) was therefore used to support study interpretation.

<table>
<tr><td>QT assessment pathway</td><td>☐ Thorough QT study
☒ Substitute for thorough QT study (5.1)
☐ Alternative QT study when a thorough QT study is not feasible (6.1)</td></tr>
<tr><td>Clinical QT study findings[1]</td><td>• Clinical exposure (with food): 7.5 µg/mL
• High clinical exposure (severe renal impairment with 150/100 mg nirmatrelvir/ritonavir plus food): 10.8 µg/mL
• Exposure coverage in QT assessment: 1.47
<table>
<tr><th>Treatment</th><th>Concentration</th><th>ΔΔQTcF (msec)</th><th>90% CI (msec)</th></tr>
<tr><td>Nirmatrelvir 2250 mg and ritonavir 100 mg</td><td>15943.7</td><td>0.5</td><td>(-2.4 to 3.4)</td></tr>
</table></td></tr>
<tr><td>In vitro findings[2]</td><td>
<table>
<tr><th></th><th>Safety Margin</th><th>Reference Drugs</th><th>Best Practice Deviations</th></tr>
<tr><td>Nirmatrelvir</td><td>>44x (12% inhibition). Extrapolation using h (ranging from 0.5 to 1.5) yield a minimum IC50 of 1158 uM (173x)</td><td>3 - 60x</td><td>Unable to determine IC50, which is addressed by assuming a range of hill slopes (0.5 – 1.5).</td></tr>
</table></td></tr>
<tr><td>In vivo findings</td><td>• No QTc prolongation was observed in the vivo monkey study at exposures expected to exceed the high clinical exposure scenario.</td></tr>
</table>

[1]The findings of the exposure-response analysis are further supported by the lack of QTc prolongation in the by-time analysis (section 4.3) and categorical analysis (section 4.4). [2]Negative integrated nonclinical risk assessment (hERG and in vivo QT) is provided in section 3.1.3).

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

(b) (4) in the label submitted to eCTD 0026 (link).

Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics Cardiac Electrophysiology At (b) (4) times the (b) (4) recommended dose, nirmatrelvir does not prolong the QT interval to any clinically relevant extent.
We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance. (b) (4)

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Paxlovid is a combination product of nirmatrelvir (PF-07321332, MW: 499.54) 150 mg and ritonavir 100 mg. Nirmatrelvir is a SARS-CoV-2 main protease (M^{pro}: also referred to as $3CL^{pro}$ or nsp5 protease) inhibitor, while ritonavir is a HIV-1 protease inhibitor and a CYP3A inhibitor which was approved previously for treatment of HIV infection in combination with other antiretrovirals. Notably, ritonavir has been observed to prolong PR and QTc in a TQT study (Norvir USPI). The sponsor (Pfizer, Inc) has developed paxlovid for the proposed indication of treatment of mild-to-moderate corona virus disease 2019 (COVID-19) in adults (b) (4) The maximum recommended dose of paxlovid for this indication is nirmatrelvir/ritonavir 300/100 mg BID for 5 days.

The sponsor's QT assessment plan for nirmatrelvir was reviewed by IRT previously (see previous IRT reviews). In brief, the sponsor proposed an integrated clinical and nonclinical QT assessments under ICH E14 Q&A 5.1. The sponsor planned to conduct concentration-QTc analysis of time matched PK and ECG data collected from the first in human study, Study C4671001, which was a 5 part study evaluating single ascending doses in Part 1, multiple ascending doses in Part 2, relative bioavailability and food effect in Part 3, metabolism and excretion in Part 4 and safety of supratherapeutic exposures in Part 5.

Part 1 of the study was a randomized, double-blind (open-label, sponsor), placebo-controlled study evaluating safety, tolerability, and pharmacokinetics of single escalating oral doses of nirmatrelvir in healthy subjects. Part 1 included 2 interleaving cohorts with a total of 13 subjects with 3-period cross-over in each cohort (150, 500, 1500, 250 mg with ritonavir, 750 mg with ritonavir, all under fasting conditions; and 250 mg under fed condition with 100 mg ritonavir at -12, 0 and 12 h; n= 4+2/cohort). The peak

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concentration (Cmax: ~5 µg/mL) observed with highest dose studied (i.e., 750 mg, with 100 mg ritonavir at -12, 0 and 12 h) only covers the therapeutic Cmax associated with the maximum proposed dose at the steady state (Cmax: ~4.7 µg/mL).

Part 5 of the study was a randomized, double-blind (open-label, sponsor), placebo-controlled, crossover (2-sequnce) study evaluating safety, tolerability, and pharmacokinetics of nirmatrelvir (at supratherapeutic exposures) in healthy subjects (n=10). Subjects received 2250 mg (administered as a split dose 750 mg at 0, 2, and 4 h with 100 mg ritonavir at -12, 0 and 12 h). Study included ECG and PK measurements in fasted state (approximately 4 h after the food) at nominal times of 0, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 12, 24, 48, 72 and 96 hours after the first dose of nirmatrelvir. The peak concentration (Cmax: ~15.9 µg/mL) observed at studied dose covers ~1.47-fold of the anticipated high clinical exposure in subjects with severe renal impairment taking paxlovid 150 mg/100 mg with food and hence does not meet the requirement for waiving a positive control (i.e., < 2-fold of high clinical Cmax). The findings of this QT study are therefore supported by a negative integrated nonclinical risk assessment (see section 3.1.3).

Part 5 included a shorter dosing regimen of ritonavir (100 mg BID for 1.5 days) than the recommended dosing regimen per label (100 mg BID for 5 days). Based on the observed ritonavir concentrations following 3 days of 100 mg BID (1.4 ug/mL, Study C4671015) clinically significant ECG changes due to ritonavir are not expected for both the recommended dosing per product label and Part 5 dosing regimen based on the reported findings of the TQT study[1].

3.1.2 Clinical Pharmacology

A summary of nirmatrelvir clinical pharmacokinetics is presented in the table of highlights of clinical pharmacology and cardiac safety.

In brief, nirmatrelvir exhibits less than dose proportional increase in exposure between 150 – 1500 mg (alone, and 75 -750 mg, with ritonavir) and reaches steady state of exposures after 2 days of BID dosing with AUC and Cmax accumulation ratio of about ~1.8-fold. The nirmatrelvir/ritonavir 300/100 mg BID dosage, under fasted condition, provides steady state geometric mean Cmax (%CV) of 4.678 (17%) µg/mL (CP summary, table 20, page 66). Based on in vitro assays, nirmatrelvir is mainly metabolized by CYP3A4. However, no metabolites are detected in plasma when nirmatrelvir is co-administered with ritonavir in humans. Except for high fat meal and renal impairment, no other intrinsic and extrinsic factors have impact on nirmatrelvir pharmacokinetics. High fat meal increases nirmatrelvir Cmax and AUC by 1.6- and 1.2-folds respectively (CP summary, table 14, page 135). The anticipated steady-state Cmax therefore includes the effect of food. Increased exposure was observed in patients with severe renal impairment compared to healthy subjects (AUC: ~3-fold; Cmax: ~1.5-fold). In the sponsor's

[1] Per the ritonavir label: The maximum recommended ritonavir dose for treatment of HIV is 600 mg BID (Cmax,ss: 11.2 ug/ml; under fed condition). In a thorough QT study, which evaluated 1.5x Cmax,ss of 600 mg BID, a maximum mean increase of 5.5 msec (95% upper CI: 7.6) and 22 (25 msec) for QTcF and PR, respectively.

proposed label, paxlovid will not be recommended in patient with severe renal impairment, and its dose will be reduced by 50% in patients with moderate renal impairment. Since paxlovid is not contraindicated in subjects with severe renal impairment, physicians may opt to prescribe the drug in this population at a reduced dose. Paxlovid 150 mg/100 mg (nirmatrelvir/ritonavir) is the potential dose in severe renal impairment since the smallest dose unit for nirmatrelvir is 150 mg unscored tablets. The high clinical exposure scenario is therefore 150/100 mg in patients with severe renal impairment under fed conditions. The predicted clinical and high clinical exposure is shown in Table 1 and is based on observed Cmax,ss following 300 / 100 mg in healthy volunteers and predicted Cmax,ss in severe renal impaired patients using superpositioning (QT evaluation report, Table 2).

Table 1: Summary of dose and exposure assessment

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen	Nirmatrelvir/ritonavir 300/100 mg BID for 5 days with food	7.5[1] µg/mL ($C_{max,ss}$)
Sponsor's high clinical exposure scenario	Severe renal impairment taking 150 mg/100 mg with food[2]	10.8 µg/mL
Highest dose in QT assessment	2250 mg nirmatrelvir (split dosing) with 100 mg ritonavir BID	15.9 µg/mL
C_{max} Ratio	1.47	

1: Steady-state Cmax from C4671015 in healthy participants given 300 / 100 mg nirmatrelvir / ritonavir (4.68 µg/mL) x 1.6 (food effect). 2: Predicted steady-state Cmax using superposition for severe renal impaired patients given 100 / 100 mg nirmatrelvir / ritonavir (4.52 µg/mL) x 1.5 (assuming dose proportionality) x 1.6 (food effect).

3.1.3 Nonclinical Safety Pharmacology Assessments

The sponsor assessed the effects of nirmatrelvir and three reference drugs (dofetilide, ondansetron and moxifloxacin) on hERG current (study reports 22LJ022 and 22LJ025). Original electrophysiology records for ion channel studies were provided by the sponsor. We reanalyzed these records of hERG assay to assess data quality and verify study report conclusions (see Appendix 5.2).

The GLP in vivo monkey study (20GR275) assessed pharmacological effects of nirmatrelvir on the cardiovascular system including ECG changes (see Appendix 5.2).

Reviewer's comment: *The hERG assays met most of the best practice recommendations for an in vitro assay according to the new ICH S7B Q&A 2.1 (link). The hERG results showed that nirmatrelvir has a hERG safety margin of >44x (12% inhibition at 300 µM, the highest tested concentration). The estimated IC50 of nirmatrelvir on hERG current are from 1158 µM to 18266 µM with the safety margin from 173x to 2726x by fitting data to hill equation with a hill slope from 1.5 to 0.5, respectively. Three reference drugs dofetilide, ondansetron and moxifloxacin have hERG safety margins of 59x, 2.9 x and 21.8x, respectively. The estimated safety margin of nirmatrelvir is larger than the safety margins of dofetilide, ondansetron and moxifloxacin. The results from the hERG assay*

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suggest that nirmatrelvir has a low risk for QT prolongation by directly inhibiting the hERG current at high clinical exposure.

No QTc prolongation was observed at exposures exceeding the anticipated high clinical exposure in the in vivo monkey study.

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

The primary analysis for PF-07321332 was based on exposure-response analysis, please see section 3.2.3 for additional details.

Reviewer's comment: *The sponsor's by-time analysis used Part 5 data only, and Part 5 with Part 1 pooled data. The reviewer evaluated the ΔΔQTcF effect using descriptive nonparametric statistics for Part 5 and Part 1 separately. Since the treatment group and placebo group are not independent in the crossover study, ΔΔQTcF is used as dependent variable for descriptive nonparametric statistics. The trend shown in by-time analysis from reviewer's analysis is similar to the trend shown in sponsor's by-time analysis. Please see Section 4.3 for details.*

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT Bias Assessment

No QT bias assessment was conducted by the sponsor.

3.2.2 Categorical Analysis

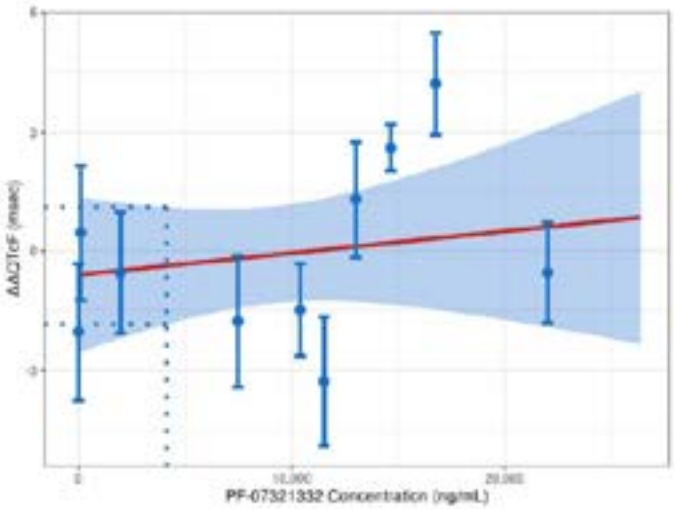
There were no significant outliers per the sponsor's analysis for QTc (i.e., >500 msec or >60 msec over baseline), HR (>100 beats/min), PR (>220 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline).

Reviewer's comment: *The reviewer's analysis results are based on subjects from Part 1 and Part 5. The reviewer's analysis results are the same with sponsor's analysis results. Please see Section 4.4 for details.*

3.2.3 Exposure-Response Analysis

CQTc analysis using the PK and ECG parameters from PART-5:SE were performed as described by Garnett et al.2 Additional sensitivity analysis by pooling with PART-1: SAD was also performed. PART-1 and PART-5 were conducted at the same site. In PART-5, one participant had concentration below limit of quantification at 6h, approximately the time of expected Cmax with split dosing; therefore, that timepoint was removed from the analyses.

The upper bounds of 90% CI for ΔΔQTcF estimates across the entire concentration range were all well below 10 ms, the threshold for potential clinical and regulatory concern. This was also consistent with the pooled analysis (Appendix 2)



The red line is the predicted ΔΔQTcF over the range of observed concentrations and shaded region is the 90% CI. Blue circles and error bars represent the observed ΔΔQTcF (using the model-estimated, time-matched placebo effect subtracted from the ΔQTcF of the active treatment group's observations) across the observed concentration bins (n = 10, with equal number of observations in each bin). The blue dotted lines correspond to the predicted lower and upper 90% CI ΔΔQTcF for the projected mean C_{max} at Phase 2/3 dose.
Source: Appendix 1, Figure 7.

Table 2. Model-derived ΔΔQTcF Prediction for Concentrations of Interest

	Concentration (ng/mL)	Mean ΔΔQTcF (90% CI) (ms)
Therapeutic exposure[a]	4140	-0.37 (-1.84, 1.1)
2x Therapeutic exposure[a]	8280	-0.15 (-1.37, 1.07)
2250 mg mean C_{max} in PART-5:C4671001	15944	0.27 (-1.42, 1.96)

a. Projected steady-state C_{max} at Phase 2/3 dosing regimen i.e. PF-07321332/ritonavir 300/100 q12h

Similar analysis was done for HR, PR, SBP, and DBP. Results from sponsor's analysis are summarized in the table below (Table 2).

Table 2: Summary of sponsor's concentration-response analysis

	Concentration	ΔΔHR (beats/min)	ΔΔPR (ms)	ΔΔSBP (mmHg)	ΔΔDBP (mmHg)
2250mg/RTV 100 mg	15944	-1.9 (-3.8, -0.05)	4.5 (2.5, 6.6)	6 (1.9, 10)	2.8 (0.3, 5.3)
300 / 100 mg nirmatrelvir / ritonavir	4140	-2.2 (-3.1, -1.2)	1.3 (0.1, 2.4)	1.5 (-0.3, 3.2)	1.3 (0.2, 2.5)

Source: Sponsor's CQT analysis of Part 5, Tables 3-6

Reviewer's comment: *The results of the concentration-QTc analysis is similar to the reviewer's independent analysis (see section 4.5.1). Notably, the concentration in the table above was based on a preliminary population PK model. Like the sponsor's analysis, the independent by-time analysis shows a numerical increase in PR (see section 4.3.3). Although, a small increase in blood pressure cannot be excluded based on the sponsor's analysis the intended treatment duration is short (i.e., 3 days) and for drugs with short-term use small increases are generally not considered meaningful.*

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3.2.4 Safety Analysis

There were no deaths or serious adverse events. All adverse events were mild in severity except for one moderate adverse event of nasopharyngitis in Part 4. One discontinuation due to adverse event (SARS-CoV-2 test positive in Part 1).

Reviewer's comment: *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., unexplained syncope, seizure, significant ventricular arrhythmias, or sudden cardiac death) occurred in this study.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| <10 beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Waveforms from Part 5 were submitted. Overall, ECG acquisition and interpretation in this study appear acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG for Part 5 and Part 1 separately. By-time analysis was performed using nonparametric statistics and observed ΔΔQTcF.

4.3.1 QTc

Figure 1 and Figure 2 display the time profile of ΔΔQTcF for different treatment groups from Part 5 and Part 1.

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Figure 1: Median and 90% CI of ΔΔQTcF Time-course (unadjusted CIs) – Part 5.

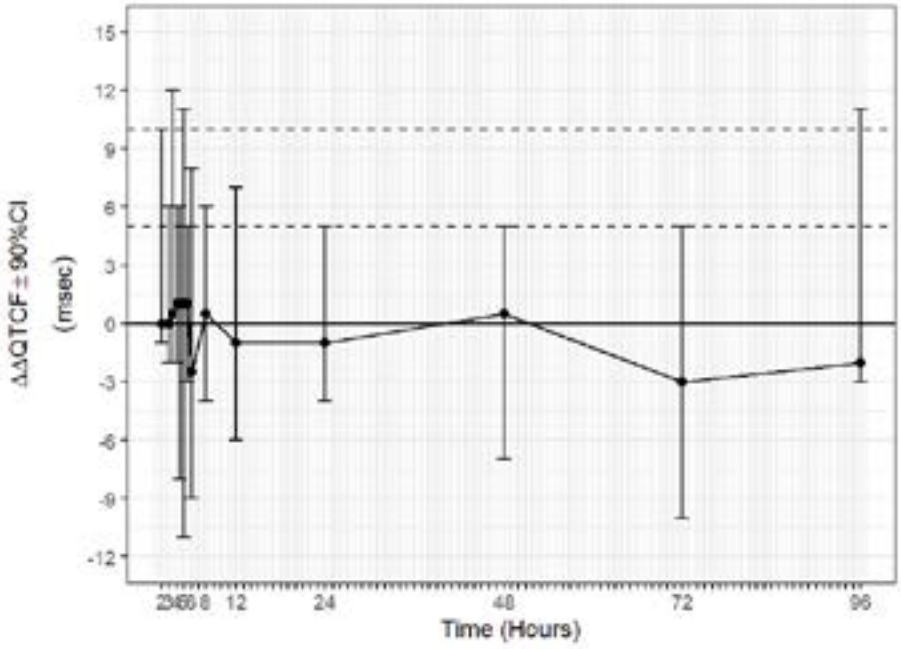
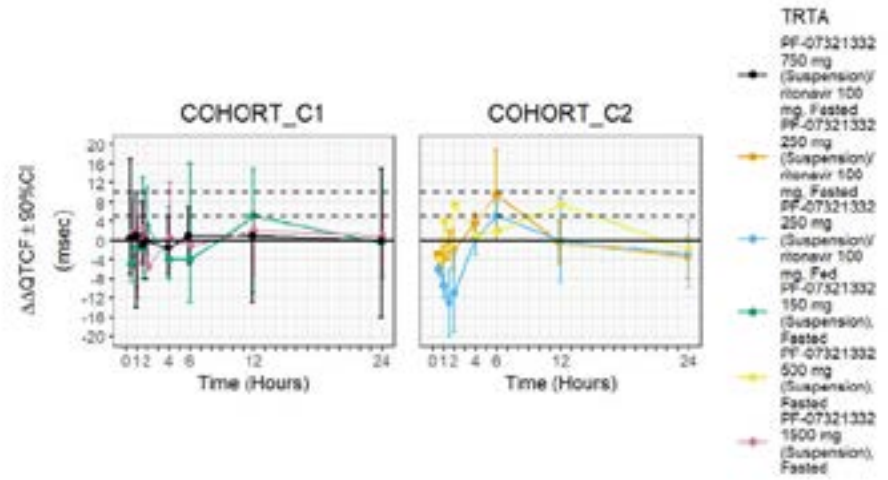


Figure 2: Median and 90% CI of ΔΔQTcF Time-course (unadjusted CIs) – Part 1.



4.3.1.1 Assay Sensitivity

Not applicable.

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4.3.2 HR

Figure 3 and Figure 4 display the time profile of ΔΔHR for different treatment groups for Part 5 and Part 1.

Figure 3: Median and 90% CI of ΔΔHR Time-course – Part 5

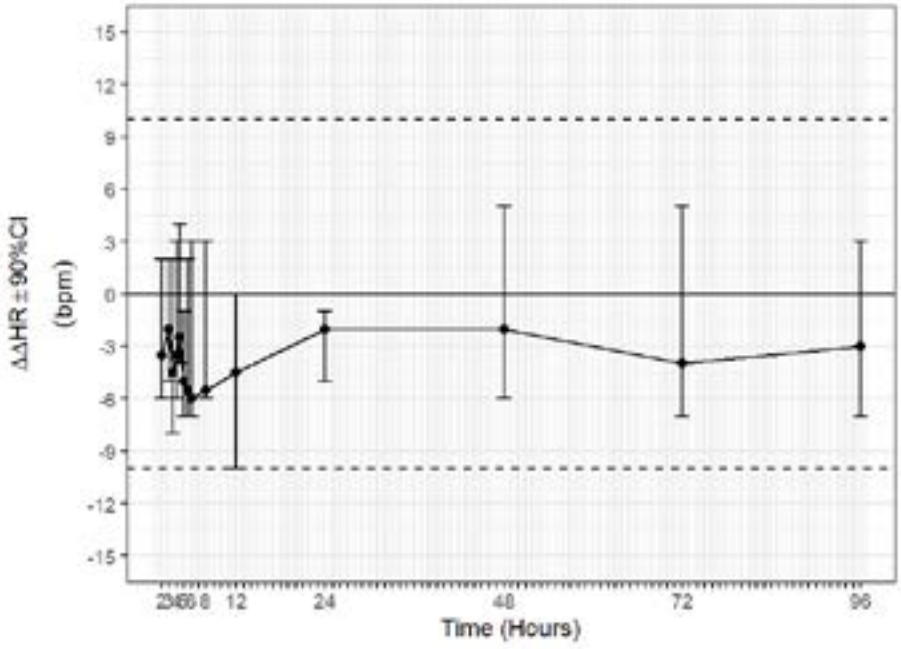
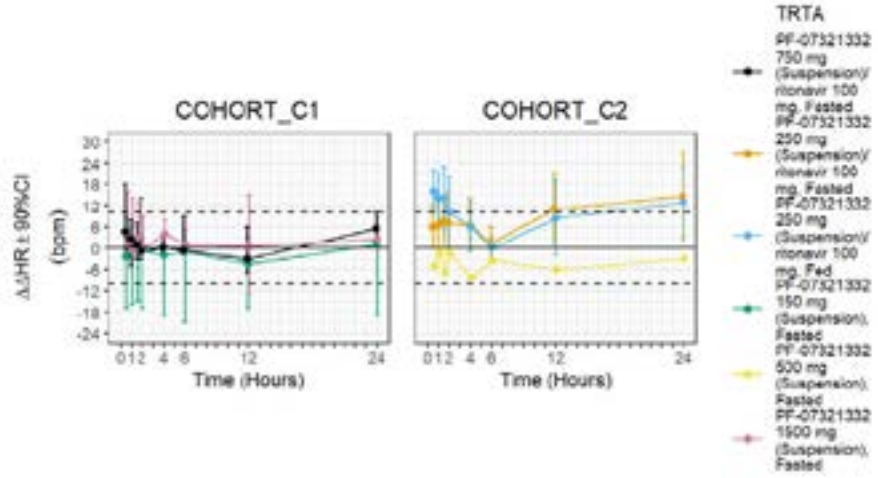


Figure 4: Median and 90% CI of ΔΔHR Time-course – Part 1



4.3.3 PR

Figure 5 and Figure 6 display the time profile of ΔΔPR for different treatment groups for Part 5 and Part 1. Numerical increase in ΔΔPR was observed in both Parts 1 and 5.

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While, nirmatrelvir is administered with ritonavir (which has observed to prolong the PR interval) ritonavir is unlikely to have contributed to the observed PR prolongation based on dosing regimen in this study (see section 3.1.1). The findings of the by-time analysis are consistent with the sponsor's concentration-PR analysis (see section 3.2.3). There were no PR > 220 msec in the study (see section 4.4.3) and the numerical increase was observed at exposures exceeding high clinical (see section 3.1.2).

Figure 5: Median and 90% CI of ΔΔPR Time-course – Part 5

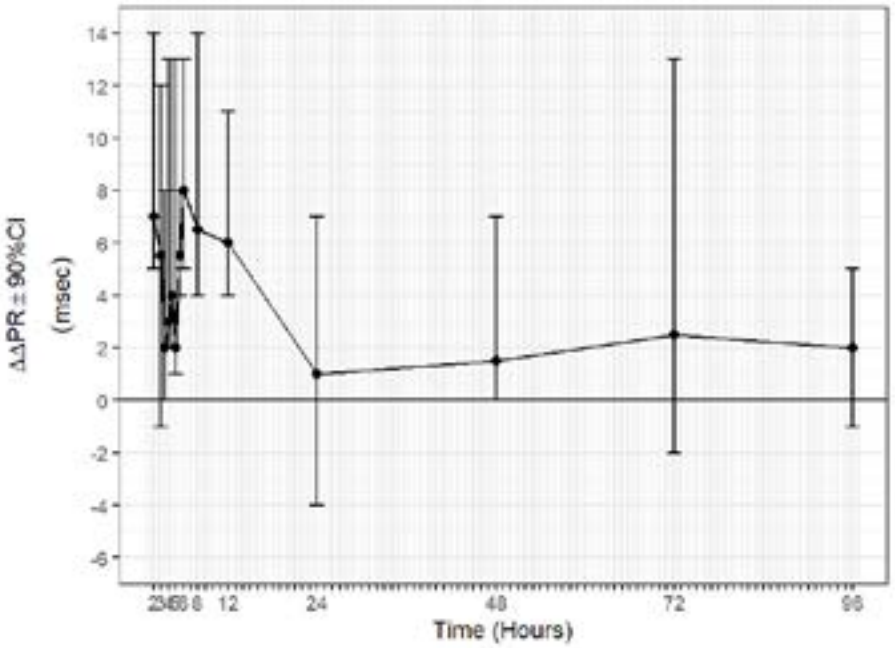
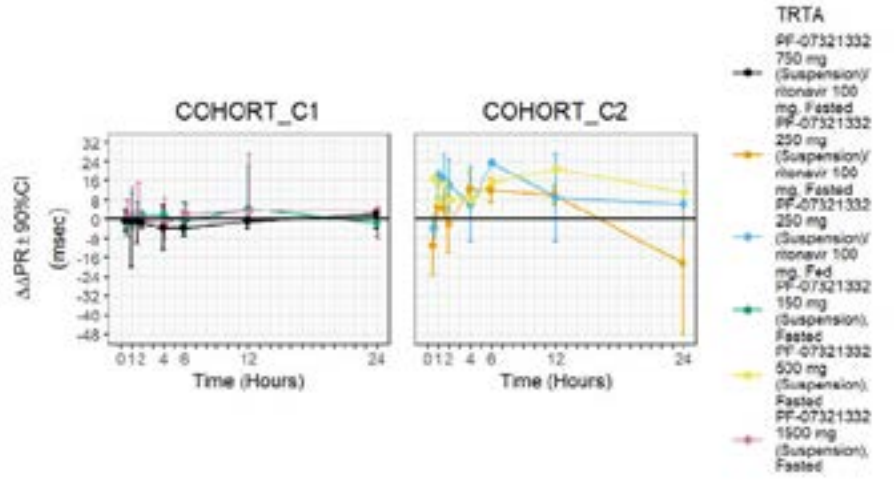


Figure 6: Median and 90% CI of ΔΔPR Time-course – Part 1



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4.3.4 QRS

Figure 7 and Figure 8 display the time profile of ΔΔQRS for different treatment groups for Part 5 and Part 1. Numerical increase in QRS was observed following nirmatrelvir 500 mg. The time-course of the increase does not appear to follow nirmatrelvir concentration and QRS prolongation was not observed in Part 5, which evaluated higher exposures of nirmatrelvir. Furthermore, no QRS outliers were observed across Parts 1 and 5 (see section 4.4.4).

Figure 7: Median and 90% CI of ΔΔQRS Time-course – Part 5

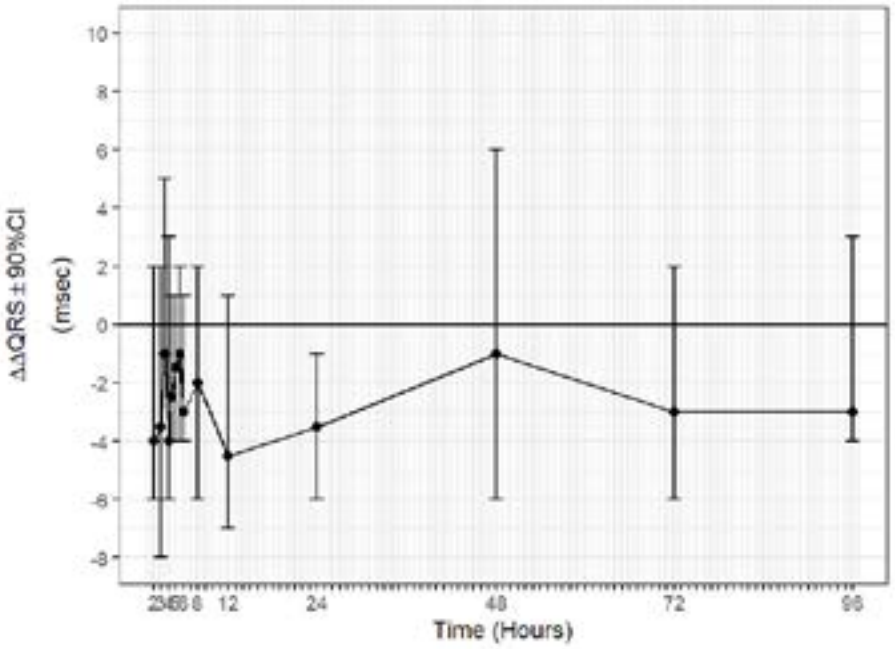
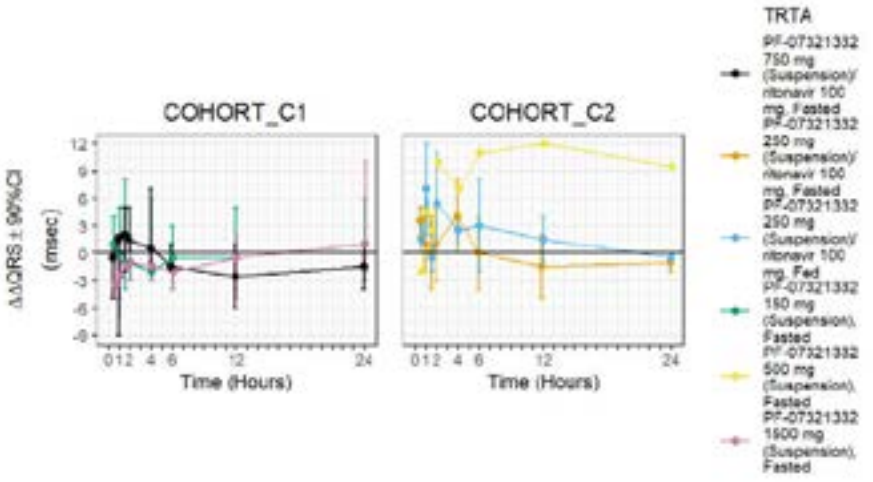


Figure 8: Median and 90% CI of ΔΔQRS Time-course – Part 1



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4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs for Part 5 and Part 1.

4.4.1 QTc

There were no subjects having observed QTcF above 450 msec or change from baseline above 30 msec.

4.4.2 HR

There were no subjects having observed maximum HR above 100 beats/min.

4.4.3 PR

None of the subjects experienced PR >220 msec in any of the treatment groups.

4.4.4 QRS

None of the subjects experienced QRS >120 msec and 25% increase over baseline in any of the treatment groups.

4.5 EXPOSURE-RESPONSE ANALYSIS

Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK for Part 5 only, which achieved the highest exposures. The participant who had concentration below limit of quantification at 6 h is included in the reviewer's analyses. Consistency with by-time analysis, ΔΔQTcF is used as the dependent variable in the model. The model includes nirmatrelvir concentration and baseline as covariates. Subject is included as a random effect on both intercept and slope terms.

4.5.1 QTc

Prior to evaluating the relationship between drug concentration and QTcF using a linear model, the three key assumptions of the model need to be evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) absence of delay between plasma concentration and ΔΔQTcF; and 3) absence of a nonlinear relationship.

Figure 3 shows the time-course of ΔΔHR, with an absence of significant ΔΔHR changes. Figure 9 offers an evaluation of the relationship between time-course of drug concentration and ΔΔQTcF, with no appearance of significant hysteresis. Figure 10 shows the relationship between drug concentration and ΔΔQTcF, and supports the use of a linear model.

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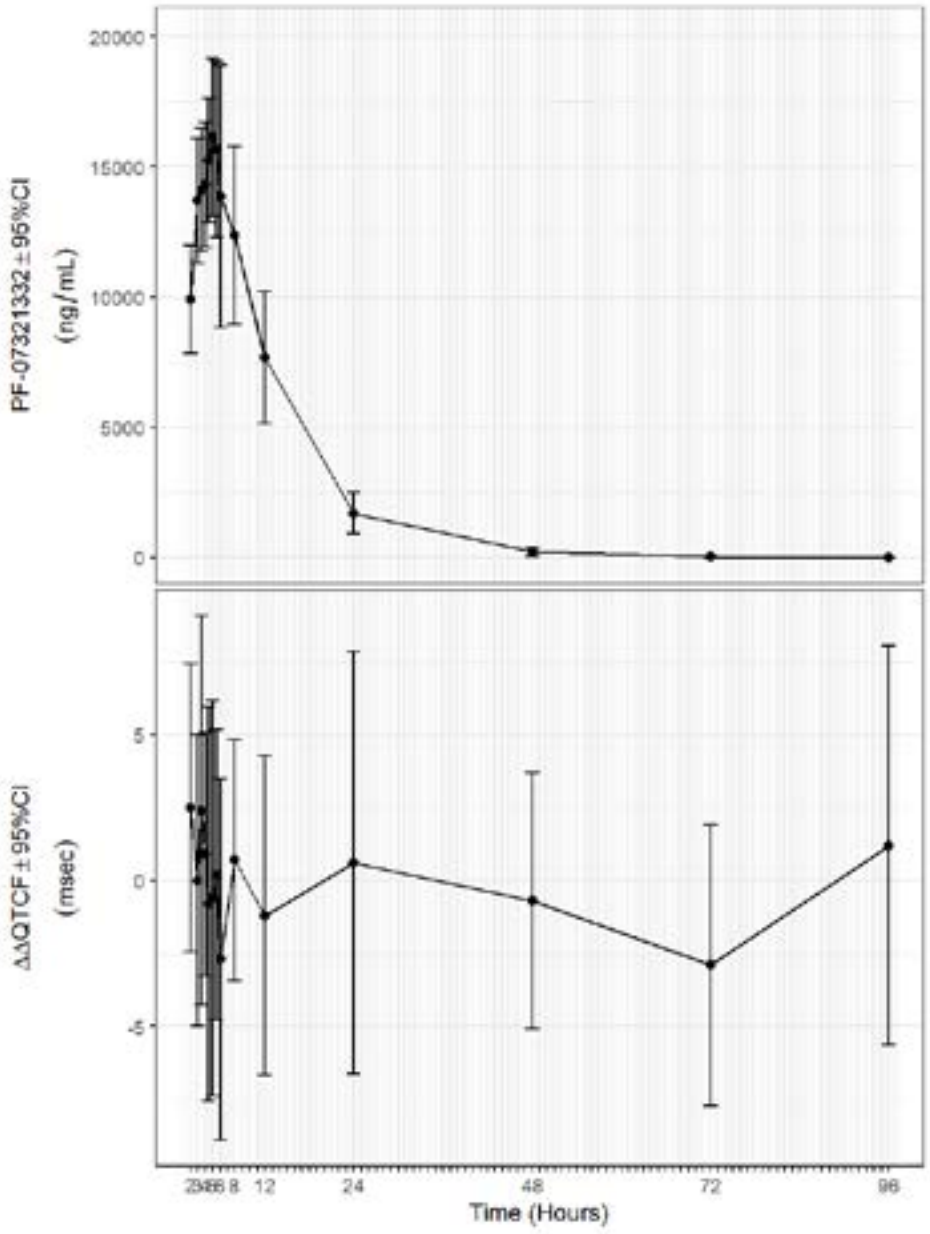
Figure 9: Time-course of Drug Concentration (top) and QTcF (bottom)[2]



[2] ΔΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1: Median and 90% CI of ΔΔQTcF Time-course (unadjusted CIs) – Part 5..

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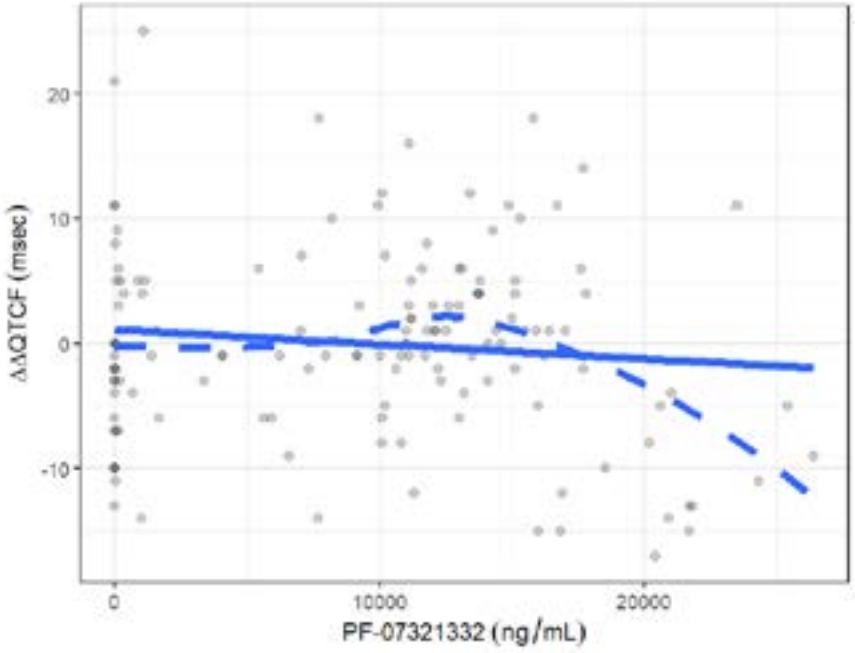
Figure 10: Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 11. Predictions from the concentration-QTcF model are provided in Table 3.

Figure 11: Goodness-of-fit Plot for QTcF

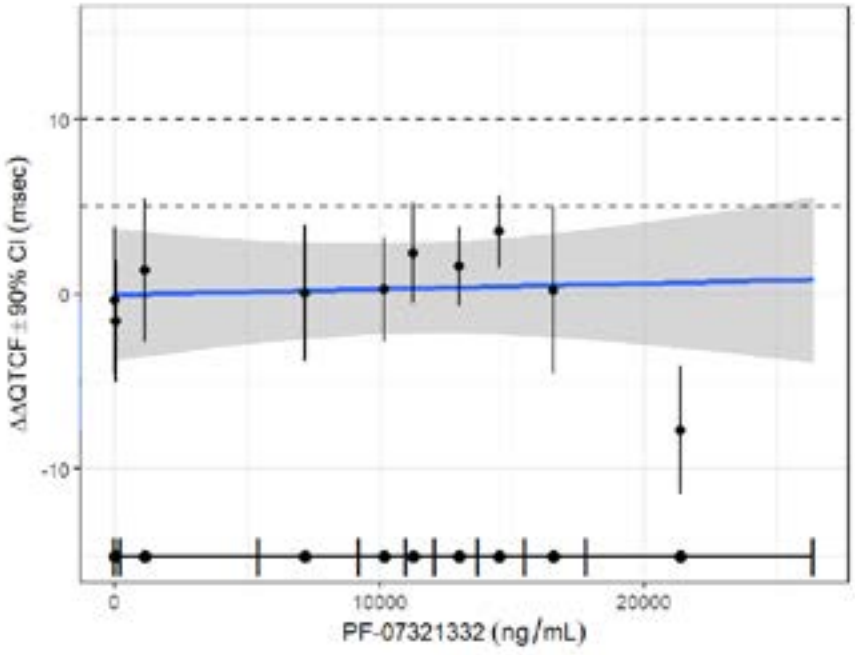


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Table 3: Predictions from Concentration-QTcF Model

Actual Treatment	Analysis Nominal Period Day (C)	PF-07321332 (ng/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
PF-07321332 2250 mg (Suspension)/ritonavir 100 mg	1	15,943.7	0.5	(-2.4 to 3.4)

4.5.1.1 Assay Sensitivity

Not applicable.

4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted.

5 APPENDIX

5.1 EVALUATION OF CLINICAL QT ASSESSMENT PLAN

Protocol previously reviewed (DARRTS 01/28/2022).

5.2 REVIEW OF SUPPORTING NONCLINICAL DATA

The sponsor is developing nirmatrelvir for the treatment of COVID-19. Nirmatrelvir (MW: 499.54 Da) inhibits SARS-CoV-2 and human coronavirus 3CL protease inhibitor. Nirmatrelvir is intended to be administered with ritonavir as a booster to enhance the systemic exposures of nirmatrelvir. Previously the IRT agreed the sponsor's strategy to use an integrated clinical (Study #C4671001) and integrated nonclinical assessment (hERG study 22LJ022 and in vivo QT study 20GR275) to support the QT assessment under ICH E14 Q&A 5.1, and recommended using dofetilide, moxifloxacin and ondansetron as the reference compounds in the proposed hERG assay. The sponsor now submitted the hERG raw data for review.

5.2.1 In vitro hERG assay

5.2.1.1 Sponsor's results

The GLP hERG study report 22LJ022 (CRO study number: 211129.QHJ, link) describes the potential effects of nirmatrelvir on the hERG current in HEK293 cells. Another hERG study report 22LJ025 (CRO study number: 220210.QHJ, link) evaluates the potential effects of three reference drugs dofetilide, ondansetron, moxifloxacin, and on hERG current. The hERG current was assessed at near-physiological temperature (35-37^{o}C), using the hERG current protocol recommended by the FDA (link). A full blocker (1 µM E-4031) was added at the end of the experiment to assess the contribution of the non-hERG currents. Solution samples were collected from the outflow of the perfusion apparatus on the day of experiment for drug concentration verification. According to the sponsor's responses to the information request (link), solution samples were collected at the end of the perfusion tube (before the recording chamber) using the same batch of the solution in the experiment. The sponsor provided a picture of the chamber showing that the tip of the perfusing tube is located in the middle of the cell chamber, indicating the patched cell can directly receive perfusion solution from the tube. The timing of sample collection ranged from 14 mins to 2 hours before the start of the hERG recording, which were within the formulation stability period which was assessed in extracellular (EC) or perfusion solution (~28 hours). The analysis results met the acceptance criteria (100 ± 15% of nominal concentrations). Therefore, the nominal concentrations were used to describe the drug effects.

Nirmatrelvir inhibited hERG current by (Mean ± SEM; n = 4) 4.6 ± 3.7% at 30 µM and 12.6 ± 0.7% at 300 µM. The IC50 for the inhibitory effect of nirmatrelvir on hERG potassium current could not be calculated but was estimated to be greater than 300 µM. Positive control drug ondansetron inhibited hERG current by (Mean ± SEM; n = 4) 17.1 ± 1.2% at 0.3 µM, 41.8 ± 1.1% at 1 µM, 63.6 ± 3.4% at 3 µM and 86.2 ± 1.7% at 10 µM. The IC50 of ondansetron on hERG potassium current was 1.53 µM (Hill coefficient = 0.93)

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In another hERG assay (22LJ025), reference drug ondansetron inhibited the hERG current by 35.0%, 55.8%, 74.0% and 90.5% at 0.3, 1, 3 and10 µM, respectively. The IC50 of ondansetron on hERG potassium current was 0.71 µM (Hill coefficient = 0.76).

Reference drug moxifloxacin inhibited the hERG current by 15.4%, 40.4%, 56.6% and 76.7% at 10, 30, 100 and 300 µM, respectively. The IC50 of moxifloxacin on hERG potassium current was 64.5 µM (Hill coefficient = 0.78).

Reference drug dofetilide inhibited the hERG current by 19.4%, 34.3%, 59.2% and 90.0% at 3,10, 30 and 100 nM, respectively. The IC50 of dofetilide on hERG potassium current was 17.9 nM (Hill coefficient = 0.98)

5.2.1.2 Reviewer's assessment

Original electrophysiology records for the hERG assay was provided by the sponsor. The records were analyzed to assess data quality and verify study report conclusions. For data quality assessment, current from all traces were examined to verify stability, and time course plots were constructed to verify that current amplitude in control solution were stable prior to drug application, and that drug effects reached steady state.

The hERG current was assessed at near-physiological temperature (35-37^{o}C), at the stimulating frequency of 0.2 Hz (every 5 seconds), using the recommended hERG voltage protocol that is available at IRT's website (link). The positive control ondansetron was evaluated at four concentrations (0.3, 1, 3 and 10 µM) to allow for the estimation of the IC50 against hERG channel. A full hERG blocker (1 µM E-4031) was added at the end of the experiment to assess the non-hERG currents evoked by the voltage protocol. Solution samples were collected from outflow of perfusion apparatus at the time of experiment for drug concentration verification. Sample collected from the end of the perfusion tube is acceptable since the tip of perfusion tube is placed adjacent to the patched cell and the solution directly perfuse or feed the cell. The analysis results met the acceptance criteria (100 ± 15% of nominal concentrations). Therefore, the nominal concentrations were used to describe the drug effects.

Representative analysis from one cell of hERG study (Cell ID: S 01 LMS 220428_0000) is shown in Figure 12. The panel A shows recorded traces of each treatment group from this cell. The voltage waveform used to evoke hERG current is shown in blue. The small hyperpolarizing voltage pulse from -80 to -90 mV is designed to calculate input resistance according to Ohm's law. Two shaded gray areas on the left show measurement cursors used to calculate baseline currents at -80 mV and at -90 mV, respectively. The gray shade on the right highlights the region where peak hERG tail current was measured. Traces recorded in control solution are shown in black, following 300 µM nirmatrelvir application in light blue; and 1 µM E-4031 in red at the end of the experiment. Time course plots for peak ramp current and input resistance are shown on panels B and C, respectively.

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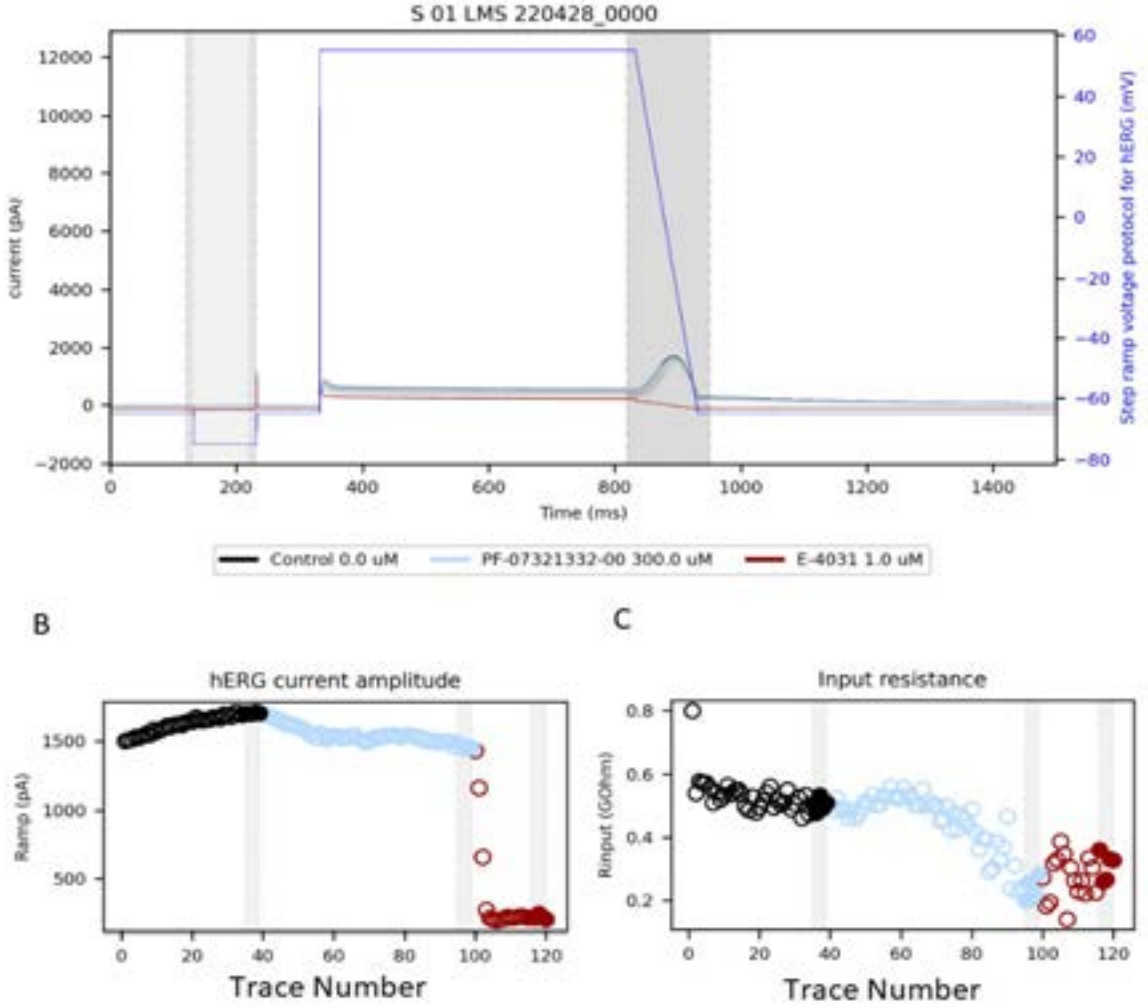
Figure 12: Representative analysis (Cell ID: S01 LMS 220428_0000)



The hERG current amplitudes from the last 5 traces acquired in control (black solid circles) and in drug solution (light blue solid circles represent drug concentration at 300 µM) were then averaged to calculate % inhibition by that concentration.

Results (with E-4031 subtraction) of nirmatrelvir, positive control and reference drugs on hERG current are summarized in Table 4.

Table 4: Effects of nirmatrelvir, positive control and reference drugs on hERG current

Test article	N	Inhibition (fraction)	SEM	IC50
nirmatrelvir 30 µM	4	0.03	0.04	>300 µM
nirmatrelvir 300 µM	4	0.12	0.01	
Ondansetron A 0.3 µM	4	0.17	0.01	1.45 µM
Ondansetron A 1 µM	4	0.42	0.01	
Ondansetron A 3 µM	4	0.65	0.01	
Ondansetron A 10 µM	4	0.88	0.01	
Ondansetron B 0.3 µM	4	0.36	0.01	0.662 µM
Ondansetron B l µM	4	0.57	0.03	

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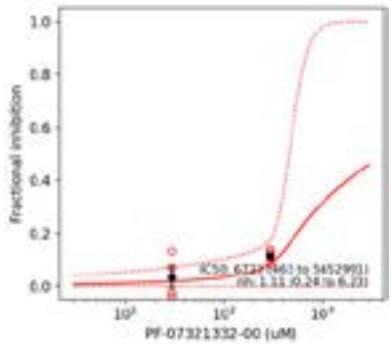
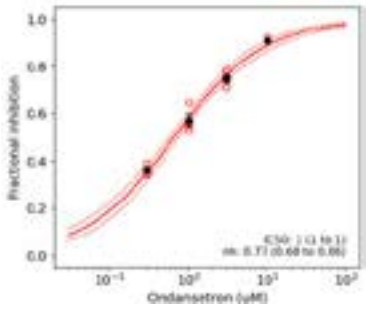
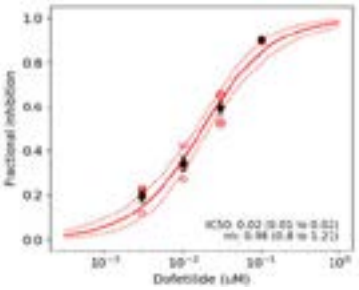
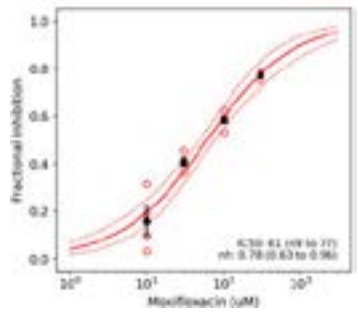
Ondansetron B 3 µM	4	0.75	0.02	
Ondansetron B 10 µM	4	0.91	0.00	
Dofetilide 3 nM	4	0.20	0.03	0.0178 µM
Dofetilide 10 nM	4	0.34	0.03	
Dofetilide 30 nM	5	0.59	0.03	
Dofetilide 100 nM	4	0.90	0.00	
Moxifloxacin 10 µM	4	0.16	0.06	61 µM
Moxifloxacin 30 µM	4	0.41	0.02	
Moxifloxacin 100 µM	5	0.58	0.01	
Moxifloxacin 300 µM	4	0.77	0.01	

While there are numerical differences in the results from FDA's independent analysis compared to the sponsor's, these do not change overall conclusions. That is, FDA's independent analysis of the submitted electrophysiology data shows that nirmatrelvir inhibited the hERG current by 3% and 12% at 30 and 300 µM, respectively. The IC50 of nirmatrelvir on hERG current is expected to be larger than 300 µM. The positive control ondansetron inhibited the hERG current with an IC50 of 1.45 µM, which is similar to the IC50 observed in the reference data (0.66 µM) and the mean IC50 value (1.33 µM) of ondansetron on hERG current from FDA (DARS lab) in the HESI-BAA project. The

concentration-response curves of nirmatrelvir and positive control ondansetron on hERG currents are summarized in Figure 13.

Figure 13: Effects of nirmatrelvir and reference drugs on hERG current

Nirmatrelvir	Ondansetron
	
Dofetilide	**Moxifloxacin**
	

5.2.1.3 **Summary**

The comparisons of sponsor's hERG assay and the best practice recommendations by the new ICH S7B Q&A 2.1 are summarized in Table 5.

Table 5: Comparison of sponsor's hERG assays with the new draft ICH S7B Q&As best practice recommendations

Best Practice Elements	Deviations/limitations	Impact from Deviations
Temperature (35-37°C)	None	
Voltage protocol	None	
Recording quality	None	
IC50 Calculation	Two concentrations were tested. The highest tested concentration was 300 µM due to solubility issues	Unable to determine the IC50
Concentration verification	None	
Positive Control	None	

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Best Practice Elements	Deviations/limitations	Impact from Deviations
Negative Control (vehicle)	None	
Good Laboratory Practice	None	

Table 6: Safety Margins of nirmatrelvir and reference drugs on hERG Current

Drug	High clinical Cmax or critical concentration (ng/mL)	Protein Binding	Free Cmax (ng/mL)	hERG IC50 (μM)	Mol Weight (g/mol)	Safety Margin (Ratio)
Nirmatrelvir	10800	69%	3348	>300 (1158)	499.63	>44x (173x)
Dofetilide	0.37	64%	0.133	0.0178	442	59x
Ondansetron	247	73%	66.69	0.66	293	2.9x
Moxifloxacin	1866	40%	1119.6	61	401	21.8x

Nirmatrelvir high clinical $C_{max,ss}$: 10800 ng/mL. Critical concentration: concentration associated with 10 msec mean QTc prolongation. The estimated IC50 values were 1158 and 18266 μM, when extrapolated from the data at 30 and 300 μM using hill coefficient of 1.5 and 0.5, respectively. The lowest estimated IC50 (1158 μM with h=1.5) is used for hERG safety margin calculation.

5.2.2 In vivo study

5.2.2.1 Sponsor's results

The in GLP vivo study (20GR275) assessed the potential effects of nirmatrelvir on ECG parameters administered as a twice per day (BID) dose at 40 (20 BID) and 150 (75 BID) mg/kg/day via oral gavage in conscious, unrestrained, radio-telemetry implanted male cynomolgus monkeys, which is summarized in Table 7. Prior to initiation of the CV phase, all animals received a single oral dose of nirmatrelvir at 150 (75 BID) mg/kg/day for provision of a PK profile (PK phase). CV phase started 8 days after PK phase. Telemetered data including ECG traces were continuously recorded from all animals for a minimum of 45 minutes prior to dosing and continuing through at least 22 hours post-dose. ECG data was binned into 1-minute bins, and then averaged into 15 min bins. Values for each telemetry endpoint were averaged into four post-dose periods for each dose level (0.75 – 5.5 h, 7.25 – 9 h, 9.25 – 16 h, 16.25 – 20.5 h). Individual animal correction was used for QT correction using vehicle control data and a linear slope.

The mean (± SD) Cmax at 150 (75 BID) mg/kg/day was 14.7 ± 9.24 μg/mL. The free Cmax were 6.4 μg/mL (the protein binding was 56.5% in monkeys). Nirmatrelvir decreased the QTc-intervals by 4.4 ms and 6.8 ms at 40 mg/kg/day and 150 mg/kg/day doses, respectively. No positive drugs were used in the study. The reported minimum

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detectable difference was reported as 9.3 msec based on power analysis of historical studies.

Table 7: Summary of in vivo QT study

QT Study							
Exposure	The 150-mg/kg (75-mg/kg-BID) dose provides a 1.9-fold margin over high clinical exposures (unbound)						
Design	Crossover: vehicle, solvate (MTBE) control + 2 dose levels of PF-07321332; N = 8						
Species	Cynomolgus monkey (male); telemetry instrumented						
Historical QTcI sensitivity	MDD: 9.1 msec (reference range 2.5th–97.5th percentile; 3.9–16.7 msec) from power analysis of historical studies						
ECG collection	~24-hour telemetry (conscious animals)						
ECG reading methodology	Fully automated; animal-specific library/template						
PK collection	Predose and approximately 6 HPD during CV phase at all doses; same-study animals predose and at 0.5, 1, 2, 4, 6 (before PM dose), 7, and 24 HPD in a standalone PK phase @ 150 mg/kg (75 mg/kg BID)						
Analysis Methods							
Data Reduction Method	0.75–5.5, 7.25–9.0, 9.25–16.0, 16.25–20.5 HPD; super-intervals						
Analysis methodology	By-time using ANOVA						
HR correction method	QTcI based on vehicle data (QT vs RR; linear slope) for each animal generating an IACF						
ECG Findings	Transient QTc decrease (−5 to −7 msec; during 7.25–16.0 HPD) at 150 mg/kg (75 mg/kg BID)						
Summary Findings							
Dose (mg/kg)	QTcI effect size after 2nd BID dose 9.25–16.0 HPD mean (95% CI)	Parent concentration at 6 HPD (µg/mL) during CV phase	C_{max} total (µg/mL) during PK phase	C_{max} unbound (µg/mL)	Fu (PPB) species	High clinical C_{max} (unbound) (µg/mL)	Exposure ratio
MTBE control	−0.36 (−7.17, 6.44)	NA	NA	NA	0.310 (0.69) Human	3.4 10.9 (total)	1.9 1.3 (total)
40 (20 BID)	−4.38 (−11.19, 2.42)	0.0334	NA	NA			
150 (75 BID)	−6.82 (−13.63, −0.01)	0.308	14.7	6.4	0.435 (0.565)		

Source: QT evaluation report, Supplemental Table 12

Reviewer's comment: *The QTc assessment in the in vivo QTc study was based on data binning and the width of the windows were broad relative to the concentration time-profile, bringing into question the sensitivity of the windowed-based analysis. To address this limitation, we considered the full time-profile as provided on page 35 of the report, which did not suggest large changes in the QTc interval. There was too limited data to establish similarity in the PK profile between the CV and PK phase (i.e., a single trough measurement) and the PK sampling following the second dose likely missed Tmax, which adds uncertainty to how the exposures in the in vivo QT study compares to clinical exposure. Overall, the in vivo monkey study (20GR275) suggests no QTc prolongation at concentrations that are expected to exceed high clinical exposures.*

5.2.3 Non-clinical Summary

In summary, the hERG assay meet most of the best practice recommendations for an in vitro assay according to the new ICH S7B Q&A 2.1 (link). The hERG results showed that nirmatrelvir has a hERG safety margin of > 44x (12% inhibition at 300 µM). The estimated IC50 and safety margin of nirmatrelvir on hERG channel are 1158 µM and 173x by fitting data to hill equation with a hill slope of 1.5, respectively. Reference drugs dofetilide, ondansetron and moxifloxacin have hERG safety margins of 59x, 2.9x and 21.8x, respectively. The hERG safety margin of nirmatrelvir is larger than the safety margins of those reference drugs. The results of hERG assay suggest that nirmatrelvir

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has a low risk for QT prolongation by directly inhibiting the hERG current at high clinical exposure**.**

No QTc prolongation was observed at exposures anticipated to exceed high clinical exposure in the in vivo monkey study.

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DONGLIN GUO
11/07/2022 03:36:44 PM

JOSE VICENTE RUIZ
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MICHAEL Y LI
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	August 29, 2022
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 217188
Product Name and Strength:	Paxlovid 300 mg;100 mg and 150 mg;100 mg Dose Pack (Nirmatrelvir 300 mg[a]; Ritonavir 100 mg tablets) and (Nirmatrelvir 150 mg; Ritonavir 100 mg tablets)
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Pfizer
FDA Received Date:	June 29, 2022
TTT ID #:	2022-33
DMEPA 1 Safety Evaluator:	Melina Fanari, R.Ph.
Acting DMEPA 1 Team Leader:	Madhuri R. Patel, PharmD
DMEPA 1 Associate Director for Nomenclature and Labeling:	Mishale Mistry, PharmD, MPH

[a] packaged as two 150 mg Nirmatrelvir tablets.

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1 REASON FOR REVIEW

As part of the approval process for Paxlovid (nirmatrelvir;ritonavir) dose pack under NDA 217188, the Division of Antivirals (DAV) requested that we review the proposed Paxlovid prescribing information (PI), patient prescribing information (PPI), carton labeling and container labels for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Paxlovid is currently authorized for emergency use under EUA 105 for the treatment of mild to moderate coronavirus disease in patients 12 years of age and older weighing at least 40 kg.

Under EUA, Paxlovid is available in the following presentations:

-Paxlovid 300 mg;100 mg Dose pack (30 tablets divided in 5 daily-dose blister cards)

-Paxlovid 150 mg;100 mg Dose pack (20 tablets divided in 5 daily-dose blister cards) for patients with moderate renal impairment (eGFR ≥30 to < 60 mL/min)

DMEPA is currently monitoring ongoing wrong dose medication error reports that are occurring with Paxlovid presentations under the EUA. We note that the majority of the ongoing wrong dose medication errors have occurred during patient self-administration and often describe patients taking the wrong dose or wrong tablets due to confusion with the packaging or labeling. On June 27, 2022, DMEPA sent an Information Request (IR) to Pfizer requesting they provide their mitigation strategies to address the ongoing wrong dose errors due to the packaging configurations. As a result, the EUA Fact Sheet for Patients, Parent and Caregivers was revised to address areas of vulnerability to medication errors. In addition, Pfizer also issued a Dear Health Care Provider (DHCP) letter and provided a commitment to investigate alternative packaging for Paxlovid. We are continuing to monitor these wrong dose errors and consider additional mitigation strategies to minimize the ongoing errors under the EUA.

We note that for the proposed NDA 217188, (b) (4) (Paxlovid 300 mg;100 mg and 150 mg;100 mg Dose Packs) are proposed by the Applicant.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D-N/A
Other	E-N/A
Labels and Labeling	F

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Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	**Appendix Section (for Methods and Results)**

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND CONCUSIONS

Paxlovid is currently authorized for emergency use under EUA 105. Under EUA review, DMEPA has previously evaluated the Fact Sheet for Healthcare Providers (FS for HCP), Fact Sheet for Patients, Parent and Caregivers (PFS), proposed carton labels, container labeling and product packaging of the two Paxlovid Dose Packs. Our evaluation of the NDA prescribing information (PI) and patient prescribing information (PPI) did not identify areas of vulnerability that may lead to medication errors. However, the PI and PPI should be revised to reflect recent revisions made to the EUA FS for HCP and PFS. We will collaborate with DAV to align these labels.

Our evaluation of the proposed container labels, carton labeling, and blister card packaging configuration identified areas of vulnerability to medication error. We continue to receive wrong dose medication error reports occurring during patient-self administration (see 1.1) and we recommend that the Applicant revise the product design and/or packaging configuration to address the wrong dose medication errors. (b) (4) Therefore, an alternative packaging configuration, such as single dose blister cards, should be developed that will maximize safe use and support all dosing regimens in the product labeling. As such, we defer any comments on the proposed container labels and carton labeling until the packaging configuration for product marketing is finalized to address the wrong dose medication errors. We provide an information request to Pfizer in Section 4 below for inclusion in the 74-day letter.

4 RECOMMENDATIONS FOR PFIZER

We note your submission dated July 12, 2022 which provided a mitigation plan in response to the Information Request (IR) dated June 27, 2022 from FDA to address the ongoing wrong dose

[b] Re: EUA 105 Response to Information Request. New York (NY): Pfizer Global Regulatory Affairs. 2022 JUL 12. Available from: \\CDSESUB1\evsprod\EUA000105\0166\m1\us

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medication errors with Paxlovid under EUA 105. You stated that evaluations are underway to "*evaluate potential blister card label prototypes to determine if changes to the blister card could improve patient medication use and address potential patient confusion*". Based on the ongoing reports of wrong dose medication errors, we continue to have concerns (b) (4) For example, you may consider developing single dose blister cards, that will maximize safe use and support all dosing regimens in product labeling under NDA 217188. Depending on revisions to the packaging configuration, additional data such as data from a human factors study, may be needed to ensure that the proposed packaging supports safe and effective use.

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APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Paxlovid that Pfizer submitted on June 29, 2022.

Table 2. Relevant Product Information for Paxlovid	
Initial Approval Date	N/A authorized for use under EUA 105 in 12/2021
Active Ingredient	nirmatrelvir copackaged with ritonavir
Indication	Treatment of adult (b) (4) who are at high risk for progression to severe COVID-19.
Route of Administration	Oral
Dosage Form	Tablet
Strength	150 mg nirmatrelvir and 100 mg ritonavir
Dose and Frequency	300 mg nirmatrelvir (2 tablets of 150 mg) and 100 mg ritonavir (one 100 mg tablet) twice daily for 5 days or For moderate renal impairment (eGFR ≥30 to <60 mL/min): 150 mg nirmatrelvir (1 tablets of 150 mg) and 100 mg ritonavir (one 100 mg tablet) twice daily for 5 days
How Supplied	Paxlovid 300 mg;100 mg Dose pack (b) (4) Paxlovid 150 mg;100 mg Dose pack (b) (4)
Storage	Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 11, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, Paxlovid and EUA 105. Our search did not identify any reviews with outstanding issues or recommendations

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APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Paxlovid labels and labeling submitted by Pfizer.

- Container label(s) and Carton labeling received on June 29, 2022
- Prescribing Information and Patient Prescribing Information (Image not shown) received on June 29, 2022, available from \\CDSESUB1\evsprod\NDA217188\0001\m1\us

F.2 Label and Labeling Images

Container label(s)

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Document 2A.14

U.S. FDA Paxlovid Approved Label

Document URL

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/217188Orig1s000lbl.pdf

Reference website URL

https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=217188

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PAXLOVID safely and effectively. See full prescribing information for PAXLOVID.

PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use
Initial U.S. Approval: 2023

WARNING: SIGNIFICANT DRUG INTERACTIONS WITH PAXLOVID
See full prescribing information for complete boxed warning.

- **PAXLOVID includes ritonavir, a strong CYP3A inhibitor, which may lead to greater exposure of certain concomitant medications, resulting in potentially severe, life-threatening, or fatal events.** ***(4, 5.1, 7)***
- **Prior to prescribing PAXLOVID: 1) Review all medications taken by the patient to assess potential drug-drug interactions with a strong CYP3A inhibitor like PAXLOVID and 2) Determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring.** ***(7)***
- **Consider the benefit of PAXLOVID treatment in reducing hospitalization and death, and whether the risk of potential drug-drug interactions for an individual patient can be appropriately managed.** ***(5.1, 7, 14)***

---------- INDICATIONS AND USAGE----------

PAXLOVID which includes nirmatrelvir, a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) main protease (M^{pro}: also referred to as $3CL^{pro}$ or nsp5 protease) inhibitor, and ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor, is indicated for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. (1)

Limitations of Use
PAXLOVID is not approved for use as pre-exposure or post-exposure prophylaxis for prevention of COVID-19. (1)

----------DOSAGE AND ADMINISTRATION----------

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. (2.1)
Nirmatrelvir must be co-administered with ritonavir. (2.1)

- Initiate PAXLOVID treatment as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset. (2.1)
- Administer orally with or without food. (2.1)
- Dosage: 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all 3 tablets taken together twice daily for 5 days. (2.2)
- **Dose reduction for moderate renal impairment (eGFR ≥30 to <60 mL/min)**: 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet), with both tablets taken together twice daily for 5 days. (2.3)
- PAXLOVID is not recommended in patients with severe renal impairment (eGFR <30 mL/min). (2 3, 8.6)
- PAXLOVID is not recommend in patients with severe hepatic impairment (Child-Pugh Class C). (2.4, 8.7)

---------- DOSAGE FORMS AND STRENGTHS----------

- Tablets: nirmatrelvir 150 mg (3)
- Tablets: ritonavir 100 mg (3)

---------- CONTRAINDICATIONS ----------

- History of clinically significant hypersensitivity reactions to the active ingredients (nirmatrelvir or ritonavir) or any other components. (4)
- Co-administration with drugs highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions. (4, 7.3)
- Co-administration with potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- The concomitant use of PAXLOVID and certain other drugs may result in potentially significant drug interactions. Consult the Full Prescribing Information prior to and during treatment for potential drug interactions. (5.1, 7)
- Hypersensitivity Reactions: Anaphylaxis, serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson syndrome), and other hypersensitivity reactions have been reported with PAXLOVID. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue PAXLOVID and initiate appropriate medications and/or supportive care. (5.2)
- Hepatotoxicity: Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir. (5.3)
- HIV-1 Drug Resistance: PAXLOVID use may lead to a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection. (5.4)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (incidence ≥1% and greater incidence than in the placebo group) are dysgeusia and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Co-administration of PAXLOVID can alter the plasma concentrations of other drugs and other drugs may alter the plasma concentrations of PAXLOVID. Consider the potential for drug interactions prior to and during PAXLOVID therapy and review concomitant medications during PAXLOVID therapy. (4, 5.1, 7, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 05/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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FULL PRESCRIBING INFORMATION

WARNING: SIGNIFICANT DRUG INTERACTIONS WITH PAXLOVID

- **PAXLOVID includes ritonavir, a strong CYP3A inhibitor, which may lead to greater exposure of certain concomitant medications, resulting in potentially severe, life-threatening, or fatal events *[see Contraindications (4), Warnings and Precautions (5.1), and Drug Interactions (7)].***
- **Prior to prescribing PAXLOVID: 1) Review all medications taken by the patient to assess potential drug-drug interactions with a strong CYP3A inhibitor like PAXLOVID and 2) Determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring *[see Drug Interactions (7)].***
- **Consider the benefit of PAXLOVID treatment in reducing hospitalization and death, and whether the risk of potential drug-drug interactions for an individual patient can be appropriately managed *[see Warnings and Precautions (5.1), Drug Interactions (7), and Clinical Studies (14)].***

1 INDICATIONS AND USAGE

PAXLOVID is indicated for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.

Limitations of Use
PAXLOVID is not approved for use as pre-exposure or post-exposure prophylaxis for prevention of COVID-19 *[see Clinical Studies (14.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Information

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. There are two different dose packs available:

- PAXLOVID (nirmatrelvir; ritonavir) co-packaged for oral use 300 mg;100 mg *[see Dosage and Administration (2.2)]*.

- PAXLOVID (nirmatrelvir; ritonavir) co-packaged for oral use 150 mg;100 mg for patients with moderate renal impairment *[see Dosage and Administration (2.3)]*.

Nirmatrelvir must be co-administered with ritonavir. Failure to correctly co-administer nirmatrelvir with ritonavir may result in plasma levels of nirmatrelvir that are insufficient to achieve the desired therapeutic effect.

Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID [see Dosage and Administration (2.2, 2.3)]. Completion of the full 5-day treatment course and continued isolation in accordance with public health recommendations are important to maximize viral clearance and minimize transmission of SARS-CoV-2.

The 5-day treatment course of PAXLOVID should be initiated as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset even if baseline COVID-19 symptoms are

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mild. Should a patient require hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID, the patient should complete the full 5-day treatment course per the healthcare provider's discretion.

If the patient misses a dose of PAXLOVID within 8 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 8 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose.

PAXLOVID (both nirmatrelvir and ritonavir tablets) can be taken with or without food *[see Clinical Pharmacology (12.3)]*. The tablets should be swallowed whole and not chewed, broken, or crushed.

2.2 Recommended Dosage

The recommended dosage for PAXLOVID is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) with all 3 tablets taken together orally twice daily for 5 days.

2.3 Dosage in Patients with Renal Impairment

No dosage adjustment is recommended in patients with mild renal impairment (eGFR ≥60 to <90 mL/min).

In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), the dosage of PAXLOVID is 150 mg nirmatrelvir (one 150 mg tablet) and 100 mg ritonavir (one 100 mg tablet) with both tablets taken together twice daily for 5 days *[see How Supplied/Storage and Handling (16)]*. *Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID.* Providers should counsel patients about renal dosing instructions *[see Patient Counseling Information (17)]*.

PAXLOVID is not recommended in patients with severe renal impairment (eGFR <30 mL/min) until more data are available; the appropriate dosage for patients with severe renal impairment has not been determined *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

2.4 Use in Patients with Hepatic Impairment

No dosage adjustment is needed in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.

No pharmacokinetic or safety data are available regarding the use of nirmatrelvir or ritonavir in subjects with severe (Child-Pugh Class C) hepatic impairment; therefore, PAXLOVID is not recommended for use in patients with severe hepatic impairment *[see Use in Specific Populations (8.7)]*.

3 DOSAGE FORMS AND STRENGTHS

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets *[see How Supplied/Storage and Handling (16)]*.

- Nirmatrelvir is supplied as oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Each tablet contains 150 mg of nirmatrelvir.

- Ritonavir is supplied as white or white to off-white film-coated tablets uniquely identified by the color, shape, and debossing. Each tablet contains 100 mg of ritonavir.

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4 CONTRAINDICATIONS

PAXLOVID is contraindicated in patients with a history of clinically significant hypersensitivity reactions [e.g., toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome] to its active ingredients (nirmatrelvir or ritonavir) or any other components of the product.

PAXLOVID is contraindicated with drugs that are primarily metabolized by CYP3A and for which elevated concentrations are associated with serious and/or life-threatening reactions and drugs that are strong CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. There are certain other drugs for which concomitant use with PAXLOVID should be avoided and/or dose adjustment, interruption, or therapeutic monitoring is recommended. Drugs listed in this section are a guide and not considered a comprehensive list of all drugs that may be contraindicated with PAXLOVID. The healthcare provider should consult other appropriate resources such as the prescribing information for the interacting drug for comprehensive information on dosing or monitoring with concomitant use of a strong CYP3A inhibitor like PAXLOVID *[see Drug Interactions (7.3)]*:

- Drugs that are primarily metabolized by CYP3A for which elevated concentrations are associated with serious and/or life-threatening reactions *[see Drug Interactions (7.3)]*:

  - Alpha 1-adrenoreceptor antagonist: alfuzosin
  - Antianginal: ranolazine
  - Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
  - Anti-gout: colchicine (in patients with renal and/or hepatic impairment *[see Table 1, Drug Interactions (7.3)]*)
  - Antipsychotics: lurasidone, pimozide
  - Benign prostatic hyperplasia agents: silodosin
  - Cardiovascular agents: eplerenone, ivabradine
  - Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
  - HMG-CoA reductase inhibitors: lovastatin, simvastatin (these drugs can be temporarily discontinued to allow PAXLOVID use *[see Table 1, Drug Interactions (7.3)]*)
  - Immunosuppressants: voclosporin
  - Microsomal triglyceride transfer protein inhibitor: lomitapide
  - Migraine medications: eletriptan, ubrogepant
  - Mineralocorticoid receptor antagonists: finerenone
  - Opioid antagonists: naloxegol
  - PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH)
  - Sedative/hypnotics: triazolam, oral midazolam
  - Serotonin receptor 1A agonist/serotonin receptor 2A antagonist: flibanserin
  - Vasopressin receptor antagonists: tolvaptan

- Drugs that are strong CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. PAXLOVID cannot be started immediately after discontinuation of any of the following medications due to the delayed offset of the recently discontinued CYP3A inducer *[see Drug Interactions (7.3)]*:

  - Anticancer drugs: apalutamide
  - Anticonvulsant: carbamazepine, phenobarbital, primidone, phenytoin
  - Antimycobacterials: rifampin, rifapentine

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- Cystic fibrosis transmembrane conductance regulator potentiators: lumacaftor/ivacaftor
- Herbal products: St. John's Wort (*hypericum perforatum*)

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Adverse Reactions Due to Drug Interactions

Initiation of PAXLOVID, which contains ritonavir, a strong CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving PAXLOVID, may increase plasma concentrations of medications metabolized by CYP3A. Medications that induce CYP3A may decrease concentrations of PAXLOVID. These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medications.
- Loss of therapeutic effect of PAXLOVID and possible development of viral resistance.

Severe, life-threatening, and/or fatal adverse reactions due to drug interactions have been reported in patients treated with PAXLOVID. The most commonly reported concomitant medications resulting in serious adverse reactions were calcineurin inhibitors (e.g., tacrolimus, cyclosporine), followed by calcium channel blockers.

Prior to prescribing PAXLOVID, review all medications taken by the patient to assess potential drug-drug interactions and determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring (e.g., calcineurin inhibitors) *[see Contraindications (4) and Drug Interactions (7)]*. See Table 1 for clinically significant drug interactions, including contraindicated drugs. Drugs listed in Table 1 are a guide and not considered a comprehensive list of all possible drugs that may interact with PAXLOVID.

Consider the benefit of PAXLOVID treatment in reducing hospitalization and death, and whether the risk of potential drug-drug interactions for an individual patient can be appropriately managed *[see Drug Interactions (7) and Clinical Studies (14)]*.

5.2 Hypersensitivity Reactions

Anaphylaxis, serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson syndrome), and other hypersensitivity reactions have been reported with PAXLOVID *[see Adverse Reactions (6.1)]*. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue PAXLOVID and initiate appropriate medications and/or supportive care.

5.3 Hepatotoxicity

Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir. Therefore, caution should be exercised when administering PAXLOVID to patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis.

5.4 Risk of HIV-1 Resistance Development

Because nirmatrelvir is co-administered with ritonavir, there may be a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection *[see Contraindications (4) and Drug Interactions (7)]*.

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6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity reactions *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of PAXLOVID is based on two Phase 2/3 randomized, placebo-controlled trials in symptomatic adult subjects 18 years of age and older with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Subjects in both studies received PAXLOVID (nirmatrelvir/ritonavir 300 mg/100 mg) or placebo every 12 hours for 5 days for the treatment of mild-to-moderate COVID-19 within 5 days of symptom onset *[see Clinical Studies (14)]*:

- Trial C4671005 (EPIC-HR) enrolled subjects who were at high risk for progression to severe disease.
- Trial C4671002 (EPIC-SR) enrolled subjects who were at standard risk for progression to severe disease (previously unvaccinated subjects at standard risk or fully vaccinated subjects with at least 1 risk factor for progression to severe disease).

Adverse reactions were those reported while subjects were on study medication and through 28 days after the last dose of study treatment.

In Trial C4671005 (EPIC-HR), 1,038 subjects received PAXLOVID and 1,053 subjects received placebo. The most common adverse reactions (≥1% incidence in the PAXLOVID group and occurring at a greater frequency than in the placebo group) were dysgeusia (5% and <1%, respectively) and diarrhea (3% and 2%, respectively).

Among vaccinated or unvaccinated subjects at standard risk or fully vaccinated subjects with at least 1 risk factor for progression to severe disease in Trial C4671002 (EPIC-SR), 540 subjects received PAXLOVID and 528 subjects received placebo. The adverse reactions observed were consistent with those observed in EPIC-HR.

Emergency Use Authorization Experience in Subjects with COVID-19

The following adverse reactions have been identified during use of PAXLOVID under Emergency Use Authorization.

Immune System Disorders: Anaphylaxis, hypersensitivity reactions *[see Warnings and Precautions (5.2)]*
Skin and Subcutaneous Tissue Disorders: Toxic epidermal necrolysis, Stevens-Johnson syndrome *[see Warnings and Precautions (5.2)]*
Nervous System Disorders: Headache
Vascular Disorders: Hypertension
Gastrointestinal Disorders: Abdominal pain, nausea, vomiting
General Disorders and Administration Site Conditions: Malaise

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7 DRUG INTERACTIONS

7.1 Potential for PAXLOVID to Affect Other Drugs

PAXLOVID (nirmatrelvir co-packaged with ritonavir) is a strong inhibitor of CYP3A, and an inhibitor of CYP2D6, P-gp and OATP1B1. Co-administration of PAXLOVID with drugs that are primarily metabolized by CYP3A and CYP2D6 or are transported by P-gp or OATP1B1 may result in increased plasma concentrations of such drugs and increase the risk of adverse events. Co-administration of PAXLOVID with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated *[see Contraindications (4) and Drug Interactions (7.3) Table 1]*. Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring as shown in Table 1.

7.2 Potential for Other Drugs to Affect PAXLOVID

Nirmatrelvir and ritonavir are CYP3A substrates; therefore, drugs that induce CYP3A may decrease nirmatrelvir and ritonavir plasma concentrations and reduce PAXLOVID therapeutic effect *[see Contraindications (4) and Drug Interactions (7.3) Table 1]*.

7.3 Established and Other Potentially Significant Drug Interactions

Table 1 provides a listing of clinically significant drug interactions, including contraindicated drugs *[see Contraindications (4) and Warnings and Precautions (5.1)]*. Drugs listed in Table 1 are a guide and not considered a comprehensive list of all possible drugs that may interact with PAXLOVID. The healthcare provider should consult other appropriate resources such as the prescribing information for the interacting drug for comprehensive information on dosing or monitoring with concomitant use of a strong CYP3A inhibitor such as ritonavir.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Alpha 1-adrenoreceptor antagonist	alfuzosin	↑ alfuzosin	Co-administration contraindicated due to potential hypotension *[see Contraindications (4)]*.
Alpha 1-adrenoreceptor antagonist	tamsulosin	↑ tamsulosin	Avoid concomitant use with PAXLOVID.
Antianginal	ranolazine	↑ ranolazine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions *[see Contraindications (4)]*.
Antiarrhythmics	amiodarone, dronedarone, flecainide, propafenone, quinidine	↑ antiarrhythmic	Co-administration contraindicated due to potential for cardiac arrhythmias *[see Contraindications (4)]*.
Antiarrhythmics	lidocaine (systemic), disopyramide	↑ antiarrhythmic	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics if available.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Anticancer drugs	apalutamide	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.
Anticancer drugs	abemaciclib, ceritinib, dasatinib, encorafenib, ibrutinib, ivosidenib, neratinib, nilotinib, venetoclax, vinblastine, vincristine	↑ anticancer drugs	Avoid co-administration of encorafenib or ivosidenib due to potential risk of serious adverse events such as QT interval prolongation. Avoid use of neratinib, venetoclax or ibrutinib. Co-administration of vincristine and vinblastine may lead to significant hematologic or gastrointestinal side effects. For further information, refer to individual product label for anticancer drug.
Anticoagulants	warfarin	↑↓ warfarin	Closely monitor international normalized ratio (INR) if co-administration with warfarin is necessary.
	rivaroxaban	↑ rivaroxaban	Increased bleeding risk with rivaroxaban. Avoid concomitant use.
	dabigatran[a]	↑ dabigatran	Increased bleeding risk with dabigatran. Depending on dabigatran indication and renal function, reduce dose of dabigatran or avoid concomitant use. Refer to the dabigatran product label for further information.
	apixaban	↑ apixaban	Combined P-gp and strong CYP3A inhibitors increase blood levels of apixaban and increase the risk of bleeding. Dosing recommendations for co-administration of apixaban with PAXLOVID depend on the apixaban dose. Refer to the apixaban product label for more information.
Anticonvulsants	carbamazepine[a], phenobarbital, primidone, phenytoin	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.
Anticonvulsants	clonazepam	↑ anticonvulsant	A dose decrease may be needed for clonazepam when co-administered with PAXLOVID and clinical monitoring is recommended.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Antidepressants	bupropion	↓ bupropion and active metabolite hydroxy-bupropion	Monitor for an adequate clinical response to bupropion.
	trazodone	↑ trazodone	Adverse reactions of nausea, dizziness, hypotension, and syncope have been observed following co-administration of trazodone and ritonavir. A lower dose of trazodone should be considered. Refer to trazadone product label for further information.
Antifungals	voriconazole	↓ voriconazole	Avoid concomitant use of voriconazole.
	ketoconazole, isavuconazonium sulfate, itraconazole[a]	↑ ketoconazole ↑ isavuconazonium sulfate ↑ itraconazole	Refer to ketoconazole, isavuconazonium sulfate, and itraconazole product labels for further information.
		↑ nirmatrelvir/ritonavir	A nirmatrelvir/ritonavir dose reduction is not needed.
Anti-gout	colchicine	↑ colchicine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment *[see Contraindications (4)]*.
Anti-HIV protease inhibitors	atazanavir, darunavir, tipranavir	↑ protease inhibitor	For further information, refer to the respective protease inhibitors' prescribing information. Patients on ritonavir- or cobicistat-containing HIV regimens should continue their treatment as indicated. Monitor for increased PAXLOVID or protease inhibitor adverse events.
Anti-HIV	efavirenz, maraviroc, nevirapine, zidovudine, bictegravir/ emtricitabine/ tenofovir	↑ efavirenz ↑ maraviroc ↑ nevirapine ↓ zidovudine ↑ bictegravir ↔ emtricitabine ↑ tenofovir	For further information, refer to the respective anti-HIV drugs prescribing information.
Anti-infective	clarithromycin, erythromycin	↑ clarithromycin ↑ erythromycin	Refer to the respective prescribing information for anti-infective dose adjustment.
Antimycobacterial	rifampin, rifapentine	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance. Alternate antimycobacterial drugs such as rifabutin should be considered *[see Contraindications (4)]*.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Antimycobacterial	bedaquiline	↑ bedaquiline	Refer to the bedaquiline product label for further information.
	rifabutin	↑ rifabutin	Refer to rifabutin product label for further information on rifabutin dose reduction.
Antipsychotics	lurasidone, pimozide	↑ lurasidone ↑ pimozide	Co-administration contraindicated due to serious and/or life-threatening reactions such as cardiac arrhythmias *[see Contraindications (4)]*.
Antipsychotics	quetiapine	↑ quetiapine	If co-administration is necessary, reduce quetiapine dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations.
	clozapine	↑ clozapine	If co-administration is necessary, consider reducing the clozapine dose and monitor for adverse reactions.
Benign prostatic hyperplasia agents	silodosin	↑ silodosin	Co-administration contraindicated due to potential for postural hypotension *[see Contraindications (4)]*.
Calcium channel blockers	amlodipine, diltiazem, felodipine, nicardipine, nifedipine, verapamil	↑ calcium channel blocker	Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with PAXLOVID. If co-administered, refer to individual product label for calcium channel blocker for further information.
Cardiac glycosides	digoxin	↑ digoxin	Caution should be exercised when co-administering PAXLOVID with digoxin, with appropriate monitoring of serum digoxin levels. Refer to the digoxin product label for further information.
Cardiovascular agents	eplerenone	↑ eplerenone	Co-administration with eplerenone is contraindicated due to potential for hyperkalemia *[see Contraindications (4)]*.
	ivabradine	↑ ivabradine	Co-administration with ivabradine is contraindicated due to potential for bradycardia or conduction disturbances *[see Contraindications (4)]*.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Cardiovascular agents	aliskiren, ticagrelor, vorapaxar	↑ aliskiren ↑ ticagrelor ↑ vorapaxar	Avoid concomitant use with PAXLOVID.
	clopidogrel	↓ clopidogrel active metabolite	
	cilostazol	↑ cilostazol	Dosage adjustment of cilostazol is recommended. Refer to the cilostazol product label for more information.
Corticosteroids primarily metabolized by CYP3A	betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, methylprednisolone, mometasone, triamcinolone	↑ corticosteroid	Co-administration with corticosteroids (all routes of administration) of which exposures are significantly increased by strong CYP3A inhibitors can increase the risk for Cushing's syndrome and adrenal suppression. However, the risk of Cushing's syndrome and adrenal suppression associated with short-term use of a strong CYP3A inhibitor is low. Alternative corticosteroids including beclomethasone, prednisone, and prednisolone should be considered.
Cystic fibrosis transmembrane conductance regulator potentiators	lumacaftor/ivacaftor	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.
Cystic fibrosis transmembrane conductance regulator potentiators	ivacaftor	↑ ivacaftor	Reduce dosage when co-administered with PAXLOVID. Refer to individual product labels for more information.
	elexacaftor/tezacaftor/ivacaftor	↑ elexacaftor/tezacaftor/ivacaftor	
	tezacaftor/ivacaftor	↑ tezacaftor/ivacaftor	
Dipeptidyl peptidase 4 (DPP4) inhibitors	saxagliptin	↑ saxagliptin	Dosage adjustment of saxagliptin is recommended. Refer to the saxagliptin product label for more information.
Endothelin receptor antagonists	bosentan	↑ bosentan ↓ nirmatrelvir/ritonavir	Discontinue use of bosentan at least 36 hours prior to initiation of PAXLOVID. Refer to the bosentan product label for further information.
Ergot derivatives	dihydroergotamine, ergotamine, methylergonovine	↑ dihydroergotamine ↑ ergotamine ↑ methylergonovine	Co-administration contraindicated due to potential for acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system *[see Contraindications (4)]*.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Hepatitis C direct acting antivirals	elbasvir/grazoprevir	↑ antiviral	Increased grazoprevir concentrations can result in alanine transaminase (ALT) elevations.
	glecaprevir/pibrentasvir		Avoid concomitant use of glecaprevir/pibrentasvir with PAXLOVID.
	ombitasvir/paritaprevir/ ritonavir and dasabuvir		Refer to the ombitasvir/paritaprevir/ritonavir and dasabuvir label for further information.
	sofosbuvir/velpatasvir/ voxilaprevir		Refer to the sofosbuvir/velpatasvir/voxilaprevir product label for further information.
			Patients on ritonavir-containing HCV regimens should continue their treatment as indicated. Monitor for increased PAXLOVID or HCV drug adverse events with concomitant use.
Herbal products	St. John's Wort (*hypericum perforatum*)	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.
HMG-CoA reductase inhibitors	lovastatin, simvastatin	↑ lovastatin ↑ simvastatin	Co-administration contraindicated due to potential for myopathy including rhabdomyolysis *[see Contraindications (4)]*. If treatment with PAXLOVID is considered medically necessary, discontinue use of lovastatin and simvastatin at least 12 hours prior to initiation of PAXLOVID, during the 5 days of PAXLOVID treatment, and for 5 days after completing PAXLOVID.
HMG-CoA reductase inhibitors	atorvastatin, rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Consider temporary discontinuation of atorvastatin and rosuvastatin during treatment with PAXLOVID. Atorvastatin and rosuvastatin do not need to be withheld prior to or after completing PAXLOVID.
Hormonal contraceptive	ethinyl estradiol	↓ ethinyl estradiol	An additional, non-hormonal method of contraception should be considered during the 5 days of PAXLOVID treatment and until one menstrual cycle after stopping PAXLOVID.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Immunosuppressants	voclosporin	↑ voclosporin	Co-administration contraindicated due to potential for acute and/or chronic nephrotoxicity *[see Contraindications (4)]*.
Immunosuppressants	calcineurin inhibitors: cyclosporine, tacrolimus	↑ cyclosporine ↑ tacrolimus	Avoid concomitant use of calcineurin inhibitors with PAXLOVID when close monitoring of immunosuppressant concentrations is not feasible. If co-administered, dose adjustment of the immunosuppressant and close and regular monitoring for immunosuppressant concentrations and adverse reactions are recommended during and after treatment with PAXLOVID. Obtain expert consultation to appropriately manage the complexity of this coadministration *[see Warnings and Precautions (5.1)]*.
	mTOR inhibitors: everolimus, sirolimus	↑ everolimus ↑ sirolimus	Avoid concomitant use of everolimus and sirolimus and PAXLOVID. Refer to the individual immunosuppressant product label and latest guidelines for further information.
Janus kinase (JAK) inhibitors	tofacitinib	↑ tofacitinib	Dosage adjustment of tofacitinib is recommended. Refer to the tofacitinib product label for more information.
	upadacitinib	↑ upadacitinib	Dosing recommendations for co-administration of upadacitinib with PAXLOVID depends on the upadacitinib indication. Refer to the upadacitinib product label for more information.
Long-acting beta-adrenoceptor agonist	salmeterol	↑ salmeterol	Avoid concomitant use with PAXLOVID. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Microsomal triglyceride transfer protein (MTTP) inhibitor	lomitapide	↑ lomitapide	Co-administration contraindicated due to potential for hepatotoxicity and gastrointestinal adverse reactions *[see Contraindications (4)]*.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Migraine medications	eletriptan	↑ eletriptan	Co-administration of eletriptan within at least 72 hours of PAXLOVID is contraindicated due to potential for serious adverse reactions including cardiovascular and cerebrovascular events *[see Contraindications (4)]*.
	ubrogepant	↑ ubrogepant	Co-administration of ubrogepant with PAXLOVID is contraindicated due to potential for serious adverse reactions *[see Contraindications (4)]*.
Migraine medications	rimegepant	↑ rimegepant	Avoid concomitant use with PAXLOVID.
Mineralocorticoid receptor antagonists	finerenone	↑ finerenone	Co-administration contraindicated due to potential for serious adverse reactions including hyperkalemia, hypotension, and hyponatremia *[see Contraindications (4)]*.
Muscarinic receptor antagonists	darifenacin	↑ darifenacin	The darifenacin daily-dose should not exceed 7.5 mg when co-administered with PAXLOVID. Refer to the darifenacin product label for more information.
Narcotic analgesics	fentanyl, hydrocodone, oxycodone, meperidine	↑ fentanyl ↑ hydrocodone ↑ oxycodone ↑ meperidine	Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl, hydrocodone, oxycodone, or meperidine is concomitantly administered with PAXLOVID. If concomitant use with PAXLOVID is necessary, consider a dosage reduction of the narcotic analgesic and monitor patients closely at frequent intervals. Refer to the individual product label for more information.
	methadone	↓ methadone	Monitor methadone-maintained patients closely for evidence of withdrawal effects and adjust the methadone dose accordingly.
Neuropsychiatric agents	suvorexant	↑ suvorexant	Avoid concomitant use of suvorexant with PAXLOVID.
	aripiprazole, brexpiprazole, cariprazine, iloperidone, lumateperone, pimavanserin	↑ aripiprazole ↑ brexpiprazole ↑ cariprazine ↑ iloperidone ↑ lumateperone ↑ pimavanserin	Dosage adjustment of aripiprazole, brexpiprazole, cariprazine, iloperidone, lumateperone, and pimavanserin is recommended. Refer to individual product label for more information.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Opioid antagonists	naloxegol	↑ naloxegol	Co-administration contraindicated due to the potential for opioid withdrawal symptoms *[see Contraindications (4)]*.
Pulmonary hypertension agents (PDE5 inhibitors)	sildenafil (Revatio®)	↑ sildenafil	Co-administration of sildenafil with PAXLOVID is contraindicated for use in pulmonary hypertension due to the potential for sildenafil associated adverse events, including visual abnormalities hypotension, prolonged erection, and syncope *[see Contraindications (4)]*.
Pulmonary hypertension agents (PDE5 inhibitors)	tadalafil (Adcirca®)	↑ tadalafil	Avoid concomitant use of tadalafil with PAXLOVID for pulmonary hypertension.
Pulmonary hypertension agents (sGC stimulators)	riociguat	↑ riociguat	Dosage adjustment is recommended for riociguat when used for pulmonary hypertension. Refer to the riociguat product label for more information.
Erectile dysfunction agents (PDE5 inhibitors)	avanafil	↑ avanafil	Do not use PAXLOVID with avanafil because a safe and effective avanafil dosage regimen has not been established.
	sildenafil, tadalafil, vardenafil	↑ sildenafil ↑ tadalafil ↑ vardenafil	Dosage adjustment is recommended for use of sildenafil, tadalafil or vardenafil with PAXLOVID when used for erectile dysfunction. Refer to individual product label for more information.
Sedative/hypnotics	triazolam, oral midazolam[a]	↑ triazolam ↑ midazolam	Co-administration contraindicated due to potential for extreme sedation and respiratory depression *[see Contraindications (4)]*.
Sedative/hypnotics	buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem	↑ sedative/hypnotic	A dose decrease may be needed for these drugs when co-administered with PAXLOVID and monitoring for adverse events.
	midazolam (administered parenterally)	↑ midazolam	Co-administration of midazolam (parenteral) should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered. Refer to the midazolam product label for further information.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Serotonin receptor 1A agonist/ serotonin receptor 2A antagonist	flibanserin	↑ flibanserin	Co-administration contraindicated due to potential for hypotension, syncope, and CNS depression *[see Contraindications (4)]*.
Vasopressin receptor antagonists	tolvaptan	↑ tolvaptan	Co-administration contraindicated due to potential for dehydration, hypovolemia and hyperkalemia *[see Contraindications (4)]*.

a. See Pharmacokinetics, Drug Interaction Studies Conducted with Nirmatrelvir and Ritonavir (12.3).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data on the use of nirmatrelvir during pregnancy are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Published observational studies on ritonavir use in pregnant women have not identified an increase in the risk of major birth defects. Published studies with ritonavir are insufficient to identify a drug associated risk of miscarriage *(see Data).* There are maternal and fetal risks associated with untreated COVID-19 in pregnancy *(see Clinical Considerations).*

In an embryo-fetal development study with nirmatrelvir, reduced fetal body weights following oral administration of nirmatrelvir to pregnant rabbits were observed at systemic exposures (AUC) approximately 11 times higher than clinical exposure at the approved human dose of PAXLOVID. No other adverse developmental outcomes were observed in animal reproduction studies with nirmatrelvir at systemic exposures (AUC) greater than or equal to 3 times higher than clinical exposure at the approved human dose of PAXLOVID *(see Data)*.

In embryo-fetal developmental studies with ritonavir, no evidence of adverse developmental outcomes was observed following oral administration of ritonavir to pregnant rats and rabbits at systemic exposures (AUC) 5 (rat) or 8 (rabbits) times higher than clinical exposure at the approved human dose of PAXLOVID *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated Maternal and/or Embryo-fetal Risk
COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

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Data

Human Data

Ritonavir
Based on prospective reports to the antiretroviral pregnancy registry of live births following exposure to ritonavir-containing regimens (including over 3,500 live births exposed in the first-trimester and over 3,500 live births exposed in the second and third trimesters), there was no difference in the rate of overall birth defects for ritonavir compared with the background birth defect rate of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The prevalence of birth defects in live births was 2.4% [95% confidence interval (CI): 1.9%, 2.9%] following first-trimester exposure to ritonavir-containing regimens and 2.9% (95% CI: 2.4%, 3.5%) following second and third trimester exposure to ritonavir-containing regimens. While placental transfer of ritonavir and fetal ritonavir concentrations are generally low, detectable levels have been observed in cord blood samples and neonate hair.

Animal Data

Nirmatrelvir
Embryo-fetal developmental (EFD) toxicity studies were conducted in pregnant rats and rabbits administered oral nirmatrelvir doses of up to 1,000 mg/kg/day during organogenesis [on Gestation Days (GD) 6 through 17 in rats and GD 7 through 19 in rabbits]. No biologically significant developmental effects were observed in the rat EFD study. At the highest dose of 1,000 mg/kg/day, the systemic nirmatrelvir exposure (AUC_{24}) in rats was approximately 9 times higher than clinical exposures at the approved human dose of PAXLOVID. In the rabbit EFD study, lower fetal body weights (9% decrease) were observed at 1,000 mg/kg/day in the absence of significant maternal toxicity findings. At 1,000 mg/kg/day, the systemic exposure (AUC_{24}) in rabbits was approximately 11 times higher than clinical exposures at the approved human dose of PAXLOVID. No other significant developmental toxicities (malformations and embryo-fetal lethality) were observed up to the highest dose tested, 1,000 mg/kg/day. No developmental effects were observed in rabbits at 300 mg/kg/day resulting in systemic exposure (AUC_{24}) approximately 3 times higher than clinical exposures at the approved human dose of PAXLOVID. A pre- and postnatal developmental (PPND) study in pregnant rats administered oral nirmatrelvir doses of up to 1,000 mg/kg/day from GD 6 through Lactation Day (LD) 20 showed no adverse findings. Although no difference in body weight was noted at birth when comparing offspring born to nirmatrelvir-treated versus control animals, a decrease in the body weight of offspring was observed on Postnatal Day (PND) 17 (8% decrease) and PND 21 (up to 7% decrease) in the absence of maternal toxicity. No significant differences in offspring body weight were observed from PND 28 to PND 56. The maternal systemic exposure (AUC_{24}) at 1,000 mg/kg/day was approximately 9 times higher than clinical exposures at the approved human dose of PAXLOVID. No body weight changes in the offspring were noted at 300 mg/kg/day, where maternal systemic exposure (AUC_{24}) was approximately 6 times higher than clinical exposures at the approved human dose of PAXLOVID.

Ritonavir
Ritonavir was administered orally to pregnant rats (at 0, 15, 35, and 75 mg/kg/day) and rabbits (at 0, 25, 50, and 110 mg/kg/day) during organogenesis (on GD 6 through 17 in rats and GD 6 through 19 in rabbits). No evidence of teratogenicity due to ritonavir was observed in rats and rabbits at systemic exposures (AUC) 5 (rats) or 8 (rabbits) times higher than exposure at the approved human dose of PAXLOVID. Increased incidences of early resorptions, ossification delays, and developmental variations, as well as decreased fetal body weights were observed in rats in the presence of maternal toxicity, at systemic exposures (AUC) approximately 10 times higher than exposure at the approved human dose of PAXLOVID. In rabbits, resorptions, decreased litter size, and decreased fetal weights were observed at maternally toxic doses, at systemic exposures greater than 8 times higher than exposure at the approved human dose of PAXLOVID. In a PPND study in rats, administration of

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0, 15, 35, and 60 mg/kg/day ritonavir from GD 6 through PND 20 resulted in no developmental toxicity, at ritonavir systemic exposures greater than 10 times the exposure at the approved human dose of PAXLOVID.

8.2 Lactation

Risk Summary

There are no available data on the presence of nirmatrelvir in human or animal milk, the effects on the breastfed infant, or the effects on milk production. A transient decrease in body weight was observed in the nursing offspring of rats administered nirmatrelvir *(see Data)*. Limited published data reports that ritonavir is present in human milk. There is no information on the effects of ritonavir on the breastfed infant or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PAXLOVID and any potential adverse effects on the breastfed infant from PAXLOVID or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

Data

In the PPND study, transiently lower body weight (up to 8%) was observed in the offspring of pregnant rats administered nirmatrelvir at maternal systemic exposure (AUC_{24}) approximately 9 times higher than clinical exposures at the approved human dose of PAXLOVID. No body weight changes in the offspring were noted at maternal systemic exposure (AUC_{24}) approximately 6 times higher than clinical exposures at the approved human dose of PAXLOVID.

8.3 Females and Males of Reproductive Potential

Contraception

Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Advise patients using combined hormonal contraceptives to use an effective alternative contraceptive method or an additional barrier method of contraception *[see Drug Interactions (7.3)]*.

8.4 Pediatric Use

The optimal dose of PAXLOVID has not been established in pediatric patients.

8.5 Geriatric Use

Clinical studies of PAXLOVID include subjects 65 years of age and older and their data contributes to the overall assessment of safety and efficacy *[see Adverse Reactions (6.1) and Clinical Studies (14.1)]*. Of the total number of subjects in the integrated dataset consisting of EPIC-HR and EPIC-SR who were randomized to and received PAXLOVID (N=1,578), 165 (10%) were 65 years of age and older and 39 (2%) were 75 years of age and older. No overall differences in safety were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in safety between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

Renal impairment increases nirmatrelvir exposure, which may increase the risk of PAXLOVID adverse reactions. No dosage adjustment is recommended in patients with mild renal impairment (eGFR ≥60 to <90 mL/min). Reduce the PAXLOVID dosage in patients with moderate renal impairment (eGFR ≥30 to

<60 mL/min). PAXLOVID is not recommended for use in patients with severe renal impairment (eGFR <30 mL/min) or patients with end stage renal disease (eGFR <15 mL/min) receiving dialysis until more data are available. The appropriate dosage for patients with severe renal impairment has not been determined *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]. Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID.* Providers should counsel patients about renal dosing instructions *[see Patient Counseling Information (17)]*.

8.7 Hepatic Impairment

No dosage adjustment of PAXLOVID is recommended for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic or safety data are available regarding the use of nirmatrelvir or ritonavir in subjects with severe (Child-Pugh Class C) hepatic impairment, therefore, PAXLOVID is not recommended for use in patients with severe (Child-Pugh Class C) hepatic impairment *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

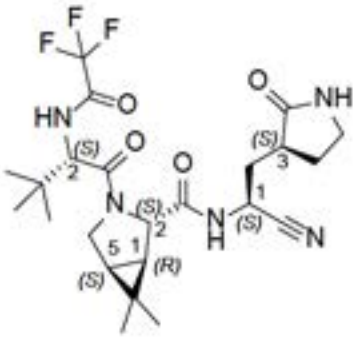
Treatment of overdose with PAXLOVID should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with PAXLOVID.

11 DESCRIPTION

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. Nirmatrelvir is a SARS-CoV-2 main protease (M^{pro}) inhibitor, and ritonavir is an HIV-1 protease inhibitor and CYP3A inhibitor.

Nirmatrelvir

The chemical name of active ingredient of nirmatrelvir is (1*R*,2*S*,5*S*)-*N*-((1*S*)-1-Cyano-2-((3*S*)-2-oxopyrrolidin-3-yl)ethyl)-3-((2*S*)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide]. It has a molecular formula of $C_{23}H_{32}F_3N_5O_4$ and a molecular weight of 499.54. Nirmatrelvir has the following structural formula:



Nirmatrelvir is available as immediate-release, film-coated tablets. Each tablet contains 150 mg nirmatrelvir with the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, and sodium stearyl fumarate. The following are the ingredients in the film coating: hydroxy propyl methylcellulose, iron oxide red, polyethylene glycol, and titanium dioxide.

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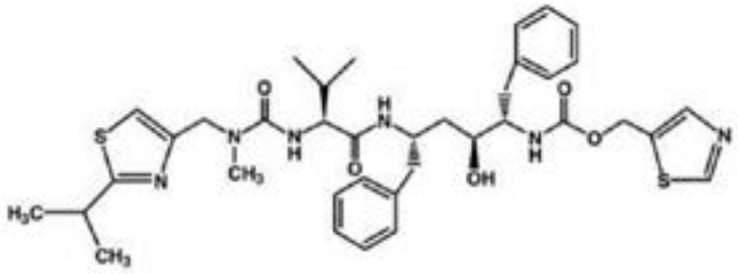
Ritonavir

Ritonavir is chemically designated as 10-Hydroxy-2-methyl-5-(1-methylethyl)-1- [2-(1 methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12- tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]. Its molecular formula is $C_{37}H_{48}N_6O_5S_2$, and its molecular weight is 720.95. Ritonavir has the following structural formula:



Ritonavir is available as film-coated tablets. Each tablet contains 100 mg ritonavir with the following inactive ingredients: anhydrous dibasic calcium phosphate, colloidal silicon dioxide, copovidone, sodium stearyl fumarate, and sorbitan monolaurate. The film coating may include the following ingredients: colloidal anhydrous silica, colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, polyethylene glycol, polysorbate 80, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nirmatrelvir is a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antiviral drug *[see Microbiology (12.4)]*.

Ritonavir is an HIV-1 protease inhibitor but is not active against SARS-CoV-2 M^{pro}. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At 3 times the steady state peak plasma concentration (C_{max}) at the recommended dose, nirmatrelvir does not prolong the QTc interval to any clinically relevant extent.

12.3 Pharmacokinetics

The pharmacokinetics of nirmatrelvir/ritonavir were similar in healthy subjects and in subjects with mild-to-moderate COVID-19.

Nirmatrelvir AUC increased in a less than dose proportional manner over a single dose range from 250 mg to 750 mg (0.83 to 2.5 times the approved recommended dose) and multiple dose range from 75 mg to 500 mg (0.25 to 1.67 times the approved recommended dose), when administered in combination with 100 mg ritonavir. Nirmatrelvir steady state was achieved on Day 2 following administration of the approved recommended dosage and the mean accumulation ratio was approximately 2-fold.

The pharmacokinetic properties of nirmatrelvir/ritonavir are displayed in Table 2.

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Table 2: Pharmacokinetic Properties of Nirmatrelvir and Ritonavir in Healthy Subjects

	Nirmatrelvir (When Given With Ritonavir)	Ritonavir
Absorption		
T_{max} (hr), median	3.00[a]	3.98[a]
Food effect	Test/reference (fed/fasted) ratios of adjusted geometric means (90% CI) AUC_{inf} and C_{max} for nirmatrelvir were 119.67 (108.75, 131.68) and 161.01 (139.05, 186.44), respectively.[b]	
Distribution		
% bound to human plasma proteins	69%	98-99%
Blood-to-plasma ratio	0.60	0.14[d]
V_z/F (L), mean	104.7[c]	112.4[c]
Elimination		
Major route of elimination	Renal elimination[d]	Hepatic metabolism
Half-life ($T_{½}$) (hr), mean	6.05[a]	6.15[a]
Oral clearance (CL/F) (L/hr), mean	8.99[c]	13.92[c]
Metabolism		
Metabolic pathways	Nirmatrelvir is a CYP3A substrate but when dosed with ritonavir, metabolic clearance is minimal.	Major CYP3A, Minor CYP2D6
Excretion		
% drug-related material in feces	35.3%[e]	86.4%[f]
% of dose excreted as total (unchanged drug) in feces	27.5%[e]	33.8%[f]
% drug-related material in urine	49.6%[e]	11.3%[f]
% of dose excreted as total (unchanged drug) in urine	55.0%[e]	3.5%[f]

Abbreviations: CL/F=apparent clearance; hr=hour; L/hr=liters per hour; $T_{½}$=terminal elimination half-life; T_{max}=the time to reach C_{max}; V_z/F=apparent volume of distribution.

a. Represents data after a single dose of 300 mg nirmatrelvir (2 x 150 mg tablet formulation) administered together with 100 mg ritonavir tablet in healthy subjects.
b. Following a single oral dose of nirmatrelvir 300 mg boosted ritonavir 100 mg at -12 hours, 0 hours and 12 hours, administered under fed (high fat and high calorie meal) or fasted conditions.
c. 300 mg nirmatrelvir (oral suspension formulation) co-administered with 100 mg ritonavir (tablet formulation) twice daily for 3 days.
d. Red blood cell to plasma ratio.
e. Determined by ^{19}F-NMR analysis following 300 mg nirmatrelvir oral suspension administered at 0 hr enhanced with 100 mg ritonavir at -12 hours, 0 hours, 12 hours, and 24 hours.
f. Determined by ^{14}C analysis following 600 mg ^{14}C-ritonavir oral solution (6 times the approved ritonavir dose).

The predicted Day 5 nirmatrelvir exposure parameters in adult subjects with mild-to-moderate COVID-19 who were treated with PAXLOVID in EPIC-HR are presented in Table 3.

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Table 3: Predicted Day 5 Nirmatrelvir Exposure Parameters Following Administration of Nirmatrelvir/Ritonavir 300 mg/100 mg Twice Daily in Subjects with Mild-to-Moderate COVID-19

Pharmacokinetic Parameter (units)[a]	Nirmatrelvir[b]
C_{max} (µg/mL)	3.43 (2.59, 4.52)
AUC_{tau} (µg*hr/mL)[c]	30.4 (22.9, 39.8)
C_{min} (µg/mL)	1.57 (1.16, 2.10)

Abbreviations: C_{max}=predicted maximal concentration; C_{min}=predicted minimal concentration (C_{trough}).

a. Data presented as geometric mean (10^{th} and 90^{th} percentile).
b. Based on 1,016 subjects with their post hoc PK parameters.
c. AUC_{tau}=predicted area under the plasma concentration-time profile from time 0 to 12 hours for twice-daily dosing.

Effect of Food

No clinically significant differences in the pharmacokinetics of nirmatrelvir were observed following administration of a high fat meal (800-1000 calories; 50% fat) to healthy subjects.

Specific Populations

There were no clinically significant differences in the pharmacokinetics of nirmatrelvir based on age (18 to 86 years), sex, or race/ethnicity.

Pediatric Patients

The pharmacokinetics of nirmatrelvir/ritonavir in patients less than 18 years of age have not been established.

Patients with Renal Impairment

The pharmacokinetics of nirmatrelvir in patients with renal impairment following administration of a single oral dose of nirmatrelvir 100 mg (0.33 times the approved recommended dose) co-administered with ritonavir 100 mg are presented in Table 4. Compared to healthy controls with no renal impairment, the C_{max} and AUC of nirmatrelvir in patients with mild renal impairment was 30% and 24% higher, in patients with moderate renal impairment was 38% and 87% higher, and in patients with severe renal impairment was 48% and 204% higher, respectively.

Table 4: Impact of Renal Impairment on Nirmatrelvir/Ritonavir Pharmacokinetics

	Normal Renal Function (n=8)	Mild Renal Impairment (n=8)	Moderate Renal Impairment (n=8)	Severe Renal Impairment (n=8)
C_{max} (µg/mL)	1.60 (31)	2.08 (29)	2.21 (17)	2.37 (38)
AUC_{inf} (µg*hr/mL)	14.46 (20)	17.91 (30)	27.11 (27)	44.04 (33)
T_{max} (hr)	2.0 (1.0 - 4.0)	2.0 (1.0 – 3.0)	2.50 (1.0 – 6.0)	3.0 (1.0 - 6.1)
$T_{½}$ (hr)	7.73 ± 1.82	6.60 ± 1.53	9.95 ± 3.42	13.37 ± 3.32

Abbreviations: AUC_{inf}=area under the plasma concentration-time profile from time zero extrapolated to infinite time; C_{max}=the observed maximum concentration; CV=coefficient of variation; SD=standard deviation; $T_{½}$=terminal elimination half-life; T_{max}=the time to reach C_{max}.
Values are presented as geometric mean (geometric % CV) except median (range) for T_{max} and arithmetic mean ± SD for $T_{½}$.

Patients with Hepatic Impairment

The pharmacokinetics of nirmatrelvir were similar in patients with moderate (Child-Pugh Class B) hepatic impairment compared to healthy subjects following administration of a single oral dose of nirmatrelvir 100 mg (0.33 times the approved recommended dose) co-administered with ritonavir 100 mg. The impact of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of nirmatrelvir or ritonavir has not been studied.

Clinical Drug Interaction Studies

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Table 5 describes the effect of other drugs on the C_{max} and AUC of nirmatrelvir.

Table 5: The Effect of Other Drugs on the Pharmacokinetic Parameters of Nirmatrelvir

Co-administered Drug	Dose (Schedule)		N	Percent Ratio (in combination with co-administered drug/alone) of Nirmatrelvir Pharmacokinetic Parameters (90% CI); No Effect=100	
	Co-administered Drug	Nirmatrelvir/ Ritonavir		C_{max}	AUC[a]
Carbamazepine[b]	300 mg twice daily (16 doses)	300 mg/100 mg once daily (2 doses)	10	56.82 (47.04, 68.62)	44.50 (33.77, 58.65)
Itraconazole	200 mg once daily (8 doses)	300 mg/100 mg twice daily (5 doses)	11	118.57 (112.50, 124.97)	138.82 (129.25, 149.11)

Abbreviations: AUC=area under the plasma concentration-time curve; AUC_{inf}=area under the plasma concentration-time profile from time zero extrapolated to infinite time; AUC_{tau}=area under the plasma concentration-time profile from time zero to time tau (τ), the dosing interval. CI=confidence interval; C_{max}=observed maximum plasma concentrations.

a. For carbamazepine, AUC=AUC_{inf}; for itraconazole, AUC=AUC_{tau}.

b. Carbamazepine titrated up to 300 mg twice daily on Day 8 through Day 15 (e.g., 100 mg twice daily on Day 1 through Day 3 and 200 mg twice daily on Day 4 through Day 7).

Table 6 describes the effect of nirmatrelvir/ritonavir on the C_{max} and AUC of other drugs.

Table 6: Effect of Nirmatrelvir/Ritonavir on Pharmacokinetics of Other Drugs

Co-administered Drug	Dose (Schedule)		N	Percent Ratio of Test/Reference of Geometric Means (90% CI); No Effect=100	
	Co-administered Drug	Nirmatrelvir/ Ritonavir		C_{max}	AUC[a]
Midazolam[b]	2 mg (1 dose)	300 mg/100 mg twice daily (9 doses)	10	368.33 (318.91, 425.41)	1430.02 (1204.54, 1697.71)
Dabigatran[b]	75 mg (1 dose)	300 mg/100 mg twice daily (4 doses)[b]	24	233.06 (172.14, 315.54)	194.47 (155.29, 243.55)

Abbreviations: AUC=area under the plasma concentration-time curve; CI=confidence interval; C_{max}=observed maximum plasma concentrations; P-gp=p-glycoprotein.

a. AUC=AUC_{inf} for both midazolam and dabigatran.

b. For midazolam, Test=nirmatrelvir/ritonavir plus midazolam, Reference=Midazolam. Midazolam is an index substrate for CYP3A. For dabigatran, Test=nirmatrelvir/ritonavir plus dabigatran, Reference=Dabigatran. Dabigatran is an index substrate for P-gp.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes:

- Nirmatrelvir is a reversible and time-dependent inhibitor of CYP3A, but not an inhibitor CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Nirmatrelvir is an inducer of CYP2B6, 2C8, 2C9, and 3A4, but there is minimal risk for pharmacokinetic interactions arising from induction of these CYP enzymes at the proposed therapeutic dose.
- Ritonavir is a substrate of CYP2D6 and CYP3A. Ritonavir is an inducer of CYP1A2, CYP2C9, CYP2C19, CYP2B6, and CYP3A.

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Transporter Systems: Nirmatrelvir is an inhibitor of P-gp and OATP1B1. Nirmatrelvir is a substrate for P-gp, but not BCRP, MATE1, MATE2K, NTCP, OAT1, OAT2, OAT3, OCT1, OCT2, PEPT1, OATP1B1, OATP1B3, OATP2B1, or OATP4C1.

12.4 Microbiology

Mechanism of Action

Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (M^{pro}), also referred to as 3C-like protease ($3CL^{pro}$) or nonstructural protein 5 (nsp5) protease. Inhibition of SARS-CoV-2 M^{pro} renders it incapable of processing the viral polyproteins pp1a and pp1ab, preventing viral replication. Nirmatrelvir inhibited the activity of recombinant SARS-CoV-2 M^{pro} in a biochemical assay with a K_i value of 3.1 nM and an IC_{50} value of 19.2 nM. Nirmatrelvir was found to bind directly to the SARS-CoV-2 M^{pro} active site by X-ray crystallography.

Antiviral Activity

Cell Culture Antiviral Activity
Nirmatrelvir exhibited antiviral activity against SARS-CoV-2 (USA-WA1/2020 isolate) infection of differentiated normal human bronchial epithelial (dNHBE) cells with EC_{50} and EC_{90} values of 62 nM (31 ng/mL) and 181 nM (90 ng/mL), respectively, after 3 days of drug exposure.

The antiviral activity of nirmatrelvir against the Omicron sub-variants BA.2, BA.2.12.1, BA.4, BA.4.6, BA.5, BF.7, BQ.1, BQ.1.11, and XBB.1.5 was assessed in Vero E6-TMPRSS2 cells in the presence of a P-gp inhibitor. Nirmatrelvir had a median EC_{50} value of 83 nM (range: 39-146 nM) against the Omicron sub-variants, reflecting EC_{50} value fold-changes ≤1.5 relative to the USA-WA1/2020 isolate.

In addition, the antiviral activity of nirmatrelvir against the SARS-CoV-2 Alpha, Beta, Gamma, Delta, Lambda, Mu, and Omicron BA.1 variants was assessed in Vero E6 P-gp knockout cells. Nirmatrelvir had a median EC_{50} value of 25 nM (range: 16-141 nM). The Beta variant was the least susceptible variant tested, with an EC_{50} value fold-change of 3.7 relative to USA-WA1/2020. The other variants had EC_{50} value fold-changes ≤1.1 relative to USA-WA1/2020.

Clinical Antiviral Activity
In clinical trial EPIC-HR, which enrolled subjects who were primarily infected with the SARS-CoV-2 Delta variant, PAXLOVID treatment was associated with a 0.83 log_{10} copies/mL greater median decline in viral RNA shedding levels in nasopharyngeal samples through Day 5 (mITT1 analysis set, all treated subjects with onset of symptoms ≤5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment); similar results were observed in the mITT2 analysis set (all treated subjects with onset of symptoms ≤5 days). In the EPIC-SR trial, which included subjects who were infected with SARS-CoV-2 Delta (79%) or Omicron (19%) variants, PAXLOVID treatment was associated with a 1.05 log_{10} copies/mL greater median decline in viral RNA shedding levels in nasopharyngeal samples through Day 5, with similar declines observed in subjects infected with Delta or Omicron variants. The degree of reduction in viral RNA levels relative to placebo following 5 days of PAXLOVID treatment was similar between unvaccinated high-risk subjects in EPIC-HR and vaccinated high-risk subjects in EPIC-SR.

Antiviral Resistance

In Cell Culture and Biochemical Assays
SARS-CoV-2 M^{pro} residues potentially associated with nirmatrelvir resistance have been identified using a variety of methods, including SARS-CoV-2 resistance selection, testing of recombinant SARS-CoV-2 viruses

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with M^{pro} substitutions, and biochemical assays with recombinant SARS-CoV-2 M^{pro} containing amino acid substitutions. Table 7 indicates M^{pro} substitutions and combinations of M^{pro} substitutions that have been observed in nirmatrelvir-selected SARS-CoV-2 in cell culture. Individual M^{pro} substitutions are listed regardless of whether they occurred alone or in combination with other M^{pro} substitutions. Note that the M^{pro} S301P and T304I substitutions overlap the P6 and P3 positions of the nsp5/nsp6 cleavage site located at the C-terminus of M^{pro}. Substitutions at other M^{pro} cleavage sites have not been associated with nirmatrelvir resistance in cell culture. The clinical significance of these substitutions is unknown.

Table 7: SARS-CoV-2 M^{pro} Amino Acid Substitutions Selected by Nirmatrelvir in Cell Culture

Single Substitutions (EC_{50} value fold change)	T21I (1.1-4.6), L50F (1.5-4.2), P108S (ND), T135I (ND), F140L (4.1), S144A (2.2-5.3), C160F (ND), E166A (3.3), E166V (25-288), L167F (ND), T169I (ND), H172Y (ND), A173V (0.9-1.7), V186A (ND), R188G (ND), A191V (ND), A193P (ND), P252L (5.9), S301P (ND), and T304I (1.4-5.5).
≥2 Substitutions (EC_{50} value fold change)	T21I+S144A (9.4), T21I+E166V (83), T21I+A173V (3.1), T21I+T304I (3.0-7.9), L50F+E166V (34-175), L50F+T304I (5.9), T135I+T304I (3.8), F140L+A173V (10.1), H172Y+P252L (ND), A173V+T304I (20.2), T21I+L50F+A193P+S301P (28.8), T21I+S144A+T304I (27.8), T21I+C160F+A173V+V186A+T304I (28.5), T21I+A173V+T304I (15), and L50F+F140L+L167F+T304I (54.7).

Abbreviation: ND=no data.

In a biochemical assay using recombinant SARS-CoV-2 M^{pro} containing amino acid substitutions, the following SARS-CoV-2 M^{pro} substitutions led to ≥3-fold reduced nirmatrelvir activity (fold-change based on K_i values): Y54A (25), F140A (21), F140L (7.6), F140S (260), G143S (3.6), S144A (46), S144E (480), S144T (170), H164N (6.7), E166A (35), E166G (6.2), E166V (7,700), H172Y (250), A173S (4.1), A173V (16), R188G (38), Q192L (29), Q192P (7.8), and V297A (3.0). In addition, the following combinations of M^{pro} substitutions led to ≥3-fold reduced nirmatrelvir activity: T21I+S144A (20), T21I+E166V (11,000), T21I+A173V (15), L50F+E166V (4,500), T135I+T304I (5.1), F140L+A173V (95), H172Y+P252L (180), A173V+T304I (28), T21I+S144A+T304I (51), T21I+A173V+T304I (55), L50F+E166A+L167F (210), T21I+L50F+A193P+S301P (7.3), L50F+F140L+L167F+T304I (190), and T21I+C160F+A173V+V186A+T304I (28). The following substitutions and substitution combinations emerged in cell culture but conferred <3-fold reduced nirmatrelvir activity in biochemical assays: T21I (1.6), L50F (0.2), P108S (2.9), T135I (2.2), C160F (0.6), L167F (0.9), T169I (1.4), V186A (0.8), A191V (0.8), A193P (0.9), P252L (0.9), S301P (0.2), T304I (1.0), T21I+T304I (1.8), and L50F+T304I (1.3). The clinical significance of these substitutions is unknown.

In Clinical Trials

Treatment-emergent substitutions were evaluated among subjects in clinical trials EPIC-HR/SR with sequence data available at both baseline and a post-baseline visit (n=907 PAXLOVID-treated subjects, n=946 placebo-treated subjects). SARS-CoV-2 M^{pro} amino acid changes were classified as PAXLOVID treatment-emergent substitutions if they occurred at the same amino acid position in 3 or more PAXLOVID-treated subjects and were ≥2.5-fold more common in PAXLOVID-treated subjects than placebo-treated subjects. The following PAXLOVID treatment-emergent M^{pro} substitutions were observed: T98I/R/del(n=4), E166V (n=3), and W207L/R/del (n=4). Within the M^{pro} cleavage sites, the following PAXLOVID treatment-emergent substitutions were observed: A5328S/V(n=7) and S6799A/P/Y (n=4). These cleavage site substitutions were not associated with the co-occurrence of any specific M^{pro} substitutions.

None of the treatment-emergent substitutions listed above in M^{pro} or M^{pro} cleavage sites occurred in PAXLOVID-treated subjects who experienced hospitalization. Thus, the clinical significance of these substitutions is unknown.

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Viral RNA Rebound (With and Without COVID-19 Symptoms) and Treatment-Emergent Substitutions

EPIC-HR and EPIC-SR were not designed to evaluate COVID-19 rebound; exploratory analyses were conducted to assess the relationship between PAXLOVID use and rebound in viral RNA shedding levels or self-reported COVID-19 symptoms.

Post-treatment increases in SARS-CoV-2 RNA shedding levels in nasopharyngeal samples were observed on Day 10 and/or Day 14 in a subset of PAXLOVID and placebo recipients in EPIC-HR and EPIC-SR, irrespective of COVID-19 symptoms. The frequency of detection of post-treatment viral RNA rebound varied according to analysis parameters, but was generally similar among PAXLOVID and placebo recipients. A similar or smaller percentage of placebo recipients compared to PAXLOVID recipients had nasopharyngeal viral RNA results < lower limit of quantitation (LLOQ) at all study timepoints in both the treatment and post-treatment periods.

In EPIC-HR, of 59 PAXLOVID-treated subjects identified with post-treatment viral RNA rebound and with available viral sequence data, treatment-emergent substitutions in M^{pro} potentially reducing nirmatrelvir activity were detected in 2 (3%) subjects, including E166V in 1 subject and T304I in 1 subject. Both subjects had viral RNA shedding levels <LLOQ by Day 14.

Post-treatment viral RNA rebound was not associated with the primary clinical outcome of COVID-19 related hospitalization or death from any cause through Day 28 following the single 5-day course of PAXLOVID treatment. The clinical relevance of post-treatment increases in viral RNA following PAXLOVID or placebo treatment is unknown.

The frequency of symptom rebound through Day 28, irrespective of viral RNA results, was similar among PAXLOVID and placebo recipients. The frequency of combined viral RNA rebound plus symptom rebound could not be fully assessed as most episodes of symptom rebound occurred after Day 14 (the last day SARS-CoV-2 RNA levels were routinely assessed).

Cross-Resistance

Cross-resistance is not expected between nirmatrelvir and remdesivir or any other anti-SARS-CoV-2 agents with different mechanisms of action (i.e., agents that are not M^{pro} inhibitors).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Nirmatrelvir

Carcinogenicity studies have not been conducted with nirmatrelvir.

Nirmatrelvir was negative for mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the *in vitro* micronucleus assay using human lymphoblastoid TK6 cells, and the *in vivo* rat micronucleus assays.

In a fertility and early embryonic development study, nirmatrelvir was administered orally to male and female rats at doses of 60, 200, or 1,000 mg/kg/day once daily beginning 14 days prior to mating, throughout the mating phase, and continued through GD 6 for females and for a total of 32 doses for males. There were no effects on fertility, reproductive performance, or early embryonic development at doses up to 1,000 mg/kg/day, resulting in systemic exposure (AUC_{24}) approximately 5 times higher than exposure at the approved human dose of PAXLOVID.

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Ritonavir

Carcinogenicity studies in mice and rats have been conducted on ritonavir. In male mice, at levels of 50, 100, or 200 mg/kg/day, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 25 times higher than the exposure in humans at the approved human dose of PAXLOVID. No carcinogenic effects were observed in females at up to the highest dose tested, resulting in systemic exposure (AUC_{24}) approximately 25 times higher than the exposure in humans at the approved human dose of PAXLOVID. In rats dosed at levels of 7, 15, or 30 mg/kg/day, there were no carcinogenic effects. In this study, the exposure at the high dose was approximately 5 times higher than the exposure in humans at the approved human dose of PAXLOVID.

Ritonavir was found to be negative for mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Ritonavir produced no effects on fertility in rats at drug exposures approximately 18 (male) and 27 (female) times higher than the exposure in humans at the approved human dose of PAXLOVID.

14 CLINICAL STUDIES

14.1 Efficacy in Subjects at High Risk of Progression to Severe COVID-19 (EPIC-HR)

EPIC-HR (NCT04960202) was a Phase 2/3, randomized, double-blind, placebo-controlled trial in non-hospitalized symptomatic adult subjects with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Eligible subjects were 18 years of age and older with at least 1 of the following risk factors for progression to severe disease: diabetes, overweight (BMI >25), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease, hypertension, sickle cell disease, neurodevelopmental disorders, active cancer, medically-related technological dependence, or were 60 years of age and older regardless of comorbidities. Subjects with COVID-19 symptom onset of ≤5 days were included in the study. Subjects were randomized (1:1) to receive PAXLOVID (nirmatrelvir/ritonavir 300 mg/100 mg) or placebo orally every 12 hours for 5 days. The trial excluded individuals with a history of prior COVID-19 infection or vaccination and excluded individuals taking any medications with clinically significant drug interactions with PAXLOVID. The primary efficacy endpoint was the proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28. The analysis was conducted in the modified intent-to-treat (mITT) analysis set [all treated subjects with onset of symptoms ≤3 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic monoclonal antibody (mAb) treatment], the mITT1 analysis set (all treated subjects with onset of symptoms ≤5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment), and the mITT2 analysis set (all treated subjects with onset of symptoms ≤5 days).

A total of 2,113 subjects were randomized to receive either PAXLOVID or placebo. At baseline, mean age was 45 years; 51% were male; 71% were White, 15% were Asian, 9% were American Indian or Alaska Native, 4% were Black or African American, and 1% was missing or unknown; 41% were Hispanic or Latino; 67% of subjects had onset of symptoms ≤3 days before initiation of study treatment; 49% of subjects were serological negative at baseline; the mean (SD) baseline viral RNA in nasopharyngeal samples was 4.71 $\log_{10}$ copies/mL (2.89); 27% of subjects had a baseline viral RNA of ≥10^7 ($\log_{10}$ copies/mL); 6% of subjects either received or were expected to receive COVID-19 therapeutic monoclonal antibody treatment at the time of randomization and were excluded from the mITT and mITT1 analyses.

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The baseline demographic and disease characteristics were balanced between the PAXLOVID and placebo groups.

The proportions of subjects who discontinued treatment due to an adverse event were 2.0% in the PAXLOVID group and 4.2% in the placebo group.

Table 8 provides results of the primary endpoint in mITT1 analysis population. For the primary endpoint, the relative risk reduction in the mITT1 analysis population for PAXLOVID compared to placebo was 86% (95% CI: 72%, 93%).

Table 8: COVID-19 Related Hospitalization or Death from Any Cause Through Day 28 in Non-Hospitalized Adults with COVID-19 (mITT1 Analysis Set): EPIC-HR

	PAXLOVID (**N**=977)	**Placebo** (**N**=989)
COVID-19 Related Hospitalization or Death from Any Cause Through Day 28		
n (%)	9 (0.9%)	64 (6.5%)
Reduction Relative to Placebo[a] (95% CI), %	-5.6 (-7.3, -4.0)	
COVID-19 Related Hospitalization Through Day 28, %	9 (0.9%)	63 (6.4%)
All-cause Mortality Through Day 28[b], %	0	12 (1.2%)

Abbreviations: CI=confidence interval; COVID-19=coronavirus disease 2019; mAb=monoclonal antibody; mITT1=modified intent-to-treat 1 (all treated subjects with onset of symptoms ≤5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment).

The determination of primary efficacy was based on a planned interim analysis of 754 subjects in mITT population. The estimated risk reduction was -6.5% with a 95% CI of (-9.3%, -3.7%) and 2-sided p-value <0.0001.

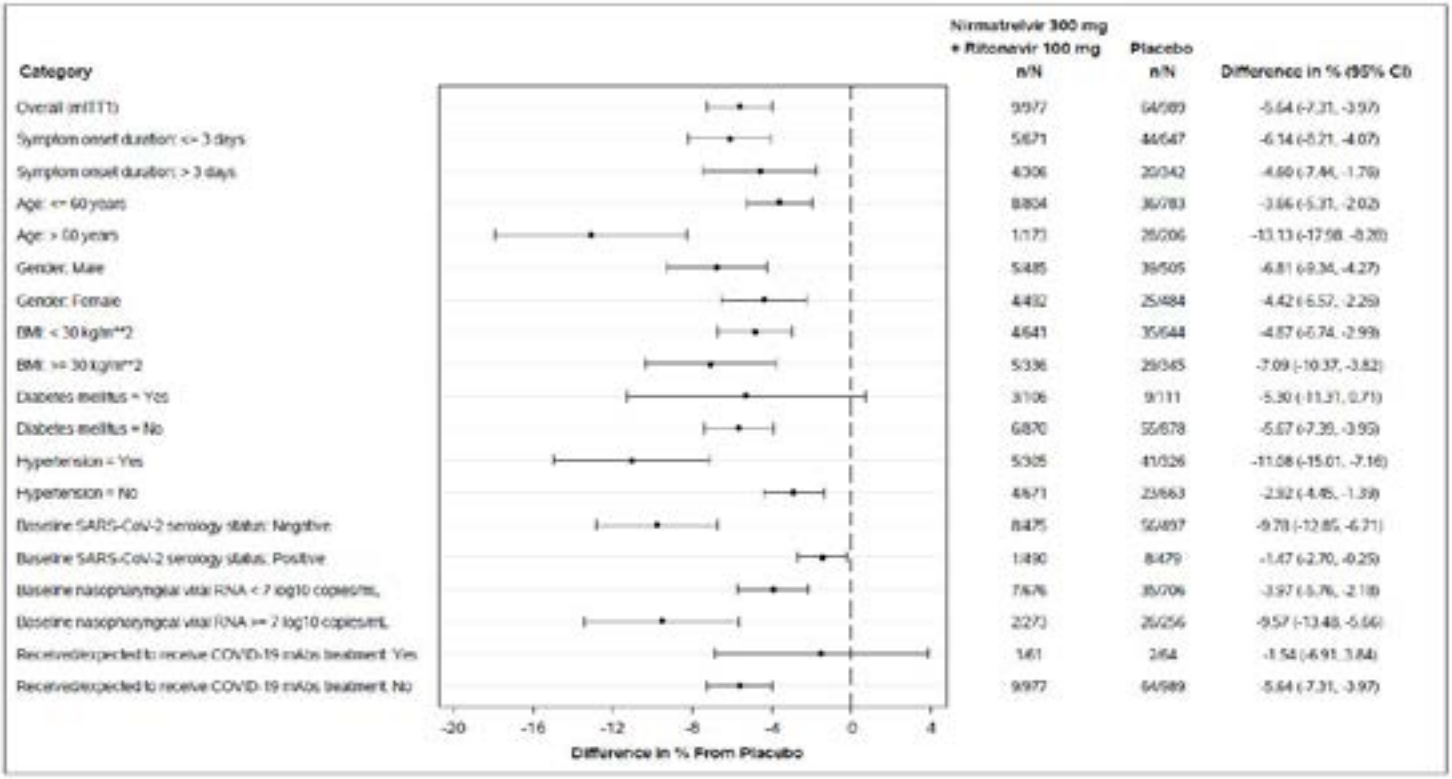
a. The estimated cumulative proportion of subjects hospitalized or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.

b. For the secondary endpoint of all-cause mortality through Week 24, there were 0 and 15 (1%) events in the PAXLOVID arm and placebo arm, respectively.

Consistent results were observed in the mITT and mITT2 analysis populations.

Similar trends have been observed across subgroups of subjects *(see Figure 1)*.

Figure 1: Subgroup Analysis of Adults with COVID-19 Dosed within 5 Days of Symptom Onset with COVID-19 Related Hospitalization or Death from Any Cause Through Day 28: EPIC-HR



Abbreviations: BMI=body mass index; COVID-19=coronavirus disease 2019; mAb=monoclonal antibody; mITT=modified intent-to-treat; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.
N=number of subjects in the category of the analysis set.
All categories are based on mITT1 population except for COVID-19 mAb treatment which is based on mITT2 population.
Seropositivity was defined if results were positive in either Elecsys anti-SARS-CoV-2 S or Elecsys anti-SARS-CoV-2 (N) assay.
The difference of the proportions in the 2 treatment groups and its 95% confidence interval based on normal approximation of the data are presented.

Among subjects who were SARS-CoV-2 seropositive at baseline, 1/490 (0.2%) PAXLOVID recipients versus 8/479 (1.7%) placebo recipients met the primary endpoint of COVID-19 related hospitalization or death from any cause through Day 28 [reduction relative to placebo -1.47% (-2.70%, -0.25%)].

14.2 Trial in Unvaccinated Subjects Without a Risk Factor for Progression to Severe COVID-19 or Subjects Fully Vaccinated Against COVID-19 With at Least One Factor for Progression to Severe COVID-19 (EPIC-SR)

PAXLOVID is not indicated for the treatment of COVID-19 in patients without a risk factor for progression to severe COVID-19.

EPIC-SR (NCT05011513) was a Phase 2/3, randomized, double-blind, placebo-controlled trial in non-hospitalized symptomatic adult subjects with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Eligible subjects were 18 years of age or older with COVID-19 symptom onset of ≤5 days who were at standard risk for progression to severe disease. The trial included previously unvaccinated subjects with no risk factors for progression to severe disease or subjects fully vaccinated against COVID-19 (i.e., completed a primary vaccination series) with at least 1 of the risk factors for progression to severe disease as defined in EPIC-HR. Through the December 19, 2021, data cutoff, a total of 1,075 subjects were randomized (1:1) to receive PAXLOVID or placebo orally every 12 hours for 5 days; of these, 59% were fully vaccinated high-risk subjects.

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The primary endpoint in this trial, the difference in time to sustained alleviation of all targeted COVID-19 signs and symptoms through Day 28 among PAXLOVID versus placebo recipients, was not met.

In an exploratory analysis of the subgroup of fully vaccinated subjects with at least 1 risk factor for progression to severe disease, a non-statistically significant numerical reduction relative to placebo for the secondary endpoint of COVID-19 related hospitalization or death from any cause through Day 28 was observed.

14.3 Post-Exposure Prophylaxis Trial

PAXLOVID is not indicated for the post-exposure prophylaxis of COVID-19.

In a double-blind, double-dummy, placebo-controlled trial, the efficacy of PAXLOVID when administered for 5 or 10 days as post-exposure prophylaxis of COVID-19 was evaluated. Eligible subjects were asymptomatic adults 18 years of age and older who were SARS-CoV-2 negative at baseline and who lived in the same household with symptomatic individuals with a recent diagnosis of SARS-CoV-2. A total of 2,736 subjects were randomized (1:1:1) to receive PAXLOVID orally every 12 hours for 5 days, PAXLOVID orally every 12 hours for 10 days, or placebo.

The primary endpoint for this trial was not met. The primary endpoint was the risk reduction between the 5-day and 10-day PAXLOVID regimens versus placebo in the proportion of subjects who developed RT-PCR or RAT-confirmed symptomatic SARS-CoV-2 infection through Day 14 who had a negative SARS-CoV-2 RT-PCR result at baseline. The proportion of subjects who had events through Day 14 was 2.6% for the 5-day PAXLOVID regimen, 2.4% for the 10-day PAXLOVID regimen, and 3.9% for placebo. There was not a statistically significant risk reduction versus placebo for either the 5-day or 10-day PAXLOVID regimen.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. It is supplied in two different Dose Packs.

Nirmatrelvir tablets and ritonavir tablets are supplied in separate blister cavities within the same child-resistant blister card.

Dose Pack	Content	NDC	Description
300 mg nirmatrelvir; 100 mg ritonavir	**Each Carton Contains:** 30 tablets divided in 10 blister cards	0069-5001-30	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Ritonavir tablets: White film-coated ovaloid tablets debossed with the “a” logo and the code NK.
		Or	
		0069-5045-30	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side.

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Dose Pack	Content	NDC	Description
			Ritonavir tablets: White to off-white, capsule-shaped, film-coated tablets debossed with “H” on one side and “R9” on the other side.
		Or	
		0069-5321-30	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Ritonavir tablets: White film-coated ovaloid tablets debossed with “NK” on one side.
	Each Blister Card Contains: 2 nirmatrelvir tablets (150 mg each) and 1 ritonavir tablet (100 mg)	0069-5001-06	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Ritonavir tablets: White film-coated ovaloid tablets debossed with the “a” logo and the code NK.
		Or	
		0069-5045-06	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Ritonavir tablets: White to off-white, capsule-shaped, film-coated tablets debossed with “H” on one side and “R9” on the other side.
		Or	
		0069-5321-03	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Ritonavir tablets: White film-coated ovaloid tablets debossed with “NK” on one side.
150 mg nirmatrelvir; 100 mg ritonavir	**Each Carton Contains:** 20 tablets divided in 10 blister cards	0069-5017-20	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Ritonavir tablets: White film-coated ovaloid tablets debossed with the “a” logo and the code NK.
		Or	

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Dose Pack	Content	NDC	Description
		0069-5317-20	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Ritonavir tablets: White film-coated ovaloid tablets debossed with "NK" on one side.
	Each Blister Card Contains: 1 nirmatrelvir tablet (150 mg) and 1 ritonavir tablet (100 mg)	0069-5017-04	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Ritonavir tablets: White film-coated ovaloid tablets debossed with the "a" logo and the code NK.
		Or	
		0069-5317-02	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Ritonavir tablets: White film-coated ovaloid tablets debossed with "NK" on one side.

Storage and Handling

Store at USP controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Drug Interactions

Inform patients that PAXLOVID may interact with certain drugs and is contraindicated for use with certain drugs; therefore, advise patients to report to their healthcare provider the use of any prescription, non-prescription medication, or herbal products *[see Boxed Warning, Contraindications (4), Warnings and Precautions (5.1), and Drug Interactions (7)]*.

Hypersensitivity Reactions

Inform patients that anaphylaxis, serious skin reactions, and other hypersensitivity reactions have been reported, even following a single dose of PAXLOVID. Advise them to immediately discontinue the drug and to inform their healthcare provider at the first sign of a skin rash, hives or other skin reactions, difficulty in swallowing or breathing, any swelling suggesting angioedema (for example, swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction *[see Warnings and Precautions (5.2)]*.

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Dosage Modification in Patients with Moderate Renal Impairment

To ensure appropriate dosing in patients with moderate renal impairment, instruct such patients that they will be taking one 150 mg nirmatrelvir tablet with one 100 mg ritonavir tablet together twice daily for 5 days *[see Dosage and Administration (2.3)]*.

Administration Instructions

Inform patients to take PAXLOVID with or without food as instructed. Advise patients to swallow all tablets for PAXLOVID whole and not to chew, break, or crush the tablets. Alert the patient of the importance of completing the full 5-day treatment course and to continuing isolation in accordance with public health recommendations to maximize viral clearance and minimize transmission of SARS-CoV-2. If the patient misses a dose of PAXLOVID within 8 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 8 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose *[see Dosage and Administration (2)]*.

This product's labeling may have been updated. For the most recent prescribing information, please visit www.pfizer.com. For Medical Information about PAXLOVID, please visit www.pfizermedinfo.com or call 1-800-438-1985.

LAB-1523-0.12a

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PATIENT INFORMATION
PAXLOVID (pax-LO-vid)
(nirmatrelvir tablets; ritonavir tablets)
co-packaged for oral use

What is the most important information I should know about PAXLOVID?

PAXLOVID can interact with other medicines causing severe or life-threatening side effects or death. It is important to know the medicines that should not be taken with PAXLOVID.

Do not take PAXLOVID if:

- you are taking any of the following medicines:
  - alfuzosin
  - amiodarone
  - apalutamide
  - carbamazepine
  - colchicine
  - dihydroergotamine
  - dronedarone
  - eletriptan
  - eplerenone
  - ergotamine
  - finerenone
  - flecainide
  - flibanserin
  - ivabradine
  - lomitapide
  - lovastatin
  - lumacaftor/ivacaftor
  - lurasidone
  - methylergonovine
  - midazolam (oral)
  - naloxegol
  - phenobarbital
  - phenytoin
  - pimozide
  - primidone
  - propafenone
  - quinidine
  - ranolazine
  - rifampin
  - rifapentine
  - St. John's Wort (*hypericum perforatum*)
  - sildenafil (Revatio®) for pulmonary arterial hypertension
  - silodosin
  - simvastatin
  - tolvaptan
  - triazolam
  - ubrogepant
  - voclosporin

These are not the only medicines that may cause serious or life-threatening side effects if taken with PAXLOVID. PAXLOVID may increase or decrease the levels of multiple other medicines. It is very important to tell your healthcare provider about all of the medicines you are taking because additional laboratory tests or changes in the dose of your other medicines may be necessary during treatment with PAXLOVID. Your healthcare provider may also tell you about specific symptoms to watch out for that may indicate that you need to stop or decrease the dose of some of your other medicines.

- you are allergic to nirmatrelvir, ritonavir, or any of the ingredients in PAXLOVID. See the end of this leaflet for a complete list of ingredients in PAXLOVID. See **"What are the possible side effects of PAXLOVID?"** for signs and symptoms of allergic reactions.

What is PAXLOVID?

PAXLOVID is a prescription medicine used to treat mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.
PAXLOVID is not approved for use as pre-exposure or post-exposure treatment for prevention of COVID-19.

Before taking PAXLOVID, tell your healthcare provider about all of your medical conditions, including if you:

- have kidney problems. You may need a different dose of PAXLOVID.
- have liver problems, including hepatitis.
- have Human Immunodeficiency Virus 1 (HIV-1) infection. PAXLOVID may lead to some HIV-1 medicines not working as well in the future.
- are pregnant or plan to become pregnant. It is not known if PAXLOVID can harm your unborn baby. Tell your healthcare provider right away if you are or if you become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if PAXLOVID can pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with PAXLOVID.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

- Your healthcare provider can tell you if it is safe to take PAXLOVID with other medicines.
- You can ask your healthcare provider or pharmacist for a list of medicines that interact with PAXLOVID.
- Do not start taking a new medicine without telling your healthcare provider.

Tell your healthcare provider if you are taking combined birth control (hormonal contraceptive). PAXLOVID may affect how your hormonal contraceptives work. Females who are able to become pregnant should use another effective alternative form of contraception or an additional barrier method of contraception during treatment with PAXLOVID. Talk to your healthcare provider if you have any questions about contraceptive methods that might be right for you.

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How should I take PAXLOVID?

- Take PAXLOVID exactly as your healthcare provider tells you to take it.
- **PAXLOVID consists of 2 medicines: nirmatrelvir tablets and ritonavir tablets. The 2 medicines are taken together 2 times each day for 5 days.**
  - Nirmatrelvir is an oval, pink tablet.
  - Ritonavir is a white or off-white tablet.
- PAXLOVID is available in 2 Dose Packs (see **Figures A and B** below). Your healthcare provider will prescribe the PAXLOVID Dose Pack that is right for you.
- **If you have kidney disease, your healthcare provider may prescribe a lower dose (see Figure B). Talk to your healthcare provider to make sure you receive the correct Dose Pack.**

Figure A

If you are prescribed PAXLOVID 300 mg; 100 mg Dose Pack: each dose contains 3 tablets

How to take PAXLOVID 300 mg; 100 mg Dose Pack

Take the 2 pink nirmatrelvir tablets and
1 white to off-white ritonavir tablet together
2 times a day (in morning and at bedtime).

Figure B

If you are prescribed PAXLOVID 150 mg; 100 mg Dose Pack: each dose contains 2 tablets

How to take PAXLOVID 150 mg; 100 mg Dose Pack

Take the 1 pink nirmatrelvir tablet and
1 white to off-white ritonavir tablet together
2 times a day (in morning and at bedtime).

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- Do not remove your PAXLOVID tablets from the blister card before you are ready to take your dose.
  - Take your first dose of PAXLOVID in the morning or at bedtime, depending on when you pick up your prescription, or as your healthcare provider tells you to.
  - **Take all tablets from your blister card at the same time as one dose.**
- Swallow the tablets whole. Do not chew, break, or crush the tablets.
- Take PAXLOVID with or without food.
- Do not stop taking PAXLOVID without talking to your healthcare provider, even if you feel better.
- If you miss a dose of PAXLOVID within 8 hours of the time it is usually taken, take it as soon as you remember. If you miss a dose by more than 8 hours, skip the missed dose and take the next dose at your regular time. Do not take 2 doses of PAXLOVID at the same time.
- If you take too much PAXLOVID, call your healthcare provider or go to the nearest hospital emergency room right away.
- If you are taking a ritonavir- or cobicistat-containing medicine to treat hepatitis C or HIV-1 infection, you should continue to take your medicine as prescribed by your healthcare provider.

Talk to your healthcare provider if you do not feel better or if you feel worse after 5 days.

What are the possible side effects of PAXLOVID?

PAXLOVID may cause serious side effects, including:

- **Allergic reactions, including severe allergic reactions (anaphylaxis) have** happened during treatment with PAXLOVID. Stop taking PAXLOVID and get medical help right away if you get any of the following symptoms of an allergic reaction:
  - skin rash, hives, blisters or peeling skin
  - painful sores or ulcers in the mouth, nose, throat or genital area
  - swelling of the mouth, lips, tongue or face
  - trouble swallowing or breathing
  - throat tightness
  - hoarseness
- **Liver problems**. Tell your healthcare provider right away if you get any of the following signs and symptoms of liver problems during treatment with PAXLOVID:
  - loss of appetite
  - yellowing of your skin and the white of eyes
  - dark-colored urine
  - pale colored stools
  - itchy skin
  - stomach-area (abdominal) pain

The most common side effects of PAXLOVID include: altered sense of taste and diarrhea.

Other possible side effects include:

- headache
- vomiting
- abdominal pain
- nausea
- high blood pressure
- feeling generally unwell

These are not all of the possible side effects of PAXLOVID. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store PAXLOVID?

- Store PAXLOVID at room temperature between 68°F to 77°F (20°C to 25°C).

Keep PAXLOVID and all medicines out of the reach of children.

General information about the safe and effective use of PAXLOVID.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use PAXLOVID for a condition for which it was not prescribed. Do not give PAXLOVID to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for more information about PAXLOVID that is written for health professionals.

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What are the ingredients in PAXLOVID?

Active ingredient: nirmatrelvir and ritonavir

Nirmatrelvir inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, and sodium stearyl fumarate. Film-coating contains: hydroxy propyl methylcellulose, iron oxide red, polyethylene glycol, and titanium dioxide.

Ritonavir inactive ingredients: anhydrous dibasic calcium phosphate, colloidal silicon dioxide, copovidone, sodium stearyl fumarate, and sorbitan monolaurate. The film coating may contain: colloidal anhydrous silica, colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, polyethylene glycol, polysorbate 80, talc, and titanium dioxide.

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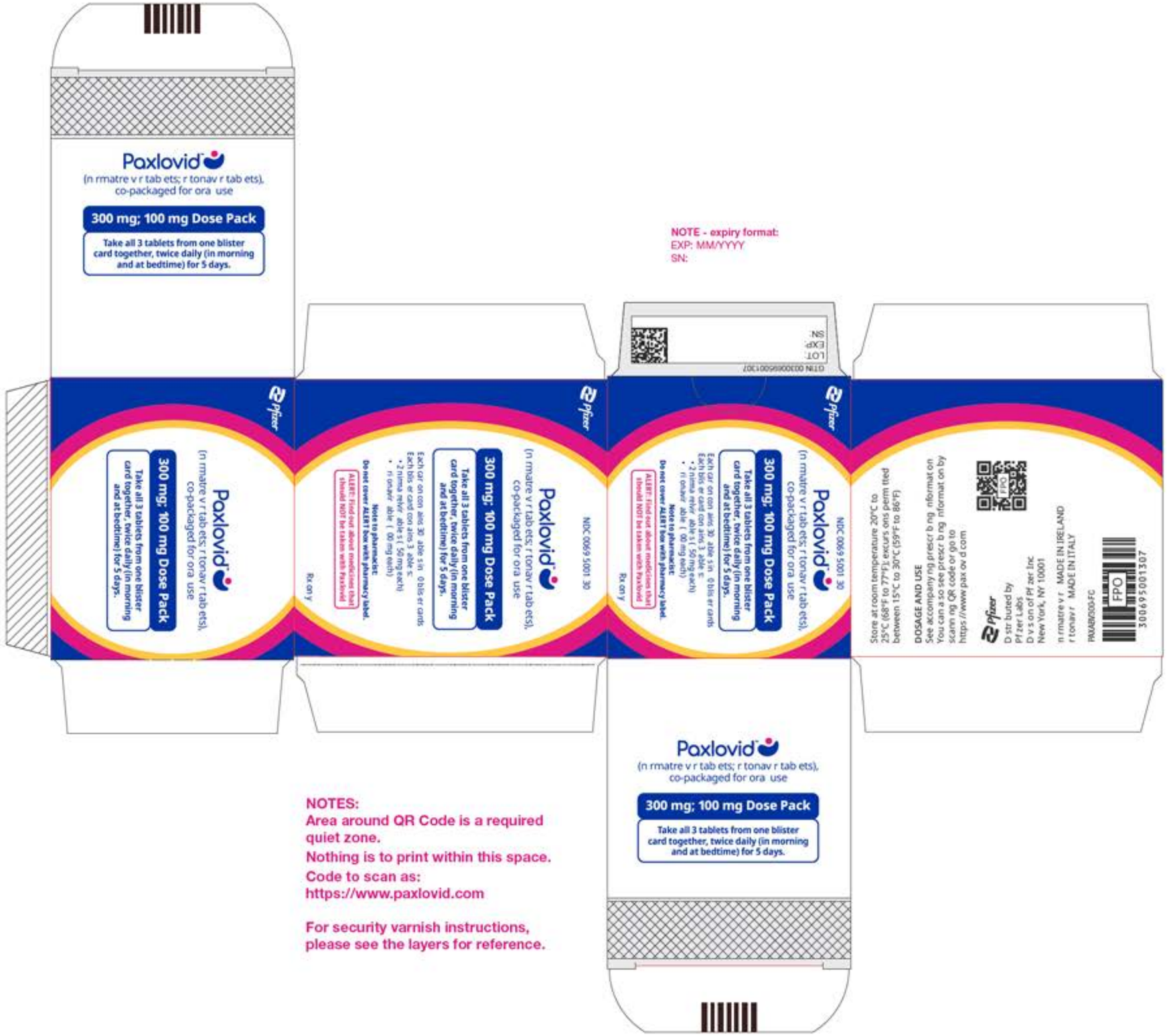

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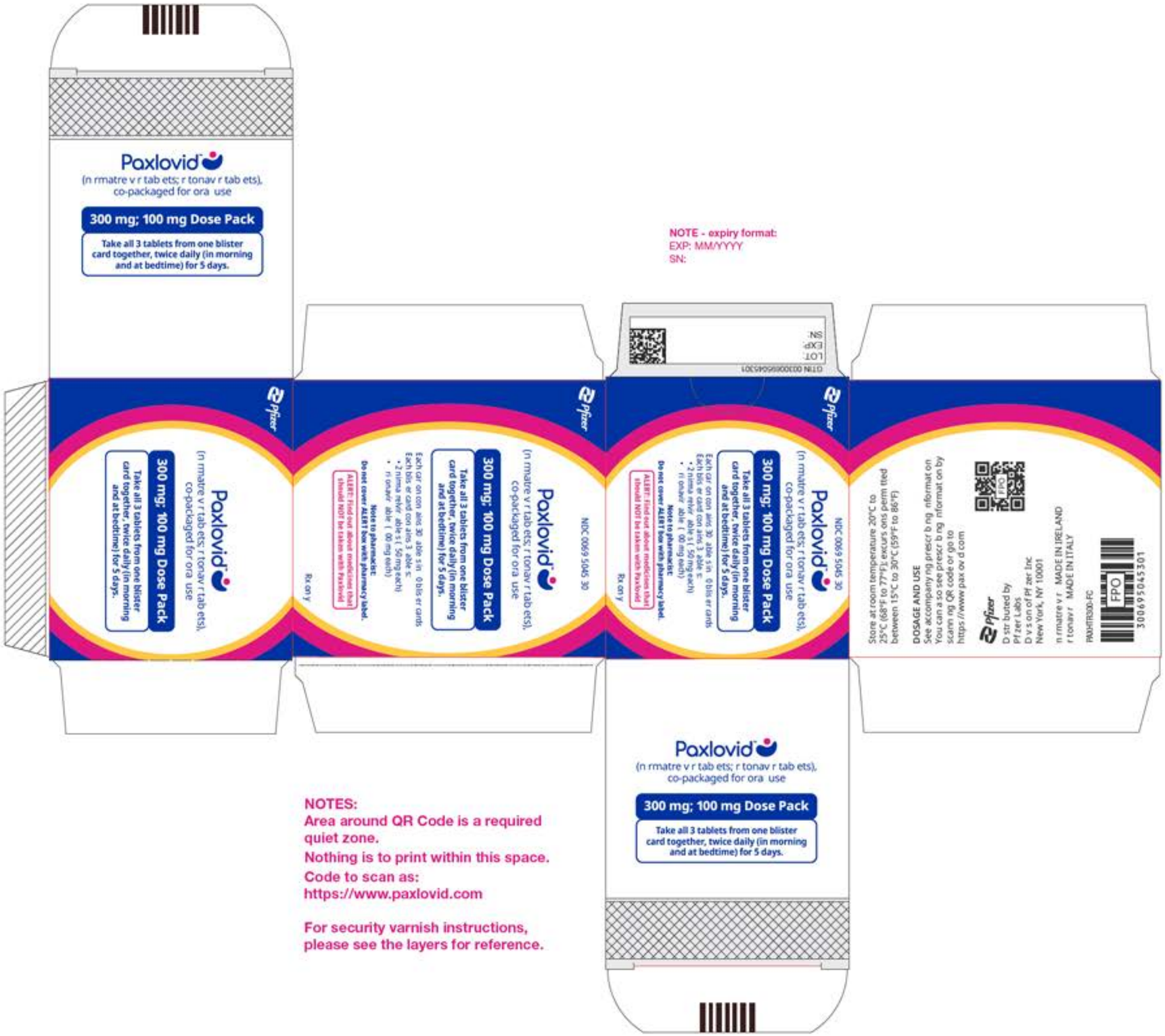
For security varnish instructions, please see the layers for reference.



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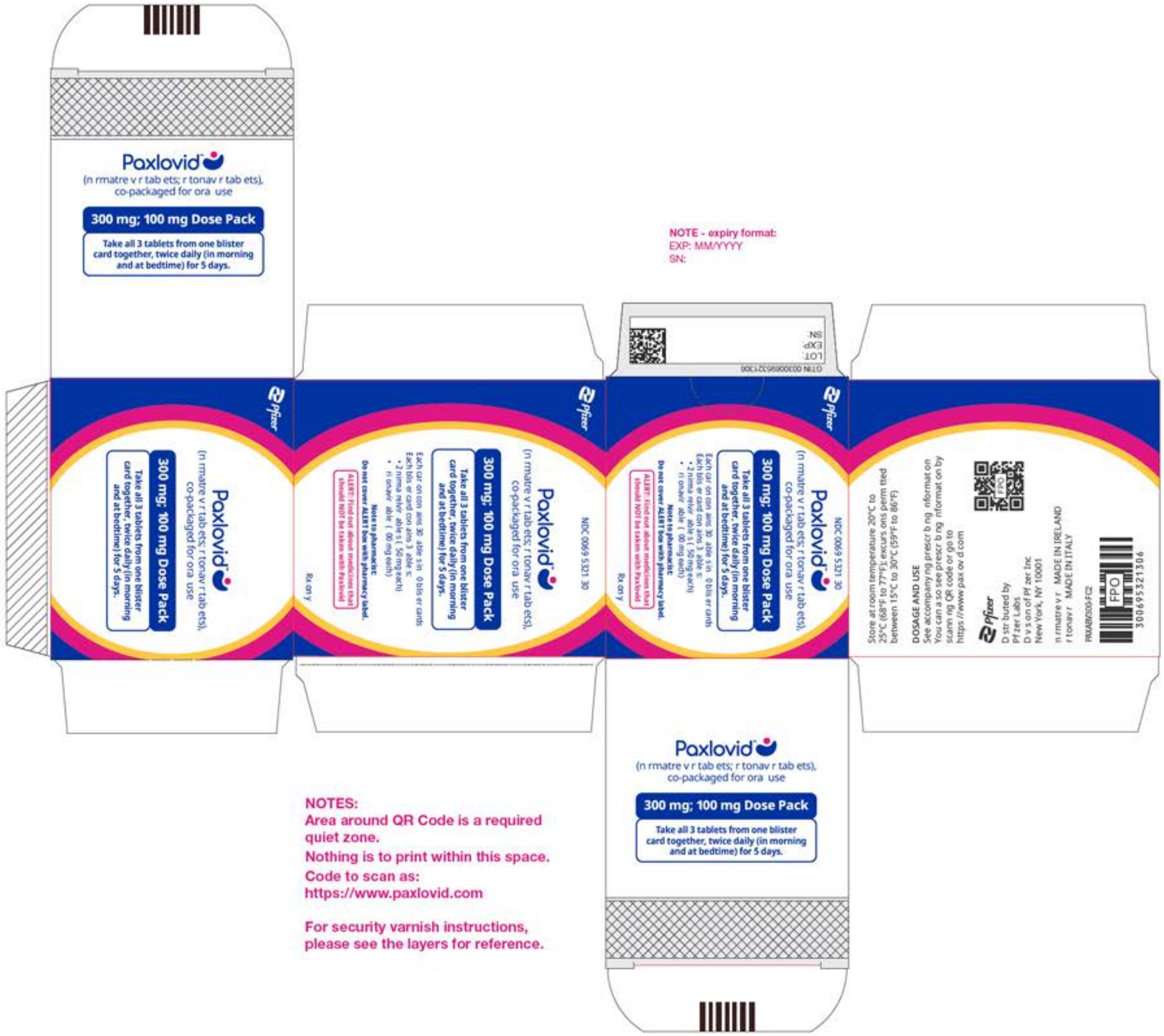

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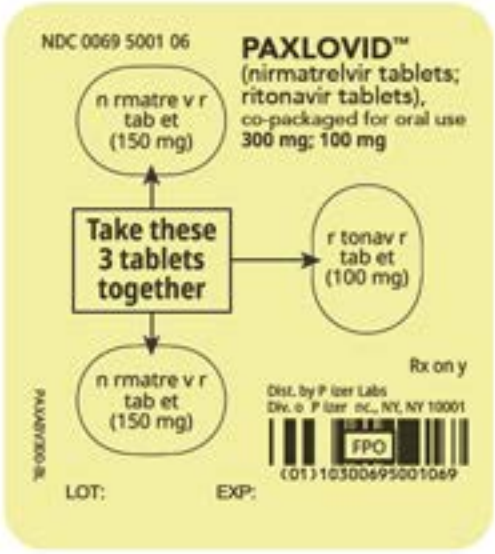

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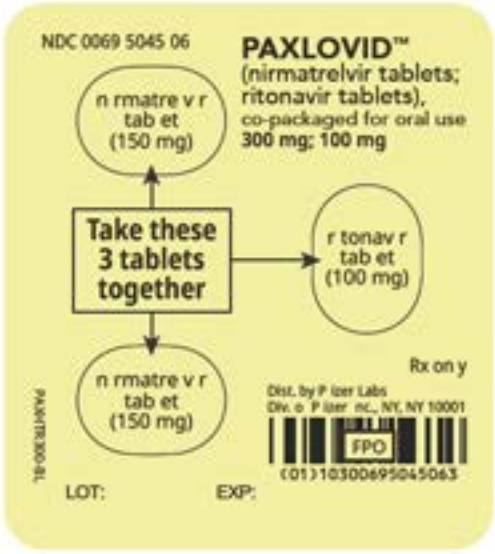

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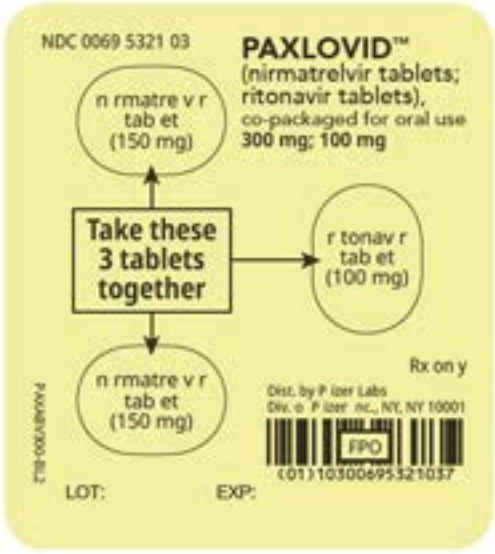

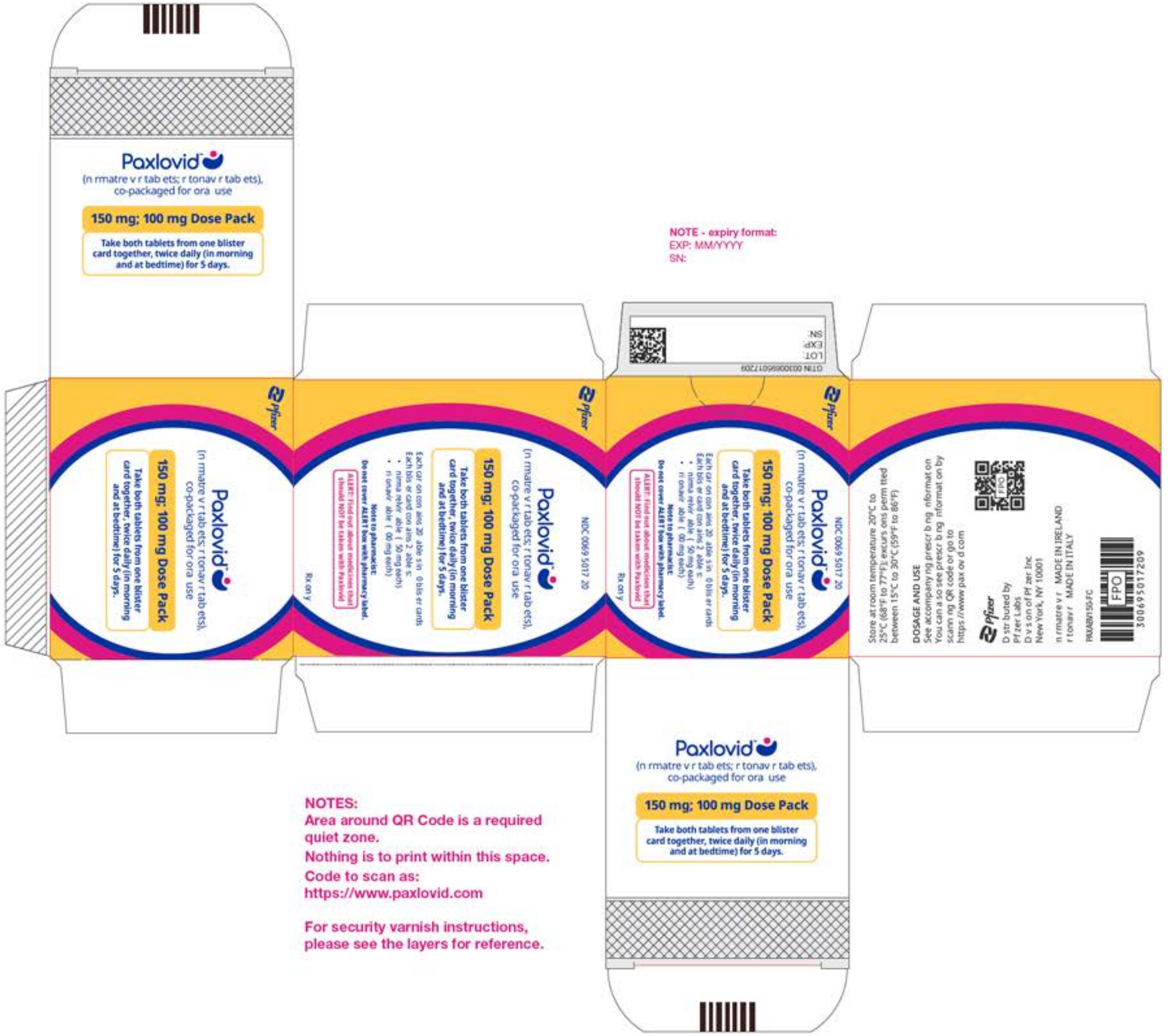

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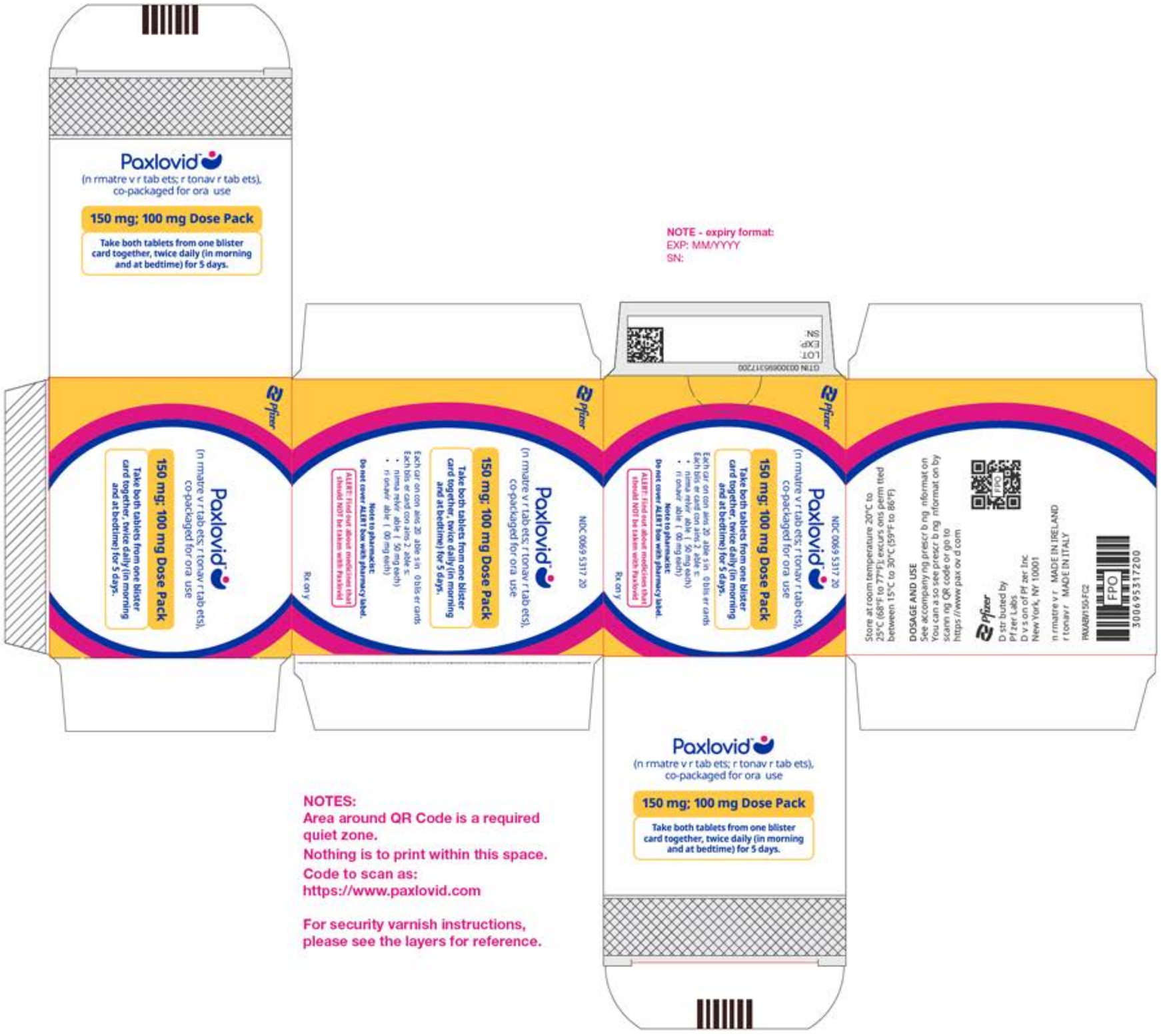

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Document 2A.15

U.S. FDA Emergency Use Authorization (EUA) for Paxlovid (nirmatrelvir tablets co-packaged with ritonavir tablets) Center for Drug Evaluation and Research (CDER) Review (December 22, 2021)

Document URL

https://www.fda.gov/media/155194/download

Reference website URL

https://www.fda.gov/drugs/coronavirus-covid-19-drugs/cder-scientific-review-documents-supporting-emergency-use-authorizations-drug-and-biological

License

Emergency Use Authorization (EUA) for
Paxlovid (nirmatrelvir tablets co-packaged with ritonavir tablets)
Center for Drug Evaluation and Research (CDER) Review

Identifying Information

Application Type (EUA or Pre-EUA) If EUA, designate whether pre-event or intra-event EUA request.	EUA
EUA Application Number(s)[1]	EUA 105
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	Pfizer Inc. 235 East 42nd Street New York, NY 10017-5755 Karen Baker- Director Global Regulatory Affairs – Brand Hospital Products Email: (b) (6) Phone: (b) (6)
Manufacturer, if different from Sponsor	
Submission Date(s)	October 21, 2021 November 11, 2021 Full EUA request- November 16, 2021
Receipt Date(s)	October 21, 2021 November 11, 2021 Full EUA request- November 16, 2021
OND Division / Office	Division of Antivirals/Office of Infectious Diseases
Reviewer Name(s)/Discipline(s)	• ADL: Stacey Min • Clinical: Stephanie Troy/Sarah Connelly • Clin Virology: Pat Harrington/Jules O'Rear/Nonclinical Virology: Jonathon Rawson • Biometrics: Jie Cong/Thamban Valappil/Karen Higgins • Pharm/Tox: (Jenny) Zheng Li /Christopher Ellis • Clinical Pharmacology: Cristina Miglis, Ye Xiong, Jiang Liu, Mario Sampson, Vikram Arya • CMC ATL: David Claffey/ • Drug Substance: Katherine Windsor/Paresma Patel

[1] If a Pre-EUA is in existence at the time of the EUA request submission and has been assigned an EUA number, the EUA request should use the same EUA number and electronic archive file.

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	• Drug Product: DP: Shalini Anand/ David Claffey • Biopharm: Gerlie Gieser/ Elsbeth Chikhale • OPMA: Abdollah Koolivand Hang Guo/Derek Smith • OMQ: Tara Gooen and Diane Bruce • RBPM: Shamika Brooks • DMEPA: Melina Fanari/Sevan Kolejian • OSE: Rachna Kapoor/Kimberly Swank/Kate McCartan/Neha Gada/Natasha Pratt/Monique Falconer/Naomi Boston/Ida-Lina Diak/Mishale Mistry/Michael Blum/ Attinello, Cristina/Danyal Chaudhry • PLT: • OPDP: Nima Ossareh/ Sam Skariah • CTECs: Brad Leissa, Liz Sadove, Andrea Gormley • OND Policy: Andrew Leboeuf • RPM: Alicia Moruf
Integrated Review Completion Date	12/22/2021
Proprietary Name	Paxlovid
Established Name/Other names used during development	Nirmatrelvir (PF-07321332) tablets; Ritonavir tablets
Dosage Forms/Strengths	300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally twice daily for 5 days.
Therapeutic Class	Nirmatrelvir is a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor that has demonstrated activity against SARS-CoV-2. Ritonavir is an HIV-1 protease inhibitor and is not active against SARS-CoV-2 Mpro. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, thereby providing increased plasma concentrations of nirmatrelvir.
Intended Use or Need for EUA	EUA for the emergency use of PAXLOVID for the treatment of mild-to-moderate Coronavirus Disease 2019 (COVID-19)
Intended Population(s)	Adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for

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	progression to severe COVID-19, including hospitalization or death
Product in the Strategic National Stockpile (SNS)	No
Distributor, if other than Sponsor	

I. EUA Determination/Declaration

On February 4, 2020, Secretary of Health and Human Services determined pursuant to section 564 of the Federal Food, Drug and Cosmetic (FD&C) Act that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad and that involves a novel (new) coronavirus (nCoV) first detected in Wuhan City, Hubei Province, China in 2019 (2019-nCoV). The virus is now named SARS-CoV-2, which causes the illness COVID-19.

On the basis of this determination, the Secretary of Health and Human Services declared, on March 27, 2020, that circumstances exist justifying the authorization of emergency use of drugs and biologics during the COVID-19 outbreak, pursuant to section 564 of the FD&C Act, subject to the terms of any authorization issued under that section.

II. Recommendations

A. Recommend EUA Issuance

The Division of Antivirals and Office of Infectious Diseases, Office of New Drugs, CDER recommends EUA issuance.

The EUA should authorize Paxlovid (nirmatrelvir co-administered with ritonavir) for emergency use as treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk[2] for progression to severe COVID 19, including hospitalization or death.

B. Eligibility of the Product for an EUA

- COVID-19 is a serious or life-threatening disease or condition caused by SARS-CoV-2, as specified in the declaration of emergency.
- Nirmatrelvir (NIR), one of the components of Paxlovid, is a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor that has demonstrated activity against SARS-CoV-2. Ritonavir (r), with which NIR is co-packaged in Paxlovid (NIR/r), is an HIV-1 protease inhibitor

[2] For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

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and potent inhibitor of the CYP3A4 enzyme that increases the plasma levels of NIR for the desired therapeutic effect.

- Based on the totality of the scientific evidence available to FDA, it is reasonable to believe that Paxlovid may be effective for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progression to severe COVID-19, including hospitalization or death. Under such conditions, the known and potential benefits outweigh the known and potential risks of this product.
- There is no adequate, approved, and available alternative to the emergency use of Paxlovid for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Remdesivir (Veklury®), which is administered by intravenous infusion, is the only product approved by FDA to treat COVID-19 at the time of FDA's EUA review of Paxlovid. Remdesivir is a nucleotide analog RNA polymerase inhibitor that has demonstrated antiviral activity against SARS-CoV-2. Remdesivir's approved indication is limited to the treatment of COVID-19 in adults and pediatric patients (12 years of age and weighing at least 40 kg) requiring hospitalization.

III. Proposed Use and Dosing of the Product Under the EUA

Proposed use under EUA

The Division recommends the following for inclusion in the EUA:

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of the unapproved product Paxlovid for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk[3] for progression to severe COVID-19, including hospitalization or death.

Paxlovid is not approved for any use, including for use for the treatment of COVID-19.

Paxlovid is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of Paxlovid under section

[3] For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

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564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

LIMITATIONS OF AUTHORIZED USE

- Paxlovid is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19.[4]
- Paxlovid is not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.
- Paxlovid is not authorized for use for longer than 5 consecutive days.

PAXLOVID may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which PAXLOVID belongs (i.e., anti-infectives).[5]

Authorized Dosage(s) under EUA

Adults and Pediatric Patients (12 years of age and older weighing at least 40 kg):

- Paxlovid, 300 mg NIR (two 150 mg tablets) co-packaged with 100 mg ritonavir (one 100 mg tablet), all three tablets taken together twice daily for 5 days, with or without food.
- The 5-day treatment course of Paxlovid should be initiated as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset. Should a patient require hospitalization due to severe or critical COVID-19 after starting treatment with Paxlovid, the patient may complete the full 5-day treatment course per the healthcare provider's discretion.
- If the patient misses a dose of Paxlovid within 8 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 8 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose.

Patients with Renal Impairment

No dose adjustment is recommended in patients with mild renal impairment [estimated glomerular filtration rate (eGFR) 60 to <90 mL/min].

In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min) the recommended dose is 150 mg NIR (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet) all taken together twice daily for 5 days.

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[4] Patients requiring hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID may complete the full 5-day treatment course per the healthcare provider's discretion.

[5] The term "State" includes any State or Territory of the United States, the District of Columbia, and the Commonwealth of Puerto Rico. See section 201(a)(1) of the Act.

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Paxlovid is not recommended in patients with severe renal impairment (eGFR <30 mL/min).

Patients with Hepatic Impairment
No dose adjustment is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic (PK) or safety data are available regarding the use of NIR or ritonavir in subjects with severe hepatic impairment (Child-Pugh Class C); therefore, Paxlovid is not recommended for use in patients with severe hepatic impairment.

Pregnant or Lactating Women
No PK or safety data are available in pregnant or lactating women; the need for Paxlovid dose adjustment in pregnant or lactating women has not been established.

Geriatric Patients
No dosage adjustment is recommended in geriatric patients. Clinical trials of Paxlovid included patients 65 years of age and older and their data contributes to the overall assessment of safety and efficacy. Of the total number of subjects in EPIC-HR randomized to receive Paxlovid (n=1,120), 13% (n=140) were 65 years of age and older and 3% (n=36) were 75 years of age and older.

Rationale for dosing regimen

- The proposed Paxlovid dosing regimen (300 mg NIR/100 mg ritonavir twice daily for 5 days) is primarily supported by the data from the EPIC-HR Study where it was generally safe and well-tolerated and may be effective at reducing the risk of COVID-19 related hospitalization or death from any cause through Day 28.
- This dosing regimen was the only regimen evaluated in EPIC-HR, which was the only Paxlovid study that evaluated the treatment of mild-to-moderate COVID-19 in symptomatic patients at high risk for progression to severe COVID-19.
- The dosing regimens for patients with renal or hepatic impairment were based on Phase 1 PK studies.
- The Paxlovid 300 mg NIR/100 mg ritonavir dose was initially chosen based on efficacy in the mouse model at concentrations approximating the in vitro EC90 (292 ng/mL) and simulations with a preliminary population PK model suggesting that greater than 90% of subjects achieve a trough concentration above the EC90 after the first dose. The 5-day treatment duration was based on the viral dynamics of SARS-CoV-2 in a quantitative systems pharmacology model.
- Paxlovid is recommended to be given without regard to food. A high fat meal did not significantly impact the AUC (AUC_{last} and $AUC_{0\text{-}inf}$) or C_{max} of NIR (approximately 15% increase in mean C_{max}, 1.5% increase in mean AUC_{last} and $AUC_{0\text{-}inf}$) following single dose administration of a 250 mg oral suspension in

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healthy subjects. (See *Section XI, Human Clinical Pharmacology* for more information on food effect and early clinical NIR formulations). In the pivotal Phase 2/3 study, the final 150 mg tablet formulation was administered without regard to food.

IV. Product Information (Dose Preparation and Administration)

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets.

- Nirmatrelvir tablets, 150 mg are oval, pink immediate-release, film-coated tablets debossed with “PFE” on one side and “3CL” on the other side.
- Ritonavir tablets, 100 mg are white film-coated ovaloid tablets debossed with the "a" logo and the code NK.

Nirmatrelvir tablets and ritonavir tablets are supplied in separate cavities within the same child-resistant blister card. Each carton contains 30 tablets divided in 5 daily-dose blister cards. Each daily blister card contains 4 nirmatrelvir tablets (150 mg each) and 2 ritonavir tablets (100 mg each) and indicates which tablets need to be taken in the morning and evening.

PAXLOVID is stored at Controlled Room Temperature 20°C to 25°C (68°F to 77°F).

Dispensing for patients with moderate renal impairment:
In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), the recommended dosage is 150 mg nirmatrelvir and 100 mg ritonavir twice daily for 5 days, which is incongruent with how PAXLOVID is packaged. Consequently, to ensure that patients with moderate renal impairment take the correct dose, a Dear Health Care Provider letter and instructions for pharmacists (that will accompany each shipment of PAXLOVID) will outline the following risk mitigation steps:

- The healthcare provider should ensure that all prescriptions specify the numeric dose for each active ingredient within PAXLOVID as follows:
    1. PAXLOVID 150 mg nirmatrelvir with 100 mg ritonavir for patients with moderate renal impairment, or
    2. PAXLOVID 300 mg nirmatrelvir with 100 mg ritonavir for patients with normal renal function or mild renal impairment
- The pharmacist should make the following changes to all 5 blister cards and the carton for patients with moderate renal impairment:
    1. Remove one of the 150 mg nirmatrelvir tablets from the morning dose and remove one of the 150 mg nirmatrelvir tablets from the evening dose of each blister card (the removed tablets should be the ones closest to the middle of the blister pack).
    2. Affix each blister card with one sticker from the provided tear pad and apply it to cover the empty blister wells and to cover the pre-printed dosing instruction that is on the blister card.

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3. Repeat steps one and two as described above for every blister card in the carton (each carton contains five blister cards).
4. Affix one sticker from the provided tear pad and carefully apply it to cover over the pre-printed dosing regimen on the carton.

- The pharmacist should counsel patients with moderate renal impairment about renal dosing instructions and notify them that their blister cards have been altered by the pharmacy.

V. Background Information on the Disease/Condition and Available Therapeutic Alternatives

Background Information on the Condition

The 2019 novel coronavirus, first identified in Wuhan China, and now identified as SARS-CoV-2, causes the disease named COVID-19. COVID-19 is a serious and life-threatening illness which can result in pneumonia, respiratory failure, multi-organ failure, and death.

On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic. According to the WHO, more than 271 million confirmed cases of COVID-19 caused by the 2019 novel coronavirus (SARS-CoV-2) have been reported globally as of December 17, 2021, including an estimated 5.3 million deaths. As of December 17, 2021, approximately 51 million cases of COVID-19, including approximately 803,000 deaths, have been reported in the United States according to CDC.

SARS-CoV-2 variants have emerged over time and continue to emerge. According to the CDC's national surveillance report, in early January 2021 <10% of SARS-CoV-2 variants circulating in the US were variants of concern or interest. However, by the end of March 2021, approximately two-thirds of SARS-CoV-2 variants circulating in the US were variants of concern or interest, with B.1.1.7 (Alpha) comprising 44% of circulating variants at the time. B.1.1.7 was supplanted as the most prevalent variant in the US in June 2021 by the Delta variant (B.1.617.2 and AY lineages), which accounted for 97% of circulating SARS-CoV-2 in the US, as well as most SARS-CoV-2 globally, by August 2021. In November 2021, the Omicron (B.1.1.529) variant was detected in South Africa and has spread globally; characteristics of this variant, including its susceptibility to currently authorized treatments, are still being discovered.

Patients with symptomatic SARS-CoV-2 infection, or COVID-19, can experience a wide range of clinical manifestations, with disease severity ranging from mild to severe/critical illness[6]. Severe/critical illness is defined as hospitalization, admission to the intensive care unit, mechanical ventilation, or death. The progression of SARS-CoV-2 infection to severe or critical COVID-19 can occur in adults of any age, but the risk increases with age. Per the CDC, over 80% of

[6] The different severities of COVID-19 illness are described in the NIH COVID-19 Treatment Guidelines at https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/.

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COVID-19 deaths occur in adults aged 65 years and older, and more than 95% of COVID-19 deaths occur in adults aged 45 years and older. Irrespective of age, certain underlying comorbidities or conditions, such as cancer, chronic kidney disease, chronic obstructive pulmonary disease, obesity, type 2 diabetes, pregnancy, and immunocompromised states, increase the risk of progression to severe COVID-19. People who have experienced long-standing systemic health and social inequities, such as many racial and ethnic minorities and those with disabilities, are also at increased risk of worse outcomes (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html).

The respiratory presentation in adolescents has been similar to that in adults. The disease is typically milder in children, but a small proportion have experienced severe disease that requires treatment in an ICU and prolonged mechanical ventilation (Götzinger et al., 2020).

Treatment Alternatives

There is no adequate, approved, and available alternative to the emergency use of Paxlovid for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Remdesivir (Veklury®) is the only product approved by FDA to treat COVID-19 at the time of FDA's EUA review of Paxlovid. Remdesivir is a nucleotide analog RNA polymerase inhibitor that has demonstrated antiviral activity against SARS-CoV-2. Remdesivir initially received emergency use authorization on May 1, 2020, and was ultimately approved on October 22, 2020, under NDA 214787. Remdesivir's approved indication is limited to the treatment of COVID-19 in adults and pediatric patients (12 years of age and weighing at least 40 kg) requiring hospitalization. At the time of this review, remdesivir also remains authorized for emergency use for treating suspected or laboratory confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg.

There are other COVID-19 treatments currently authorized for emergency use for the same use as proposed for Paxlovid: treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. These products include the following:

1. REGEN-COV (the monoclonal antibodies casirivimab and imdevimab) was authorized on November 21, 2020.
2. The monoclonal antibodies bamlanivimab and etesevimab were authorized to be administered together on February 9, 2021.
3. The monoclonal antibody sotrovimab was authorized on May 26, 2021.

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There are currently no approved therapies for treatment of mild-to-moderate COVID-19 in outpatients. Additional information on COVID-19 treatments can be found at https://www.cdc.gov/coronavirus/2019-ncov/index.html.

VI. Related Regulatory Submission(s)

Paxlovid (NIR co-packaged with ritonavir) has been studied under IND 153517 (Sponsor: Pfizer Inc.).

Product quality information supporting ritonavir tablets were referenced to (b) (4) (ritonavir) tablets).

Pfizer proposed two suppliers for blister packaging components:

- DMF (b) (4) .
- DMF (b) (4)

Both DMF (b) (4) were found adequate to support this application.

VII. Summary of Clinical Data

The data to support the authorization of Paxlovid were generated from the ongoing Phase 2/3 trial EPIC-HR. Additional data from five Phase 1 studies also support the authorization (Table 1).

Paxlovid is also being studied in two ongoing Phase 2/3 trials. However, data from these trials were not submitted to support this EUA application.

1. Five days of Paxlovid (300 mg NIR and 100 mg ritonavir po bid) is being studied in EPIC-SR (C4671002), a Phase 2/3 COVID-19 treatment trial in 1140 non-hospitalized adults at low risk for severe disease.
2. Five days versus 10 days of Paxlovid (300 mg NIR and 100 mg ritonavir po bid) is being studied in EPIC-PEP (C4671006), a Phase 2/3 COVID-19 post-exposure prophylaxis trial in 2,660 asymptomatic, SARS-CoV-2 negative adult household contacts of individuals infected with SARS-CoV-2.

Table 1: Clinical Trials with Data Submitted to Support this EUA Application

Study Number	IND, NDA, or Literature Reference	Type of Study	Population (N)	Study Design and Type of Control	Test Product(s); Dosing Regimens; Dosage Forms; Routes of Administration; Duration	Study Status
EPIC-HR (C4671005) NCT04960202	IND 153517	Efficacy, safety, PK	2,246* adult outpatients with COVID-19 at high risk for severe disease	Phase 2/3 randomized (1:1), double-blind, placebo-controlled trial	Nirmatrelvir 300 mg and ritonavir 100 mg po bid x 5 days versus placebo	Ongoing but enrollment complete
C4671001 NCT04756531	IND 153517	PK, safety	70 healthy adults	Phase 1, randomized, double-blind, placebo-controlled, single ascending dose, multiple ascending dose study	Single doses: nirmatrelvir 150, 250, 500, or 1500 mg or nirmatrelvir 250, 300, 750, or 2250 mg with ritonavir 100 mg at -12, 0, and 12 hours Multiple doses: nirmatrelvir 75, 250, or 500 mg bid with 100 mg ritonavir bid x 10 days	Completed
C4671010 NCT05005312	*IND 153517*	*PK, safety*	*Adults with moderate hepatic impairment (n=8) or normal hepatic function (n=8)*	*Phase 1, open-label study*	*Nirmatrelvir 100 mg po x1 with ritonavir 100 mg at -12, 0, 12, and 24 hours*	*Ongoing; topline data only^*
C4671011 NCT04909853	IND 153517	PK, safety	34 adults with renal impairment or normal renal function	Phase 1, open-label study	Nirmatrelvir 100 mg po x1 with ritonavir 100 mg at -12, 0, 12, and 24 hours	Completed
C4671014 NCT04962230	IND 153517	PK, safety	12 healthy adults	Phase 1, open-label, fixed sequence, 2-period crossover study	Period 1: single dose of nirmatrelvir 300 mg and ritonavir 100 mg Period 2: carbamazepine 100 mg bid Days 1-3, 200 mg bid Days 4-7, and 300 mg bid Days 8-15 with a single dose of nirmatrelvir 300 mg and ritonavir 100 mg on Day 13	Completed
C4671015 NCT04962022	IND 153517	PK, safety	12 healthy adults	Phase 1, open-label, fixed sequence, 2-period crossover study	Period 1: nirmatrelvir 300 mg and ritonavir 100 mg po bid x 5 doses Period 2: itraconazole 200 mg qd x 8 days with nirmatrelvir 300 mg and ritonavir 100 mg po bid x 5 doses starting on Day 4	Completed

IND = investigational new drug application, PK = Pharmacokinetics, po = orally, bid = twice a day, qd = daily
*The initial EUA application contained an interim analysis based on data from 1349 subjects, but topline efficacy and safety data from all 2246 subjects enrolled in C4671005 was provided before the end of the review (submitted 12/14/2021).
^A topline summary of preliminary unaudited data for this study was submitted midway through the review cycle.
Sources: EUA request Table 7, the individual study protocols, and clinicaltrials.gov (for the NCT numbers).

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VIII. Human Clinical Efficacy

The main source of clinical efficacy data to support this EUA request was from the Phase 2/3 study C4671005 (EPIC-HR, clinicaltrials.gov identifier NCT04960202).

EPIC-HR (C4671005) Trial Design

EPIC-HR is a Phase 2/3, randomized, double-blind, placebo-controlled trial of Paxlovid for the treatment of adult outpatients with mild-to-moderate COVID-19, who are at high-risk for progression to severe disease. Subjects with a confirmed diagnosis of SARS-CoV-2 infection and with symptom onset within five days were randomized 1:1 to receive Paxlovid (NIR 300 mg coadminstered with ritonavir 100 mg) or placebo orally q12h for 5 days (10 doses total). Randomization was stratified by geographic region and whether subjects had received or were expected to receive COVID-19 therapeutic mAb treatment (yes/no) based on the site investigator's assessment at the time of randomization. The total study duration is up to 24 weeks.

Inclusion/exclusion criteria specified that subjects had to have at least one of the following risk factors for progression to severe disease: ≥60 years of age; BMI >25; current smoker; immunosuppressive disease or immunosuppressive treatment; chronic lung disease; hypertension; cardiovascular disease; diabetes; chronic kidney disease; sickle cell disease; neurodevelopmental disorders; active cancer; medical related technological dependence. Individuals who had a history of prior COVID-19 infection or vaccine were excluded.

Enrollment of subjects who had received or were expected to receive COVID-19 therapeutic mAb treatment was to be limited to approximately 25% of subjects. Enrollment of subjects who had COVID-19 symptom onset >3 days prior to randomization was expected to be approximately 25% and was to be limited to approximately 1000 subjects.

An independent external data monitoring committee (E-DMC) reviewed unblinded safety data on an ongoing basis throughout the duration of the study, and for a sentinel cohort of the first 60 subjects after completion through Day 10. In addition, the E-DMC conducted a proof-of-concept assessment using viral RNA shedding data from approximately 200 subjects from the mITT analysis set through Day 5, and a formal interim analysis for efficacy and futility (with a sample size re-estimation) after approximately 45% of subjects in the mITT analysis set completed the Day 28 assessments.

The primary analysis set was updated to include only those ≤3 days of COVID-19 symptom onset in protocol amendment 2 (8/2/2021) and the total sample size was increased from 2260 to approximately 3000. Sites in India were terminated (on 9/22/2021) due to a blinded data review of a >90% rate of serology positive

subjects at baseline and Site 1470 was terminated for GCP noncompliance (refer to *Efficacy Results* for sensitivity analysis). The E-DMC determined that the prespecified criteria for stopping the trial due to overwhelming efficacy had been achieved at the 45% interim efficacy analysis (data cutoff of 10/26/2021) and further enrollment in the study was subsequently stopped on 11/5/2021. The final efficacy analysis was conducted as a supportive analysis after all subjects completed the Day 34 visit. The follow-up analysis will be performed after all subjects have completed the Week 24 visit.

Analysis Populations

The Full Analysis Set (FAS) included all subjects randomly assigned to study intervention regardless of whether or not study intervention was administered. The following analysis populations were used for efficacy analyses.

- Modified Intent-To-Treat (mITT): All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
- Modified Intent-To-Treat 1 (mITT1): All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were dosed to receive COVID-19 therapeutic mAb treatment and were treated ≤5 days of COVID-19 symptom onset.
- Modified Intent-To-Treat 2 (mITT2): All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.

The pre-specified primary efficacy analysis population was the mITT population.

Efficacy Results

The EUA submission originally included EPIC-HR interim analysis efficacy data; later in the EUA review cycle on 12/14/2021 topline efficacy analyses on final data were submitted. Therefore, the following two subsections provide the interim analysis efficacy results along with the later submitted full topline analysis efficacy results.

Interim Analysis Efficacy Results

As of the data cutoff (10/26/2021),1,361 subjects were included in the full analysis set in the interim analysis. The table below displays demographic and baseline characteristics.

Table 2: Baseline Demographics and Disease Characteristics (FAS), Interim Analysis

	Paxlovid n=678	**Placebo n=683**

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Female	334 (49%)	314 (46%)
Hispanic or Latino	324 (48%)	330 (48%)
Black or African American	37 (5%)	25 (4%)
Asian	134 (20%)	140 (20%)
Age (median years)	42.0	45.0
Age ≥ 60 years	109 (16%)	146 (21%)
BMI (mean kg/m^2)	29.1	29.2
BMI ≥ 30 kg/m^2	246 (36%)	253 (37%)
Duration of COVID-19 symptoms ≤ 3 days	433 (64%)	426 (62%)
Viral Load (NP samples, mean, log_{10} copies/mL)	4.69	4.72
Viral Load ≥ 10^7 (units)[a]	171 (27%)	166 (26%)
Seropositive[b]	372 (56%)	368 (55%)
United States	304 (45%)	304 (45%)
COVID-19 mAb treatment received/expected to receive	55 (8%)	57 (8%)

Sources: EUA request Table 36
[a] Denominator being participants with available baseline viral load
[b] Denominator being participants with available baseline serology status

Clinical Outcomes

The primary endpoint was proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28 in the mITT population, who received treatment within 3 days of symptom onset and without COVID-19 therapeutic mAb treatment at baseline. The event rates were 27/387 (7.0%) in the placebo group, and 3/393 (0.8%) in the Paxlovid group. After accounting for premature study discontinuation by using the follow-up time in the Kaplan-Meier calculation, treatment with Paxlovid showed a 6.3% (95% CI: -9.0% to -3.6%; p<0.0001) absolute reduction, or 89.1% relative reduction compared to placebo. The reduction was statistically significant, at α-level of 0.002, which was pre-specified for the interim analysis.

Table 3: Proportion of Subjects with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28 (mITT), Interim Analysis

	Paxlovid n=393	**Placebo n=387**
Subjects with event, n (%)	3 (0.8%)	27 (7.0%)
COVID-19 hospitalization	3 (0.8%)	27 (7.0%)
Death	0	7 (1.8%)
Estimated difference in proportion (95% CI)[a]	-6.3% (-9.0%, -3.6%)	
p-value	<.0001	

Sources: Response to 06 December 2021 and 07 December 2021 Information Request, Table 2
[a] The estimated cumulative proportion of subjects hospitalized for the treatment of COVID-19 or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.

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Consistent results were shown in sensitivity analyses of the primary efficacy endpoint where data from India and Site 1470 were excluded and where subjects who received a therapeutic COVID-19 mAb treatment postbaseline were considered to have experienced a primary endpoint event.

Additionally, in a sensitivity analysis on the primary efficacy endpoint where subjects who had unknown hospitalization/death status through Day 21 were imputed to have experienced an event of COVID-19-related hospitalization or death, the result favored treatment with Paxlovid with a p-value 0.0039 in the mITT analysis set for the interim analysis data, and a finding consistent with the interim analysis (Table 3) was obtained in the mITT analysis set for the full topline data.

Treatment with Paxlovid showed no inconsistent effect in subgroup analyses of age, gender, race, BMI, baseline serology status, baseline viral RNA in NP samples, baseline comorbidities, and geographic region.

The first key secondary endpoint was the proportion of subjects with COVID-19-related hospitalization or death from any cause through Day 28 in the mITT1 analysis set, who received treatment within 5 days of symptom onset and without COVID-19 therapeutic mAb treatment at baseline. The event rates were 41/620 (6.6%) in the placebo group, and 6/617 (1.0%) in the Paxlovid group. Treatment with Paxlovid showed a 5.7% (95% CI: -7.9% to -3.6%) absolute reduction, or 85.3% relative reduction compared to placebo.

Table 4: Proportion of Subjects with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28 (mITT1), Interim Analysis

	Paxlovid n=617	**Placebo n=620**
Subjects with event, n (%)	6 (1.0%)	41 (6.6%)
COVID-19 hospitalization	6 (1.0%)	41 (6.6%)
Death	0	10 (1.6%)
Estimated difference in proportion (95% CI)[a]	-5.7% (-7.9%, -3.6%)	

Sources: Response to 06 December 2021 and 07 December 2021 Information Request, Table 3
[a] The estimated cumulative proportion of subjects hospitalized for the treatment of COVID-19 or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.

A sensitivity analysis was conducted in the mITT2 analysis set who received treatment regardless of baseline COVID-19 therapeutic mAb treatment. The event rates were 43/677 (6.4%) in the placebo group, and 7/672 (1.0%) in the Paxlovid group. Treatment with Paxlovid showed a 5.4% (95% CI: -7.4% to -3.4%) absolute reduction, or 83.6% relative reduction compared to placebo.

Table 5: Proportion of Subjects with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28 (mITT2), Interim Analysis

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	Paxlovid n=672	Placebo n=677
Subjects with event, n (%)	7 (1.0%)	43 (6.4%)
COVID-19 hospitalization	7 (1.0%)	43 (6.4%)
Death	0	10 (1.5%)
Estimated difference in proportion (95% CI)[a]	-5.4% (-7.4%, -3.4%)	

Sources: Response to 06 December 2021 and 07 December 2021 Information Request, Table 1
[a] The estimated cumulative proportion of subjects hospitalized for the treatment of COVID-19 or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.

Full Topline Analysis Efficacy Results

The full topline analysis findings were submitted on December 14, 2021; the Agency determined that these findings were important to consider for the EUA request. A total of 2,246 subjects were randomized into this study. The table below displays demographic and baseline characteristics.

Table 6: Baseline Demographics and Disease Characteristics (FAS), Full Topline Analysis

	Paxlovid n=1,120	Placebo n=1,126
Female	554 (49%)	544 (48%)
Hispanic or Latino	499 (45%)	505 (45%)
Black or African American	60 (5%)	50 (4%)
Asian	154 (14%)	161 (14%)
Age (median years)	45.0	46.5
Age ≥ 60 years	226 (20%)	260 (23%)
BMI (mean kg/m^2)	29.1	29.3
BMI ≥ 30 kg/m^2	407 (36%)	419 (37%)
Duration of COVID-19 symptoms ≤ 3 days	754 (67%)	735 (65%)
Viral Load (NP samples, mean, log_{10} copies/mL)	4.67	4.59
Viral Load ≥ 10^7 (units)[a]	300 (27%)	275 (24%)
Seropositive[b]	581 (52%)	568 (50%)
United States	463 (41%)	465 (41%)
COVID-19 mAb treatment received/expected to receive	70 (6%)	70 (6%)

Sources: Preliminary Completion Date Summary Report Study C4671005, Table 4
[a] Denominator being participants with available baseline viral load
[b] Denominator being participants with available baseline serology status

Clinical Outcomes

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Using the proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28 endpoint, Paxlovid showed an 88.9%, 87.8%, and 86.7% relative risk reduction compared to placebo in the mITT, mITT1, and mITT2 analysis sets, respectively. These results supported the efficacy conclusion from the interim analysis.

Table 7: Proportion of Subjects with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28, Full Topline Analysis

mITT: All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset		
	Paxlovid n=697	**Placebo n=682**
Subjects with event, n (%)	5 (0.7%)	44 (6.5%)
COVID-19 hospitalization	5 (0.7%)	44 (6.5%)
Death	0	9 (1.3%)
Estimated difference in proportion (95% CI)[a]	-5.8% (-7.8%, -3.8%)	
mITT1: All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset		
	Paxlovid n=1,039	**Placebo n=1,046**
Subjects with event, n (%)	8 (0.8%)	66 (6.3%)
COVID-19 hospitalization	8 (0.8%)	65 (6.2%)
Death	0	12 (1.1%)
Estimated difference in proportion (95% CI)[a, b]	-5.6% (-7.2%, -4.0%)	
mITT2: All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset		
	Paxlovid n=1,109	**Placebo n=1,115**
Subjects with event, n (%)	9 (0.8%)	68 (6.1%)
COVID-19 hospitalization	9 (0.8%)	67 (6.0%)
Death	0	12 (1.1%)
Estimated difference in proportion (95% CI)[a]	-5.4% (-6.9%, -3.8%)	

Sources: Preliminary Completion Date Summary Report Study C4671005, Table 5, Table 6, Table 7

[a] The estimated cumulative proportion of subjects hospitalized for the treatment of COVID-19 or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation

[b] The relative risk reduction in the mITT1 analysis population for PAXLOVID compared to placebo was 88% (95% CI: 75%, 94%)

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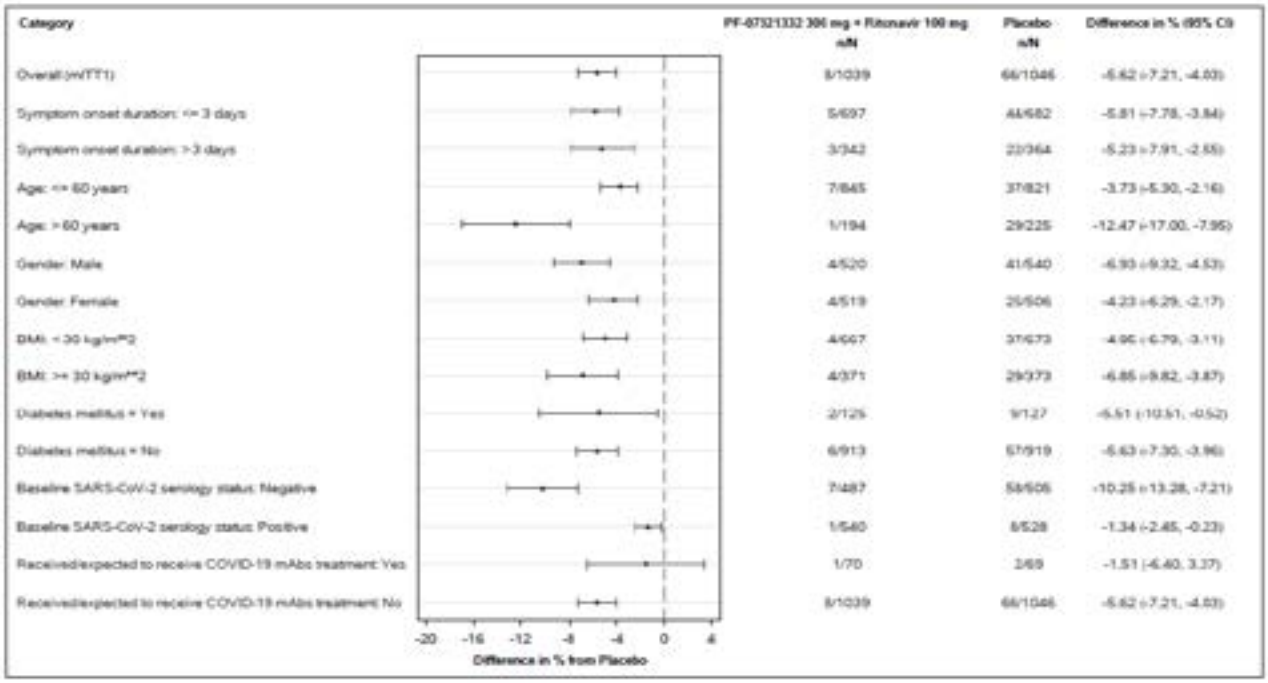
Subgroup analyses were conducted in the mITT1 analysis set by symptom onset duration (≤3 days or not), age group (≤60 or not), gender, BMI (<30 or not), diabetes melilites, baseline serology status, and in the mITT2 analysis set by mAb use status (at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment). Treatment with Paxlovid showed no inconsistent effect in any subgroup of subjects.

Figure 1: Proportion of Subjects with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28 (mITT1), Full Topline Analysis



Sources: Response to FDA Information Request, submitted 12/16/2021

Virologic Outcomes

The statistical analysis of viral RNA levels in NP swabs first occurred when approximately 200 subjects in the mITT analysis set completed the viral RNA shedding assessment at Day 5 and had valid viral RNA measurements at both Day 1 and Day 5 available for an initial proof-of-concept (POC) assessment. Only samples collected with the validated I-Swab-plus were used for formal viral RNA analysis. Subjects were excluded from the analysis due to missing or baseline viral RNA was not detected, or collection with a unvalidated (local) swab. Data reported as less than 2.0 $\log_{10}$ copies/mL were recorded as 1.69 $\log_{10}$ copies/mL and data reported as “not detected’ were recorded as 0 $\log_{10}$ copies/mL. A snapshot of the database took place on 9/20/2021 and the POC assessment included all subjects who had data in the database at the time.

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In the mITT1 analysis set, baseline viral RNA levels averaged 5.11 log_{10} copies/mL among the 303 subjects in the placebo group, and 5.41 log_{10} copies/mL among the 269 subjects in the Paxlovid group. At Day 5, after accounting for baseline viral RNA level, geographic region, serology status and symptom onset, the adjusted mean (SE) reduction in viral RNA level was -1.75 (0.09) log_{10} copies/mL in the placebo group, and -2.69 (0.10) log_{10} copies/mL in the Paxlovid group, reflecting an additional average reduction (SE) of -0.93 (0.13) log_{10} copies/mL. The adjusted mean reductions in viral RNA from baseline to Day 5 in the mITT and mITT2 analysis sets were comparable to that for the mITT1 analysis set.

During the review the sponsor provided an analysis-ready dataset of available viral RNA results from subjects in EPIC-HR. Independent FDA analyses were conducted on 852 subjects (424 Paxlovid treated, 428 Placebo treated) who had available NP swab viral RNA data, at minimum, on both Day 1 (Baseline) and Day 5 (EOT). Note that this is a larger sample size than that presented in the sponsor's initial analyses of viral RNA shedding.

Overall results of viral RNA levels in NP swabs are summarized in Table 8, and were consistent with the sponsor's POC analyses summarized above. Treatment with Paxlovid was associated with a ~0.9 log_{10} copies/mL greater median reduction in SARS-CoV-2 RNA levels in NP swabs through Day 5 (EOT). Similar trends indicating modestly greater SARS-CoV-2 RNA declines in Paxlovid treated subjects were observed across different key subgroups, including the mITT, mITT1 and mITT2 populations. In these analyses similar declines in viral RNA levels were observed in anti-SARS-CoV-2 seronegative and seropositive subjects.

Table 8. Viral RNA changes (log_{10} copies/mL) from Baseline in NP swab samples (mITT2 population, all subjects with available data at Baseline and Day 5).

	Placebo			Paxlovid		
Analysis Visit	**N**	**Mean**	**Median**	**N**	**Mean**	**Median**
Baseline	428			424		
Day 3	400	-1.2	-1.3	397	-1.7	-1.7
Day 5	428	-2.1	-2.0	424	-2.9	-2.9
Day 10	325	-3.9	-4.0	328	-4.2	-4.4
Day 14	336	-4.5	-4.7	330	-4.7	-5.0

Source: FDA analysis.

Resistance Analyses

The sponsor analyzed and submitted viral NGS analysis data from 490 subjects enrolled in EPIC-HR, of whom 216 (16% of mITT2 45% IA population) had sequence data available at both Day 1 and Day 5 (EOT) timepoints. Independent FDA analyses of the sponsor's analysis-ready amino acid frequency tables were conducted, focusing on treatment-emergent amino acid changes encoded in the Mpro (nsp5/3Clpro) gene as well as the 11 different Mpro cleavage sites (Table 9).

A large number of frameshift changes were detected at low amino acid frequencies (90% at ~6% or less frequency), which we interpreted to be predominantly sequencing artifacts, and thus we set our analysis sensitivity threshold at 5%. Given the limited available data for review, these analyses of NIR/r treatment-emergent substitutions should be considered preliminary.

Table 9. Mpro cleavage sites in SARS-CoV-2 open-reading frame 1ab (ORF1ab).

Cleavage Site	Proteins	Cleavage Sites	ORF1ab AA positions
Mpro Cleavage Site #1	nsp4/nsp5	SAVLQ↓SGFRK	3259-3268
Mpro Cleavage Site #2	nsp5/nsp6	GVTFQ↓SAVKR	3565-3574
Mpro Cleavage Site #3	nsp6/nsp7	VATVQ↓SKMSD	3855-3864
Mpro Cleavage Site #4	nsp7/nsp8	RATLQ↓AIASE	3938-3947
Mpro Cleavage Site #5	nsp8/nsp9	AVKLQ↓NNELS	4136-4145
Mpro Cleavage Site #6	nsp9/nsp10	TVRLQ↓AGNAT	4249-4258
Mpro Cleavage Site #7	nsp10/nsp11-12	EPMLQ↓SADAQ	4388-4397
Mpro Cleavage Site #8	nsp12/nsp13	HTVLQ↓AVGAC	5320-5329
Mpro Cleavage Site #9	nsp13/nsp14	VATLQ↓AENVT	5921-5930
Mpro Cleavage Site #10	nsp14/nsp15	FTRLQ↓SLENV	6448-6457
Mpro Cleavage Site #11	nsp15/nsp16	YPKLQ↓SSQAW	6794-6803

Source: adapted from interim viral sequencing report, p. 5; report PF-07321332_19Jan21_120222, p.17).

Treatment-emergent amino acid substitutions in Mpro or any Mpro cleavage sites detected at the same position in ≥2 Paxlovid treated subjects are summarized in Table 10. These substitutions included D153Y, Q189K and A260T/V in Mpro, and T6449I in Mpro cleavage site #10.

Table 10. Treatment-emergent amino acid substitutions in Mpro or Mpro cleavage sites detected at the same position in ≥2 Paxlovid treated subjects (C4671005 preliminary resistance analyses).

Substitution	In/Near (4Å) NIR Binding Site?	Number of Subjects with Tx-Emergent Substitution	
		Paxlovid (n=97)	Placebo (n=119)
Mpro_D153Y	No	2	0
Mpro_Q189K	Yes	5	7
Mpro_A260T/V	No	1(T), 3(V)	0
Mpro cl.site #10_T6449I	n/a	2	0

Source: FDA analysis.

Mpro_A260T/V appeared to have the strongest signal as possible Paxlovid treatment-emergent substitutions. The A260T substitution emerged in one Paxlovid treated subject at a variant frequency of 11%, and the A260V substitution emerged in 3 other subjects at a variant frequency of 6-21%; neither emerged in any placebo treated subjects. Nevertheless, the potential impact of either substitution on NIR resistance is unclear. This position is variable across different

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CoVs, and within the dataset baseline polymorphisms [V (n=6), T (n=3) G (n=1) or P (n=1); 1-100% frequency] were detected at this position in 11/480 (2%) subjects in the dataset, none of whom reached the clinical endpoint of hospitalization or death. In a biochemical assay with recombinant Mpro expressing A260V, no reduction in NIR susceptibility was observed. This position should be closely monitored as more resistance data are obtained from the trial.

The Mpro_Q189K substitution emerged in 5 Paxlovid- and 7 placebo-treated subjects. This substitution is notable as Q189 is highly conserved and within 4Å of the NIR binding site in Mpro, and in a biochemical assay this specific substitution conferred a 65-fold reduction in NIR activity. However, based on further analyses it is unclear if Q189K was truly a Paxlovid treatment-emergent substitution in this preliminary dataset. There is no indication Q189K was enriched in Paxlovid-treated subjects relative to placebo-treated subjects. In both Paxlovid and placebo-treated subjects, Q189K was detected at Day 5 at a frequency of 5-10%, with the two highest frequencies (~10%) observed in placebo-treated subjects. Furthermore, there is strong evidence that Q189K was a commonly observed sequencing artifact. The sponsor noted the nucleotide sequence is in an AT-rich region, and despite Q189 being highly conserved in published SARS-CoV-2 sequence data, it was detected in 53% of subjects' baseline viral sequences in the current dataset, predominantly at a <5% frequency. Therefore, considering the totality of this information, FDA currently does not consider Q189K to be a known Paxlovid treatment-emergent substitution in treated patients, but this position should also continue to be monitored closely for possible clinical evidence of Paxlovid resistance.

The Mpro_D153Y substitution emerged in 2 Paxlovid treated subjects. In both cases the substitutions were detected at a ~6% frequency, near the sensitivity cutoff used in the assay. Therefore, it is unlikely this change reflects a true treatment-emergent resistance-associated substitution, but it is noted here for future reference.

The Mpro cleavage site #10_T6449I substitution also emerged in 2 Paxlovid treated subjects and were the predominant variants at this position on Day 5 in both subjects. We currently do not view this finding as indicative of NIR resistance emergence. Given there are 11 different Mpro cleavage sites, presumably changes would need to occur either in one critical site or in multiple different cleavage sites in the same virus to confer some level of NIR resistance, and this is the only cleavage site amino acid change that was detected in ≥2 Paxlovid treated subjects. Neither subject had any amino acid changes detected in Mpro at Baseline or Day 5.

SARS-CoV-2 RNA shedding results were analyzed to further investigate any association between potential NIR resistance-associated substitutions and virologic outcomes, although conclusions cannot be drawn from these analyses due to the limited available sequence analysis data. Of the 97 Paxlovid treated

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subjects with available resistance data on Day 1 (Baseline) and Day 5, only 17 (18%) subjects had a substitution detected at either Day 1 or Day 5 at any possible resistance-associated amino acid position, defined loosely based on the totality of nonclinical and clinical resistance data analyzed to date (Table 11).

Table 11. Paxlovid treated subjects with SARS-CoV-2 amino acid substitutions in Mpro or cleavage site positions potentially associated with resistance (C4671005 preliminary resistance analyses).

Position	Possible Association w/NIR Resistance	Total # Changes (NIR/r)
G15	P15A possible minor MHV resistant-emergent change, G15S 4.4-fold change in biochemical assay	0
H41	within 5 Å of NIR	0
M49	within 5 Å of NIR	0
L50	T50K possible minor MHV resistant-emergent change	0
Y54	within 5 Å of NIR, Y54H 24-fold change in biochemical assay	0
E55	P55L emergent in resistant MHV	0
A129	T129M possible minor MHV resistant-emergent change	1 (Day 5, A129P)
T135	T135I 3.5-fold change in biochemical assay	0
F140	within 5 Å of NIR, F140A 39-fold change in biochemical assay	0
L141	within 5 Å of NIR	1 (Day 5, L141F)
N142	within 5 Å of NIR	0
G143	within 5 Å of NIR	0
S144	within 5 Å of NIR, S144A emergent in resistant MHV, 92-fold change in biochemical assay	1 (Day 5, S144P)
C145	within 5 Å of NIR	1 (Day 5, C145F)
D153	Position where tx-emergent substitutions were detected in C4671005	2 (Day 5, D153Y)
H163	within 5 Å of NIR	0
H164	within 5 Å of NIR, H164N 6.4-fold change in biochemical assay	0
M165	within 5 Å of NIR	0
E166	within 5 Å of NIR, E166A 33-fold change in biochemical assay	0
L167	within 5 Å of NIR	0
P168	within 5 Å of NIR	0
H172	within 5 Å of NIR, H172Y 233-fold change in biochemical assay	0
V186	within 5 Å of NIR	0
D187	within 5 Å of NIR	0
R188	within 5 Å of NIR	1 (Day 5, R188M)
Q189	within 5 Å of NIR, Q189K 65-fold change in biochemical assay, high freq. of suspected sequence artifacts in C4671005	6 (Q189K: 1 @ Day 1, 5 @ Day 5)
T190	within 5 Å of NIR	1 (Day 5, T190I)
A191	within 5 Å of NIR	0
Q192	within 5 Å of NIR	0
D248	D248E 3.7-fold change in biochemical assay	0
A260	Position where tx-emergent substitutions were detected in C4671005	4 (Day 5, 3 A260V, 1 A260T)
cleavage site #10 T6449	Position where tx-emergent substitutions were detected in C4671005	2 (Day 5, T6449I)
Detected at any timepoint (Baseline or Day 5) in 17/97 (18%) NIR/r treated subjects in C4671005 w/ resistance data (1 hospitalized)		

Source: FDA analysis.

SARS-CoV-2 RNA changes in NP swab samples generally did not differ substantially between Paxlovid treated subjects with or without any of the above-noted potential resistance-associated amino acid substitutions (Figure 2). Several subjects appeared to have a rebound in SARS-CoV-2 RNA levels around Day 10

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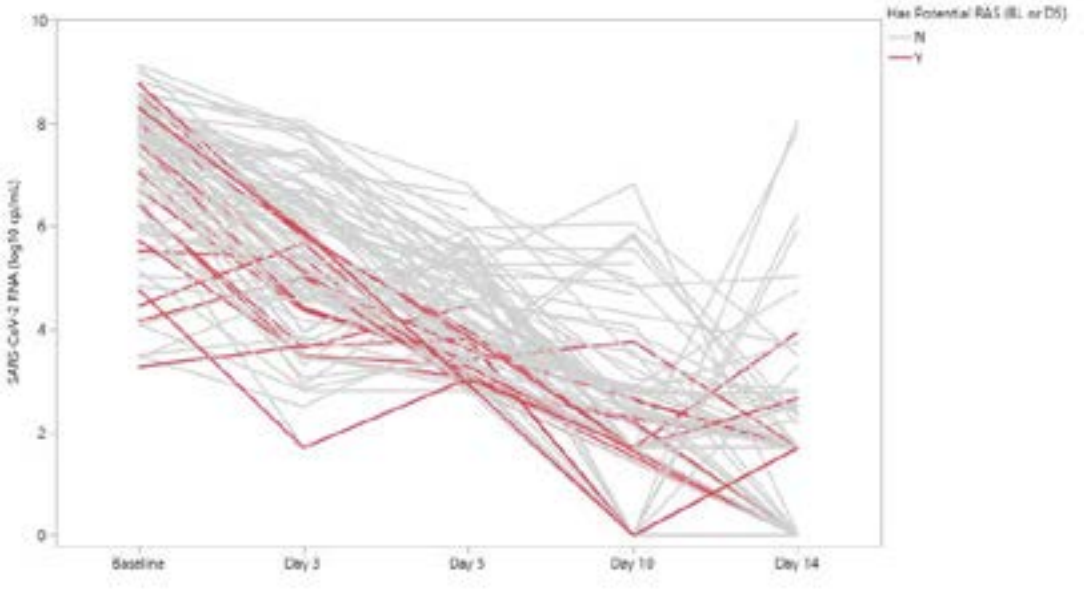
or Day 14, although this occurred among subjects with or without potential resistance-associated substitutions detected at Day 1 or Day 5.



Source: FDA analysis.

Figure 2. SARS-CoV-2 RNA levels in NP swabs among Paxlovid treated subjects with or without SARS-CoV-2 amino acid substitutions detected in Mpro or cleavage site positions potentially associated with resistance.

In summary, currently there are no clear signals of baseline or treatment-emergent NIR resistance from the preliminary analyses of clinical trial EPIC-HR. These analyses will continue to be conducted as more complete data from EPIC-HR are obtained and reported.

IX. Human Clinical Safety

Paxlovid (NIR coadminstered with ritonavir) is currently being evaluated in clinical trials for COVID-19 treatment in outpatient settings and for post-exposure prophylaxis against COVID-19 in asymptomatic household contacts of individuals with confirmed SARS-CoV-2 infection. For the proposed EUA, the safety database consists of data from EPIC-HR from 1109 adult non-hospitalized subjects with COVID-19 at high risk for severe COVID-19 who were randomized to receive Paxlovid po bid x 5 days and had follow-up data through Day 28 after initiating treatment.

- The EUA submission originally included EPIC-HR interim analysis safety data from 672 adults as well as topline preliminary safety data from an

additional 273 subjects who were randomized to receive Paxlovid in EPIC-HR and had not completed 28 days of follow-up.
- Later in the EUA review cycle on 12/16/2021 topline analysis safety data were submitted for the full safety analysis set.
- Supplemental data were also available from 7 healthy adult subjects who received Paxlovid at or above the proposed dose for at least 5 days in the Phase 1 study C4671001 (500 mg NIR with 100 mg ritonavir bid for 10 days).

In this EUA review, safety subsections provide the interim analysis safety assessment as the primary safety assessment followed by the later submitted full topline analysis safety assessment.

The safety population from EPIC-HR is most similar to the intended population for the proposed use under EUA of the currently ongoing Phase 2/3 trials in that these subjects have mild-to-moderate COVID-19 and are at high risk for severe disease. Key differences with the intended population for use under EUA include the following:
- Adolescents 12 years of age and older and weighing at least 40 kg were not included in the trials (the safety database only includes adults).
- Pregnant women were not included in the trials.
- Individuals with moderate to severe renal impairment, GFR <45 mL/min/1.73/m^2, history of active liver disease, or abnormal liver enzymes (AST or ALT ≥ 2.5 X upper limit of normal [ULN] or total bilirubin ≥ 2 X ULN) were excluded from EPIC-HR. However, separate renal impairment and hepatic impairment studies were conducted using single doses of 100 mg NIR administered with ritonavir (see Table 1).
- Individuals who received a COVID-19 vaccine were excluded from EPIC-HR and will not be excluded from the proposed EUA population (though it would be unlikely that prior COVID-19 vaccination would impact the safety profile of Paxlovid).
- A low percentage of subjects in EPIC-HR were black or African American (approximately 5%), and only one subject with HIV infection was enrolled.

<u>EPIC-HR Safety Results</u>
The safety analysis from the pivotal trial, EPIC-HR, includes 1109 Paxlovid recipients and 1115 placebo recipients with TEAEs reported up to Day 34.
- The initial EUA submission contained datasets and analysis for the interim analysis, which included 672 Paxlovid recipients and 677 placebo recipients with TEAEs reported up to Day 34 through the data cutoff date of October 26, 2021; these numbers differed from the numbers in the full analysis set because 12 subjects were not treated, and differed from the numbers in the mITT2 analysis set because 19 subjects were excluded from the mITT2 because they did not have at least one post-baseline visit through Day 28.

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- Topline preliminary data for all enrolled subjects (including an extra 437 Paxlovid recipients and 438 placebo recipients) was submitted near the end of the review on 12/14/2021.

Adverse events in EPIC-HR were graded according to a five point scale adapted from the toxicity grading scale of the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events version 2.1 (July 2017) from the National Institutes of Health. Clinical events related to COVID-19, including deaths and SAEs, could be included as AEs.

The primary safety analysis from the pivotal trial had the following major limitations (in addition to the limitations related to the population for the safety database listed previously):

1. The analysis of adverse events of special interest (hemodynamic events, inflammatory events, and thyroid related events) was not included in this submission, although data on AEs, vital signs, and laboratory markers were included.
2. In the interim analysis (with topline data suggesting similar proportions among all enrolled subjects), approximately one-third of subjects reported at least one important protocol deviation (in the full analysis set, 37% of Paxlovid recipients and 37% of placebo recipients). However, similar proportions of subjects had protocol deviations in each treatment group. In addition, the only two protocol deviations reported in >5% of subjects were ones that could negatively impact the efficacy assessment but should not affect the safety assessment: NIR or placebo and ritonavir or placebo taken >5 minutes apart (11% of subjects) and missing more than 25% of COVID-19-related symptoms diary entries (19% of subjects).

Safety Overview

Table 12 below shows the summary of safety events based on the EPIC-HR interim analysis. In general, rates of overall safety events were similar between treatment groups or higher in the placebo group, with the exception of AEs considered related to treatment. Similar results were observed in the topline safety results from all enrolled subjects.

Table 12: Summary of Overall Adverse Events in EPIC-HR through Day 34, Interim Analysis

	Paxlovid n=672	**Placebo n=677**
Any AE	133 (20%)	151 (22%)
AE related to study treatment	49 (7%)	29 (4%)
Any Grade 3 or higher AE	21 (3%)	58 (9%)
Any Grade 3 or higher AE related to study treatment	3 (<1%)	4 (<1%)
SAE	13 (2%)	46 (7%)
SAE related to study treatment	1 (<1%)	0

AEs with outcome of death	0	10 (1%)
Fatal AEs related to study treatment	0	0
AEs leading to discontinuation of study drug	16 (2%)	29 (4%)
AEs leading to discontinuation of study drug related to study treatment	7 (1%)	3 (<1%)
AEs leading to dose reduction or temporary discontinuation	1 (<1%)	4 (<1%)
AEs leading to dose reduction or temporary discontinuation related to study treatment	0	3 (<1%)

Sources: EUA request Table 41 and 42 and analysis of the EPIC-HR ADAE dataset.

Deaths

A total of 10 deaths occurred in EPIC-HR by the interim analysis, all in the placebo group and all related to COVID-19. The AEs resulting in death included COVID-19 pneumonia (n=5), COVID-19 (n=2), hypoxia (n=1), acute respiratory distress syndrome (n=1), and acute respiratory failure (n=1). The subjects who died were older than the general study population (median age 70 years, range 52 to 84) and generally had multiple comorbidities associated with severe COVID-19.

With the topline data from all enrolled subjects, an additional 3 placebo recipients died, for a total of 13 deaths in EPIC-HR (all among placebo recipients).

Serious Adverse Events

A total of 59 subjects reported SAEs in the interim analysis, 13 (2%) Paxlovid recipients versus 46 (7%) placebo recipients. Most SAEs were in the infections and infestations system organ class (SOC) [8 (1%) Paxlovid recipients versus 35 (5%) placebo recipients], with COVID-19 pneumonia being the most common single SAE [4 (<1%) Paxlovid recipients versus 21 (3%) placebo recipients]. No SAEs reported in more than one subject were reported more frequently in the Paxlovid versus placebo group.

Similar overall SAE results were observed in the topline safety results from all enrolled subjects (18/1109, or 2%, Paxlovid recipients versus 74/1115, or 7%, placebo recipients reported SAEs); a breakdown of specific SAEs was not included in the topline results.

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Adverse Events Leading to Discontinuation of Study Drug
A total of 45 subjects discontinued study treatment due to AEs in the interim analysis, 16 (2%) Paxlovid recipients versus 29 (4%) placebo recipients. AEs leading to discontinuation reported in more than 1 Paxlovid recipient included nausea (n=5 Paxlovid recipients and 2 placebo recipients), vomiting (n=4 Paxlovid recipients and 0 placebo recipients), and creatinine renal clearance decreased (n=2 Paxlovid recipients and 4 placebo recipients, also including glomerular filtration rate abnormal or decreased).

Similar numbers of overall AEs leading to discontinuation were observed in the topline safety results from all enrolled subjects (23/1109, or 2%, Paxlovid recipients versus 47/1115, or 4%, placebo recipients discontinued study drug due to AEs); a breakdown of specific AEs leading to discontinuation of study drug was not included in the topline results.

Common Adverse Events
A total of 133/672 (20%) Paxlovid recipients and 151/677 (22%) placebo recipients reported an AE by Day 34 in the interim analysis. The most common AEs are shown in Table 13. AEs reported in more Paxlovid versus placebo recipients with a difference of at least 3 subjects include dysgeusia (32 versus 1 subject), diarrhea (26 versus 13 subjects), vomiting (9 versus 2 subjects), hypertension (6 versus 1 subject), chills (5 versus 0 subjects), anosmia (3 versus 0 subjects), and oropharyngeal pain (3 versus 0 subjects), among Paxlovid and placebo recipients, respectively. AEs reported in more placebo versus Paxlovid recipients (difference of at least 3 subjects) include COVID-19 pneumonia (23 versus 5 subjects), COVID-19 (12 versus 3 subjects), fibrin D-dimer increased (11 versus 3 subjects), alanine aminotransferase increased (10 versus 4 subjects), pneumonia (7 versus 2 subjects), dyspnea (6 versus 3 subjects), hypoxia (5 versus 0 subjects), fatigue (5 versus 2 subjects), erythema (4 versus 0 subjects), acute respiratory failure (4 versus 1 subject), and pain (3 versus 0 subjects), among placebo and Paxlovid recipients, respectively.

Table 13: Adverse Events Reported by ≥1.0% of Subjects in Either Treatment Group in EPIC-HR through Day 34, Interim Analysis

Preferred Term	**Paxlovid n=672**	**Placebo n=677**
Subjects with at least 1 AE	133 (20%)	151 (22%)
Dysgeusia	32 (5%)	1 (<1%)
Diarrhea	26 (4%)	13 (2%)
Nausea	13 (2%)	14 (2%)
Headache	10 (1%)	11 (2%)
Vomiting	9 (1%)	2 (<1%)
Pyrexia	8 (1%)	7 (1%)
COVID-19 Pneumonia	5 (<1%)	23 (3%)

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Alanine aminotransferase increased	4 (<1%)	10 (1%)
COVID-19	3 (<1%)	12 (2%)
Fibrin D-dimer Increased	3 (<1%)	11 (2%)
Pneumonia	2 (<1%)	7 (1%)

Sources: EUA request Table 43 and analysis of the EPIC-HR ADAE dataset.

Similar AE results were observed in the topline safety results from all enrolled subjects. A total of 251/1109, or 23%, Paxlovid recipients versus 266/1115, or 24%, placebo recipients reported AEs. A similar pattern of specific AEs was also seen, except that an imbalance in vomiting AEs was no longer observed with the additional data (among all enrolled subjects, 12/1109, or 1%, Paxlovid recipients versus 9/1115, or 1%, placebo recipients reported an AE of vomiting). Among all enrolled subjects, the AEs reported in ≥1% of Paxlovid recipients (rounding up) that occurred at a greater frequency (≥5 subject difference) than in the placebo group were dysgeusia (62/1109 or 6% versus 3/1115 or <1%), diarrhea (34/1109 or 3% versus 18/1115 or 2%), hypertension (7/1109 or 1% versus 2/1115 or <1%), and myalgia (7/1109 or 1% versus 2/1115 or <1%, among Paxlovid versus placebo recipients, respectively).

Grade 3 and Above Adverse Events

A total of 21/672 (3%) Paxlovid recipients and 58/677 (9%) placebo recipients reported an adverse event with toxicity grade of 3 or greater. The only grade 3 or higher AEs reported in more than one Paxlovid recipient were creatinine renal clearance decreased (3 Paxlovid recipients versus 4 placebo recipients), COVID-19 pneumonia (3 Paxlovid recipients versus 19 placebo recipients), and blood fibrinogen decreased (2 Paxlovid recipients versus 0 placebo recipients). Similar overall results were observed in the topline safety results from all enrolled subjects.

Adverse Events Considered Related to Study Treatment

A total of 49/672 (7%) Paxlovid recipients and 29/677 (4%) placebo recipients reported an AE considered related to the study treatment in the interim analysis. The most common related AEs are shown in Table 14. Related AEs reported in more Paxlovid versus placebo recipients (difference of at least 2 subjects) include dysgeusia (25 versus 1 subject), diarrhea (13 versus 2 subjects), vomiting (5 versus 1 subject), dyspepsia (5 versus 2 subjects), and dizziness (2 versus 0 subjects among Paxlovid versus placebo recipients, respectively). No related AEs were reported in more placebo than Paxlovid recipients with a difference of at least 2 subjects. A total of 94% (104/111) of all AEs reported were graded as mild to moderate. None of the grade 3 or higher related AEs were reported in more than one subject. Adverse events considered related to study treatment were not reported in the topline results of all enrolled subjects.

Table 14: AEs Considered Related To Study Treatment* Reported in More than One Subject in Either Treatment Group in EPIC-HR through Day 34, Interim Analysis

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Preferred Term	Paxlovid n=672	Placebo n=677
Subjects with at least 1 Related AE	49 (7%)	29 (4%)
Dysgeusia	25 (4%)	1 (<1%)
Diarrhea	13 (2%)	2 (<1%)
Nausea	6 (<1%)	7 (1%)
Vomiting	5 (<1%)	1 (<1%)
Dyspepsia	5 (<1%)	2 (<1%)
Gastroesophageal reflux disease	2 (<1%)	1 (<1%)
Dizziness	2 (<1%)	0
Abdominal pain upper	1 (<1%)	2 (<1%)
Rash	1 (<1%)	2 (<1%)

*Considered related to study treatment by the investigator
Sources: EUA request Table 44 and analysis of the EPIC-HR ADAE dataset.

Adverse Events of Special Interest (AESIs)
Protocol-defined AESIs in EPIC-HR, based on the findings in the nonclinical studies, include hemodynamic events, inflammatory events, and thyroid-related events. Although the Applicant did not include an analysis of the AESIs in the EUA submission, a review of the submitted data related to the AESIs in the interim analysis showed the following:

- Hemodynamic Events
  - Overall, there were no notable differences in the changes in vital sign parameters over time between the Paxlovid and placebo groups.
  - As noted above, more Paxlovid recipients had an AE of hypertension (6 Paxlovid recipients versus 1 placebo recipient). Among the 6 Paxlovid recipients with an AE of HTN:
    - The median age was 60 years (range 40 to 71)
      - *The placebo recipient was 44-years-old*
    - The AE onset day was 2, 4, 4, 4, 5, and 25 (*9 for the placebo recipient*)
    - One AE was graded as moderate (onset Day 4) and one was graded as severe (onset day 5), but the remainder were graded as mild.
    - All but one of the Paxlovid recipients, as well as the placebo recipient, were given additional concomitant treatment for the AE of hypertension.
    - None of the hypertension AEs were categorized as SAEs or as related to treatment, and none resulted in discontinuation of study treatment.
      - *In the topline results of all enrolled subjects, a similar pattern for hypertension AEs was seen. Hypertension AEs were reported in 7 Paxlovid recipients (4 mild, 2 moderate, 1 severe) and 2 placebo recipients (one mild, one moderate). In addition, one grade 4 SAE of "hypertensive crisis" was reported in a Paxlovid recipient.*
  - Numerically less Paxlovid versus placebo recipients had an AE of hypotension or orthostatic hypotension (1 Paxlovid recipient versus 3 placebo recipients).
  - *Given the nonclinical findings (increased blood pressure in the safety pharmacology study in monkeys with a clinical margin of 1.9), the imbalance*

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in hypertension AEs, and the temporal clustering of 5 of 6 events during the 5-day treatment period, this may be related to study treatment despite the lack of a general increase in blood pressure during treatment in the treated population. However, this AE was infrequent. Hypertension should be included as an adverse reaction with Paxlovid in Section 6 of the fact sheet.

- Inflammatory Events
  - Overall, there were no clinically significant differences in the changes in platelet levels, leukocytes, lymphocytes, neutrophils, C-reactive protein, fibrinogen, ferritin, procalcitonin, or d-dimer over time between the Paxlovid and placebo groups, and any possible trends favored the Paxlovid group (i.e., there was a slight trend towards a faster decrease in some inflammatory markers like d-dimer and fibrinogen in subjects receiving Paxlovid).
  - Given that the disease being treated (COVID-19) can lead to inflammation, separating out AEs of inflammatory events from the sequelae of COVID-19 is challenging. However, in general, there were no concerning trends regarding AEs related to inflammatory events suggesting a higher incidence among Paxlovid recipients.
  - *At this point, there are no clinical findings related to inflammatory events that warrant inclusion in the fact sheet.*
- Thyroid-related Events
  - Overall, there were no notable differences in the changes in free thyroxine (free T4) or thyrotropin (thyroid stimulating hormone) over time between the Paxlovid and placebo groups.
  - In regards to thyroid-related AEs:
    - A total of 2 Paxlovid recipients versus 1 placebo recipient had AEs of blood thyroid stimulating hormone increased. These started on Day 2 (Paxlovid recipient) and Day 14 (Paxlovid and placebo recipient). None were SAEs.
      - Among the 2 Paxlovid recipients, the events were mild and considered not related to study treatment.
      - In the placebo recipient, the event was graded as moderate and was considered related to study treatment.
    - A total of 1 Paxlovid recipient versus 0 placebo recipients had an AE of thyroxine increased. This AE was mild, nonserious, not considered related to study treatment, started on Day 6 and ended on Day 40.
  - *At this point, there are no clinical findings for thyroid-related events that warrant inclusion in the fact sheet.*

Laboratory Findings, Vital Signs, and ECG Results

Changes in laboratory parameters and vital signs from baseline were similar between the Paxlovid and placebo groups in the interim analysis (these data were not provided in the topline results of all enrolled subjects that were provided during the EUA review). ECG results from the sentinel group in EPIC-HR were previously reviewed (see IND 153517 SDN 62 review from 8/27/2021 in DARRTS); unblinded ECG data did not show any notable changes in ECG intervals or appreciable

differences in ECG parameters on Days 3, 5, and 14 between 34 Paxlovid recipients versus 33 placebo recipients.

Please see the discussion of the imbalance in AEs of hypertension in the section above.

Safety Issues of Concern based on Ritonavir Labeling
The FDA-approved label for ritonavir, which is for a higher 600 mg bid ritonavir dose given indefinitely for use as part of HIV treatment, includes the following contraindications and warnings and precautions (in addition to those related to drug-drug interactions, which will be addressed separately) that could be relevant to the population proposed for use under the EUA; it is unclear how many of these safety issues would be a concern with the lower 100 mg bid dose and five-day course proposed for Paxlovid. AEs or other findings related to these safety issues from the interim analysis in EPIC-HR are described below.

- **Allergic/hypersensitivity reactions (including anaphylaxis, toxic epidermal necrolysis, and Stevens-Johnson syndrome)**
  - There were no cases of serious allergic or hypersensitivity reactions, and AEs in the skin and subcutaneous disorders SOC were well-balanced between treatment groups.
    - Overall, 5 Paxlovid recipients versus 7 placebo recipients had AEs in the skin and subcutaneous disorders SOC.
    - A total of 3 Paxlovid recipients and 2 placebo recipients had AEs of rash or rash maculo-papular (one graded as severe in each treatment group, the rest graded as mild).
    - One placebo recipient had mild urticaria.
    - One Paxlovid recipient had mild pruritus.
- **Hepatotoxicity**
  - Hepatotoxicity Adverse Events
    - A total of 20 subjects had AEs related to hepatotoxicity: 7 Paxlovid recipients versus 13 placebo recipients
      - 14 subjects (4 Paxlovid recipients and 10 placebo recipients) had alanine aminotransferase increased
      - 5 subjects (2 Paxlovid recipients and 3 placebo recipients) had aspartate aminotransferase increased
      - 3 subjects (1 Paxlovid recipient and 2 placebo recipients) had hepatic enzyme increased
      - One subject each had liver injury (placebo recipient), hepatitis toxic (Paxlovid recipient), and hyperbilirubinemia (Paxlovid recipient)
    - The only two subjects with hepatotoxicity AEs considered related to study treatment were placebo recipients
    - The only hepatotoxicity SAE was in a placebo recipient
    - A total of 1 Paxlovid recipient and 4 placebo recipients had grade 3 or higher hepatotoxicity AEs
  - Subjects Meeting the Sponsor's Hepatotoxicity Criteria

        - A total of 7 Paxlovid recipients and 11 placebo recipients met hepatotoxicity criteria.
            - Among Paxlovid recipients: 4 subjects had hepatic transaminase elevations exceeding 5X the ULN and 1 subject each had hepatitis toxic, cholestasis, and hyperbilirubinemia.
                - None of the Paxlovid recipients met Hy's Law Criteria
            - Among placebo recipients, 10 subjects had hepatic transaminase elevations exceeding 5X the ULN and 1 subject had liver injury
    - Laboratory Changes: There were no notable differences in the changes in prothrombin time, bilirubin, aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase over time between the Paxlovid and placebo groups.
- **Pancreatitis**
    - No subjects reported AEs of pancreatitis or elevated amylase or lipase.
    - Of note, amylase and lipase were not routinely collected as part of the laboratory assessments.
- **PR interval prolongation (with second and third degree heart block)**
    - No subjects had AEs of heart block or PR interval prolongation.
        - A total of five subjects had any AEs related to heart rate or rhythm: four subjects (2 placebo recipients and 2 Paxlovid recipients) had palpitations, one considered serious and related and leading to discontinuation of study treatment (Paxlovid recipient, discussed under the SAE section), and one placebo recipient had sinus tachycardia.
    - As noted in the ECG section above, there were no notable changes in ECG intervals with treatment observed among the subjects in the sentinel cohort in EPIC-HR.
- **Total cholesterol and triglycerides elevations**
    - One subject (placebo recipient) had an AE of mild hypertriglyceridemia. No AEs were reported related to total cholesterol levels.
    - Of note, total cholesterol and triglycerides were not routinely collected as part of the laboratory assessments.
- **New onset or exacerbations of diabetes mellitus or hyperglycemia**
    - A total of 17 subjects had AEs related to exacerbations of diabetes mellitus or hyperglycemia (preferred terms: blood glucose increased, hyperglycemia, impaired fasting glucose, diabetes mellitus, type 2 diabetes mellitus, diabetes mellitus inadequate control, and glycosylated hemoglobin increased): 7 Paxlovid recipients and 10 placebo recipients
        - None of the AEs were serious
        - The only AE that was considered related or led to study drug withdrawal was in a placebo recipient
        - The AEs were graded higher than moderate in 2 Paxlovid recipients and 4 placebo recipients
        - There was no temporal pattern
    - There were no notable differences in the changes in glucose over time between the Paxlovid and placebo groups.
- **Redistribution/accumulation of body fat**

  - No AEs were reported relating to redistribution/accumulation of body fat.
  - Weight was only recorded at screening
- **Spontaneous bleeding in patients with hemophilia**
  - The only AE reported that had to do with bleeding, vaginal hemorrhage, was reported in both a Paxlovid recipient and a placebo recipient.
  - No subjects had hemophilia

Assessment: From data available with the EPIC-HR interim analysis, there was no apparent signal observed for the above safety issues of concern in ritonavir labeling when comparing subjects who received 5 days of Paxlovid (containing 100 mg bid ritonavir) versus placebo. The lack of these safety findings may be due to the low dose and short course of ritonavir used with Paxlovid for the proposed authorized use; however, the small numbers in the trial preclude any formal conclusions. Of the above listed safety issues of concern, the Sponsor has proposed to include hepatotoxicity in the warnings and precautions of the Paxlovid fact sheet (in addition, history of clinically significant hypersensitivity reactions to the active ingredients is included in the contraindications section). This is consistent with labeling for the FDA-approved product VIEKIRA PAK, which included ritonavir 100 mg daily and was administered for 12-24 weeks. Based on the safety findings from EPIC-HR and the short course and low dose of ritonavir, inclusion of hepatotoxicity in the warnings and precautions of Paxlovid, without the other ritonavir labeled warnings and precautions listed above, is reasonable.

Special Populations:
A total of 112 subjects in the EPIC-HR interim analysis safety database (55 Paxlovid recipients and 57 placebo recipients) were flagged as having received or expected to receive COVID-19 monoclonal antibody treatment. Among these subjects:

- AEs were reported in 13/55 (24%) Paxlovid recipients and 18/57 (32%) placebo recipients.
- Treatment-related AEs were reported in 6/55 (11%) Paxlovid recipients (dysgeusia [n=4], diarrhea [n=1], and dry mouth [n=1], all grade 1) and 1/57 (2%) placebo recipients
- SAEs were reported in 1/55 (2%) Paxlovid recipients and 4/57 (7%) placebo recipients (none fatal)
- Grade 3 or higher AEs were reported in 1/55 (2%) Paxlovid recipients (worsening of COVID-19) and 8/57 (14%) placebo recipients

These proportions between Paxlovid versus placebo recipients are similar to the overall population and do not raise safety concerns about the concomitant use of Paxlovid with COVID-19 monoclonal antibody treatment.

A separation of safety data by having received or expected to receive COVID-19 monoclonal antibody treatment was not included with the topline submission of data from all enrolled subjects.

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Supplementary Safety Data (Phase 1 Trials)

Key safety data from the supplementary trials submitted with this EUA include the following:

- **Study C4671001 (the first-in-human single ascending dose, multiple ascending dose study)**
  - Single ascending dose up to 1500 mg NIR and 750 mg NIR co-administered with 100 mg ritonavir (n=4 per dose):
    - There were no serious or severe AEs and no dose-related trends in number of AEs.
    - No single AE was reported in more than one subject.
    - The only discontinuation due to an AE was due to COVID-19.
  - Multiple ascending dose up to 500 mg NIR coadministered with 100 mg ritonavir bid x 10 days (19 NIR/r recipients across dose levels, with 4 subjects receiving 75 mg NIR, 8 subjects receiving 250 mg NIR, and 7 subjects receiving 500 mg NIR bid, and 10 placebo recipients):
    - There were no serious or severe AEs, discontinuations due to an AE, or dose-related trends in AEs.
    - AEs reported in more than one subject (across dose levels) included:
      - Diarrhea (n=4 NIR/r recipients across dose levels, and n=1 placebo recipients)
      - Blood thyroid stimulating hormone increased (n=3 NIR/r recipients and n=2 placebo recipients)
      - Dysgeusia (n=3 NIR/r recipients)
      - Fatigue (n=2 NIR/r recipients, n=1 placebo recipient)
      - Headache (n=2 NIR/r recipients)
  - Single supratherapeutic dose (2250 mg NIR with 100 mg ritonavir, n=10) versus placebo with 100 mg ritonavir (n=10)
    - All AEs were mild and frequency was the same between the placebo and the treatment group (30% each group reported AEs), and no AE was reported by more than one NIR/r recipient.
    - ECG results:
      - See IND 153517 SDN 60 review from 8/27/2021 in DARRTS; there was no evidence of clinically relevant QTc interval prolongation with the supratherapeutic dose versus placebo.
      - Currently, data needed to support inclusion of ECG and QT information in the EUA Fact Sheet have not been submitted and reviewed; therefore, such data will not be included in the EUA Fact Sheet (see also Interdisciplinary Review Team (IRT) for Cardiac Safety Studies reviews from 10/14/2021 and 11/18/2021 in DARRTS).
- **Study C4671010 (hepatic impairment study: preliminary topline report)**
  - There were no SAEs, and the only AE reported in more than one subject was dysgeusia (n=2).
- **Study C4671011 (renal impairment study)**
  - This study enrolled subjects with normal renal function (n=10) and mild, moderate, or severe renal impairment (n=8 per group) as per the table

below (taken from the C4671011 clinical study report) who received 100 mg NIR on Day 1 and 100 mg ritonavir on Day 1 and at -12 hours, +12 hours, and +24 hours in relation to the Day 1 dose.

Table 2. Renal Function Categories by eGFR Ranges

Cohort	Renal impairment[a]	Estimated eGFR[b] (mL/min)
1	Moderate renal impairment	≥30 to <60
2	Mild renal impairment	60 – <90
3	None (normal)	≥90
4	Severe renal impairment	<30 and not requiring dialysis

a. Stages of renal impairment are based on KDOQI Clinical Practice Guidelines for CKD.[3]
b. Estimate of eGFR based on CKD-EPI formula. The average of the 2 screening eGFR values were used for group assignment.

Source: Appendix 16.1.1

- A higher proportion of subjects with severe renal impairment reported AEs (5/8 (62.5%) versus 1/8, 1/8, and 2/10 for the moderate renal impairment, mild renal impairment, and normal renal function groups, respectively). A total of 17 of the 22 all-causality AEs in the study were among subjects with severe renal impairment. AEs reported by >1 subject included:
  - Headache (1 subject with moderate renal impairment and 2 subjects with normal renal function)
  - Dysgeusia (2 subjects with severe renal impairment)
  - Asthenia (2 subjects with severe renal impairment)
  - Dry mouth (2 subjects with severe renal impairment)
- A higher proportion of subjects with severe renal impairment reported treatment-related adverse events (2/8, 25%, versus 0/8, 0/8, and 0/10 for the moderate renal impairment, mild renal impairment, and normal renal function groups respectively). Treatment-related adverse events included mild dysgeusia (n=2) and mild dry mouth (n=2, same two subjects as for dysgeusia).
- One subject (with severe renal impairment) reported 3 SAEs (severe pulmonary edema, moderate acute kidney injury, and moderate pneumonia) and discontinued the study due to these AEs. This one subject was responsible for 11 of the 22 AEs in the study (in addition to the three SAEs, mild asthenia, mild anemia, moderate bradycardia, moderate hyperkalemia, mild hyponatremia, moderate hypotension, moderate metabolic acidosis, and mild thrombocytopenia).
  - This subject was a 75-year-old white female with diabetes mellitus type 2, chronic kidney disease stage 4 (baseline creatinine 2.21 mg/dL), hypertension, anemia, depression, metabolic acidosis, history of left nephrectomy, history of renal cell carcinoma, and history of aortic valve replacement who received NIR 100 mg on Day 1 and 100 mg ritonavir at -12 hours, with NIR, at +12 hours, and at +24 hours. On Day 2, her creatinine had increased to 3.45 mg/dL and her potassium increased to 6.3 mmol/L, and she was sent to the emergency room where she was diagnosed with likely pneumonia based on a chest X-ray with an airspace opacity. She subsequently developed pulmonary edema and fluid overload necessitating ICU admission on Day 3. She subsequently

recovered and was discharged from the hospital on Day 7. The investigator thought her SAEs and AEs were unrelated to study drug.
    - *AEs experienced by the other 4/8 subjects with severe renal impairment who reported AEs included dry mouth (n=2), nausea (n=1), asthenia (one additional subject), and dysgeusia (n=2).*
- There were no deaths in the study.

Reviewer Comment: Two safety issues are raised by the supplementary safety data from the Phase 1 trials:

1. *Data needed to support EUA Fact Sheet information pertaining to the QT interval/cardiac electrophysiology describing supratherapeutic NIR/r dosing ECG findings have not been submitted for IRT review.*
2. *No concerning safety findings were seen in the 7 subjects who received 500 mg NIR with 100 mg ritonavir bid x 10 days in Study C4671001. However, there was an imbalance in safety findings between subjects with severe renal impairment and subjects with normal to moderate renal impairment in Study C4671011 who all received 100 mg NIR as a single dose administered with ritonavir, with one of the eight subjects with severe renal impairment developing an SAE of moderate acute kidney injury the day after receiving NIR. While it is unclear if these safety findings were related to NIR receipt or to the increased comorbidities generally associated with severe renal impairment, this finding raises safety concerns about NIR/r dosing in patients with severe renal impairment (as the therapeutic dose would be higher than 100 mg NIR administered with ritonavir); therefore, the fact sheet should convey that Paxlovid is not recommended in patients with severe renal impairment. An EUA condition of authorization should be for the sponsor to conduct a study of NIR/r for treatment of mild-to-moderate COVID-19 in patients with severe renal impairment, including patients on dialysis, to assess the safety and appropriate dose in this population.*

Noteworthy Drug Interactions

Paxlovid has multiple noteworthy drug interactions. Individuals taking concomitant medications that could have clinically significant drug interactions with Paxlovid were excluded from EPIC-HR. Please see *Section XI. Human Clinical Pharmacology* for more information on noteworthy drug interactions.

X. Specific Populations

Dosing Considerations for Specific Populations

Pediatrics

As of December 2, 2021 over 7 million children have tested positive for COVID-19 in the United States, Puerto Rico, and Guam (https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/ accessed December 10, 2021). Based on these data, for the week ending

December 2, 2021, children represented 22.4% of the weekly reported cases. While COVID-19 is typically milder in children, some pediatric patients require hospitalization and ICU-level care (Götzinger et al. 2020). Given that COVID-19 can be a serious and life-threatening disease in adolescent patients (particularly in those with risk factors for the development of severe illness and hospitalization), there is prospect of benefit for this population.

Safety and PK data are not available in pediatrics. The inclusion of pediatric patients 12 years and older and weighing at least 40 kg in the authorized use is supported by the following: 1) the extrapolation of efficacy is deemed appropriate as the course of the disease and the response to treatment are sufficiently similar in adults and children; 2) the systemic NIR/r exposures are expected to be comparable in adolescents and adult patients administered the adult dose (see details in Pharmacometrics Review); and 3) the dose of NIR/r 300/100 mg BID was well-tolerated in adults weighing 42-158 kg in the Phase 2/3 EPIC-HR Study.

Population PK simulations were conducted for pediatric patients ≥12 to < 18 years of age using the CDC National Center for Health Statistics growth chart. These simulations suggest that a dose of NIR/r 300 mg/100 mg BID in adolescents provide higher geometric mean NIR AUC_{0-12}, C_{max} and C_{trough} by 32%, 37% and 25%, respectively, as compared to adults receiving the same dose. In comparison, a dose of NIR/r 150 mg/100 mg BID in adolescents provided lower geometric mean NIR AUC_{0-12}, C_{max} and C_{trough}, by 14%, 6% and 22%, respectively, as compared to adults. The NIR/r 300 mg/100 mg BID dose is expected to maintain efficacious trough concentrations above the EC90 over the entire dosing interval and are not expected to pose additional safety risks since a supratherapeutic dose of 2250 mg NIR (3 doses of 750 mg each administered at 0 h, 2 h and 4 h) and 3 doses of ritonavir 100 mg administered at -12 h, 0 h, and 12 h post NIR dose was well tolerated in ten healthy adult subjects (See *Section XI. Human Clinical Safety*). The geometric mean C_{max} and AUC_{inf} at this supratherapeutic dose was 15.940 µg/mL and 188.800 µg.hr/mL, respectively, which are 4 fold of those predicted in adolescents at the recommended NIR/r dose.

Additional simulations were conducted to determine the predicted C_{max} for pediatrics 12 years and older by weight band using NHANES data (See Figure 4, Pharmacometrics Review). In these simulations, the 95th percentile of predicted C_{max} in adults was used as the safety threshold. While the adult dose was deemed acceptable in adolescent patients ≥ 40 kg, approximately 50% of the pediatric patients < 40 kg were predicted to achieve C_{max} values above this safety margin *(See Appendix: Pharmacometrics Review).* For this reason, the adult dose is only recommended for pediatric patients weighing ≥ 40 kg.

Based on the totality of evidence to support the prospect of benefit, and the fact that it is reasonable to believe the known and potential benefits outweigh the known and potential risks, the authorization of Paxlovid for the treatment of mild-to-moderate COVID-19 should also include adolescents who are 12 years of age and

older and who weigh at least 40 kg. No dose adjustment is recommended in pediatric individuals who weigh at least 40 kg and are 12 years of age and older. Paxlovid is not recommended for pediatric individuals weighing less than 40 kg or those less than 12 years of age. A pediatric clinical trial which will enroll children across a broad age range is planned.

Renal Impairment

The primary route of elimination of NIR when administered with ritonavir is renal excretion of intact drug. In a dedicated renal impairment study (Study 1011) subjects received a single dose of 100 mg NIR and ritonavir 100 mg administered at -12, 0, 12, and 24 hours relative to NIR dosing (0.33 times the recommended dose). This NIR dose was chosen due to the less than dose proportional increase in exposures within the 250 mg to 750 mg dose range evaluated and anticipated increased exposures in renal impairment. As ritonavir is not eliminated renally and is not expected to be significantly altered by renal impairment, no dose reduction of ritonavir was considered necessary for subjects with renal impairment. Mean AUC_{inf} values of NIR in patients with mild (eGFR 60 to <90 mL/min), moderate (eGFR ≥30 to <60 mL/min), and severe renal impairment (eGFR <30 mL/min) were 24%, 87% and 204% higher than that of healthy volunteers, respectively (Table 15).

Table 15. Study 1011: Plasma and Urine Nirmatrelvir PK Parameters

	Normal Renal Function	Mild Renal Impairment	Moderate Renal Impairment	Severe Renal Impairment
N1,n	10,10	8,8	8,6	8,7
AUC_{inf} (µg.hr/mL)	14.46 (20)	17.91 (30)	27.11 (27)	44.04 (33)
C_{max} (µg/mL)	1.60 (31)	2.08 (29)	2.21 (17)	2.37 (38)
C_{12} (µg/mL)	0.34 (35)	0.44 (30)	0.79 (33)	1.21 (33)
$T_{1/2}$ (hr)	7.73 ± 1.82	6.60 ± 1.53	9.95 ± 3.42	13.37 ± 3.32
T_{max} (hr)	2 (1- 4)	2 (1- 3)	2.5 (1- 6)	3 (1- 6)
Ae %	31.20 (45)	42.65 (23)	30.83 (56)	18.46 (50)

Source: Study 1011
Geometric mean (%CV) for all: except Median (Range) for Tmax and arithmetic mean ± SD for t1/2
N1 = Number of subjects contributing to the summary statistics.
n = Number of subjects contr buting to the summary statistics for t1/2, AUCinf, CL/F and VZ/F
Ae = amount excreted

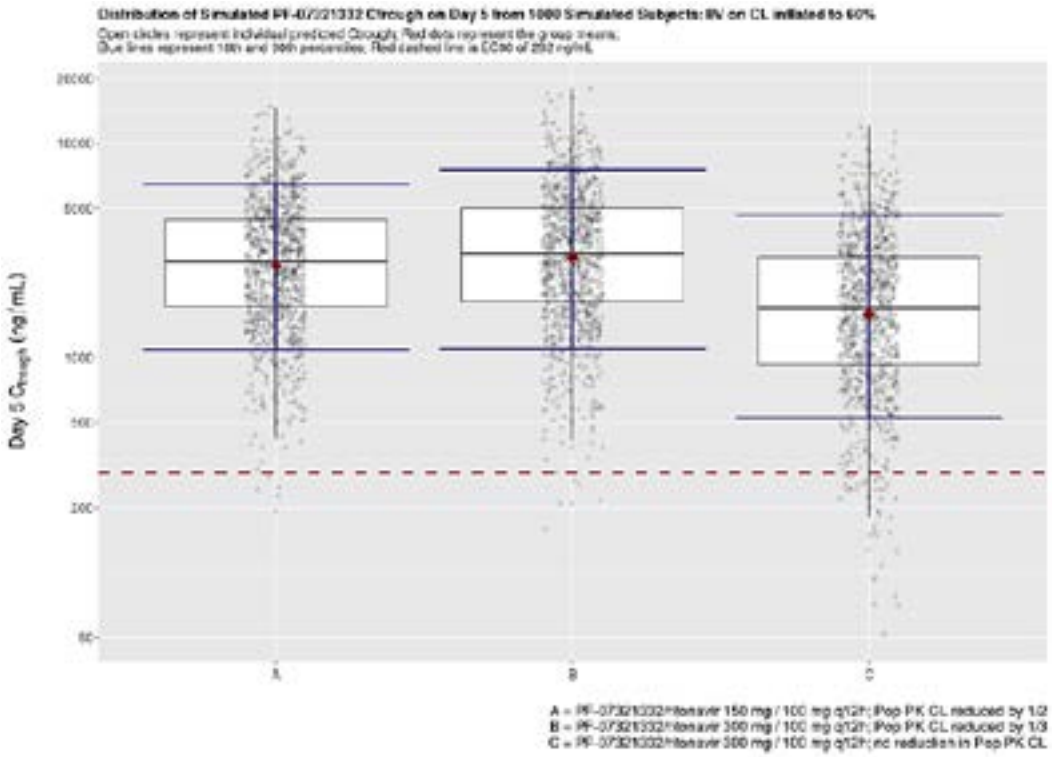
A preliminary population PK model was used to simulate C_{trough} concentrations in the following scenarios of reduced NIR clearance (Figure 3):

1. Clearance reduced by one-third to account for the 24% increase in AUC_{inf} in mild renal impairment, and dosed with 300/100 mg NIR/r twice daily
2. Clearance reduced by one-half to account for the 87% increase in AUC_{inf} in moderate renal impairment, and dosed with 150/100 mg NIR/r twice daily
3. No reduction in CL and dosed with 300/100 mg NIR/r twice daily (reference group)

Median C_{trough} values in all three scenarios exceeded the EC_{90} (292 ng/ml) shown to be efficacious in EPIC-HR. In a proof-of-concept evaluation, simulated NIR

exposures in subjects with moderate renal impairment with the proposed NIR/r dose reduction were comparable to those in subjects with normal renal function (See Figure 5, *Appendix 1: Pharmacometrics Review*). NIR/r was generally safe and well tolerated in subjects with mild and moderate renal impairment in Study 1011.

Figure 3. Predicted Nirmatrelvir C_{trough} by Dosing Regimen



Based on these simulations, no dose adjustment is recommended in patients with mild renal impairment. In patients with moderate renal impairment, the dose of Paxlovid should be reduced to 150 mg NIR and 100 mg ritonavir twice daily for 5 days. To mitigate the potential that this modified dose will lead to medication errors with the blister card packaging, specific counseling should be specified in the fact sheets and specific instructions with dispensing information should be provided to pharmacists.

Study 1011 noted a higher incidence of adverse events in patients with severe renal impairment (see *Section IX. Human Clinical Safety*). Given the 204% increase in AUC_{inf} and anticipated higher exposures at the clinical NIR dose of 300 mg BID, Paxlovid is not recommended in patients with severe renal impairment until more data are available. The appropriate dose for patients with severe renal impairment has not been determined.

<u>Hepatic Impairment</u>

Hepatic elimination is not expected to be a major route of elimination for NIR based on Phase 1 data. In plasma, the only drug-related entity was unchanged NIR. Preliminary unaudited PK data from an ongoing hepatic impairment study (Study 1010) of subjects with moderate hepatic impairment receiving a single dose of NIR 100 mg and 4 doses of ritonavir 100 mg at -12 hr, 0 hr, 12 hr, and 24 hr showed no meaningful impact of hepatic impairment on the PK of NIR compared to administration of NIR with ritonavir in healthy subjects with normal hepatic function (Table 16). These data reflect the full cohort of subjects planned for enrollment in this study.

Table 16. Study 1010: Unaudited Nirmatrelvir Plasma PK Parameters

	Normal Hepatic Function	Moderate Hepatic Impairment (Child-Pugh Class B)
N	8	8
AUC_{inf} (µg.hr/mL)	15.24 (36)	15.06 (43)
C_{max} (µg /mL)	1.89 (20)	1.92 (48)
$T_{1/2}$ (hr)	7.21 ± 2.10	5.45 ± 1.57
T_{max} (hr)	2.0 (0.6 - 2.1)	1.5 (1.0 - 2.0)

Source: Study 1010
Geometric mean (Geometric %CV) for all: except Median (Range) for Tmax and arithmetic mean ± SD for t1/2
N = Number of subjects contributing to the summary statistics

No dose adjustment is needed in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No PK or safety data are available regarding the use of NIR or ritonavir in subjects with severe hepatic impairment (Child-Pugh Class C); therefore, Paxlovid is not recommended for use in patients with severe hepatic impairment.

Pregnancy and Lactation

The need for dose adjustment in pregnant or lactating women has not been established due to the lack of PK and safety data in these patient populations.

Nonclinical Safety Considerations for Pregnancy and Lactation

- In an embryo-fetal development study with NIR, reduced fetal body weights following oral administration of NIR to pregnant rabbits were observed at systemic exposures (AUC) approximately 10 times higher than clinical exposure at the authorized human dose of Paxlovid. No other adverse developmental outcomes were observed in animal reproduction studies with NIR at systemic exposures (AUC) greater than or equal to 3 times higher than clinical exposure at the authorized human dose of Paxlovid.
- In animal reproduction studies with ritonavir, no evidence of adverse developmental outcomes was observed following oral administration of ritonavir to pregnant rats and rabbits at doses (based on body surface area conversions) or systemic exposures (AUC) greater than or equal to 3 times higher than clinical doses or exposure at the authorized human dose of Paxlovid.

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- In an ongoing pre- and postnatal developmental study, body weight decreases (up to 8%) were observed in the offspring of pregnant rats administered NIR at maternal systemic exposure (AUC_{24}) approximately 8 times higher than clinical exposures at the authorized human dose of Paxlovid. No body weight changes in the offspring were noted at maternal systemic exposure (AUC_{24}) approximately 5 times higher than clinical exposures at the authorized human dose of Paxlovid.
- Please see *Section XII* for detailed information.

XI. Human Clinical Pharmacology

Absorption, Distribution, Metabolism, and Excretion

The PK properties of NIR and ritonavir in healthy subjects are highlighted in Table 17.

Table 17. Pharmacokinetic Properties of Nirmatrelvir and Ritonavir in Healthy Subjects

	Nirmatrelvir (When Given With Ritonavir)	Ritonavir
Absorption		
T_{max} (h), median	3.00[a]	3.98[a]
Distribution		
% bound to human plasma proteins	69%	98-99%
Blood-to-plasma ratio	0.60	0.14[c]
V_z/F (L), mean	104.7[b]	112.4[b]
Elimination		
Major route of elimination	Renal elimination[d]	Hepatic metabolism
Half-life ($t_{1/2}$) (hr), mean	6.05[a]	6.15[a]
Oral clearance (CL/F), mean	8.99[b]	13.92[b]
Metabolism		
Metabolic pathways	Minimal[d]	Major CYP3A4, Minor CYP2D6
Excretion		
% drug-related material in feces	49.6%[e]	86.4%[f]
% drug-related material in urine	35.3%[e]	11.3%[f]

a. Represents data after a single dose of 300 mg nirmatrelvir (2 x 150 mg tablet formulation) administered together with 100 mg ritonavir tablet in healthy subjects.
b. 300 mg nirmatrelvir (oral suspension formulation) and 100 mg ritonavir (tablet formulation) administered together twice a day for 3 days.
c. Red blood cell to plasma ratio.
d. Nirmatrelvir is a CYP3A4 substrate but when dosed with ritonavir metabolic clearance is minimal.

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e. Determined by ^{19}F-NMR analysis following a single dose of NIR 300 mg oral suspension with 100 mg ritonavir administered at -12 hours, 0 hours, 12 hours, and 24 hours relative to NIR dosing.
f. Determined by ^{14}C analysis following 600 mg ^{14}C-ritonavir oral solution.

Pharmacokinetics

The bioanalytical assays used to measure the concentrations of NIR and/or its metabolites in plasma and urine were adequately validated and found to be acceptable.

Healthy Subjects
Single and multiple dose PK of NIR were evaluated in healthy subjects and patients with COVID-19. Pharmacokinetic data in COVID-19 patients were not available prior to EUA action but will be provided when the EPIC-HR Study data for all randomized patients become available.

In healthy subjects, NIR exposures increased in a less than dose proportional manner following administration of an oral suspension formulation at single ascending NIR doses 250 mg to 750 mg, administered with 100 mg ritonavir or multiple ascending NIR/r doses of 75/100 mg BID to 500/100 mg BID for 10 days.

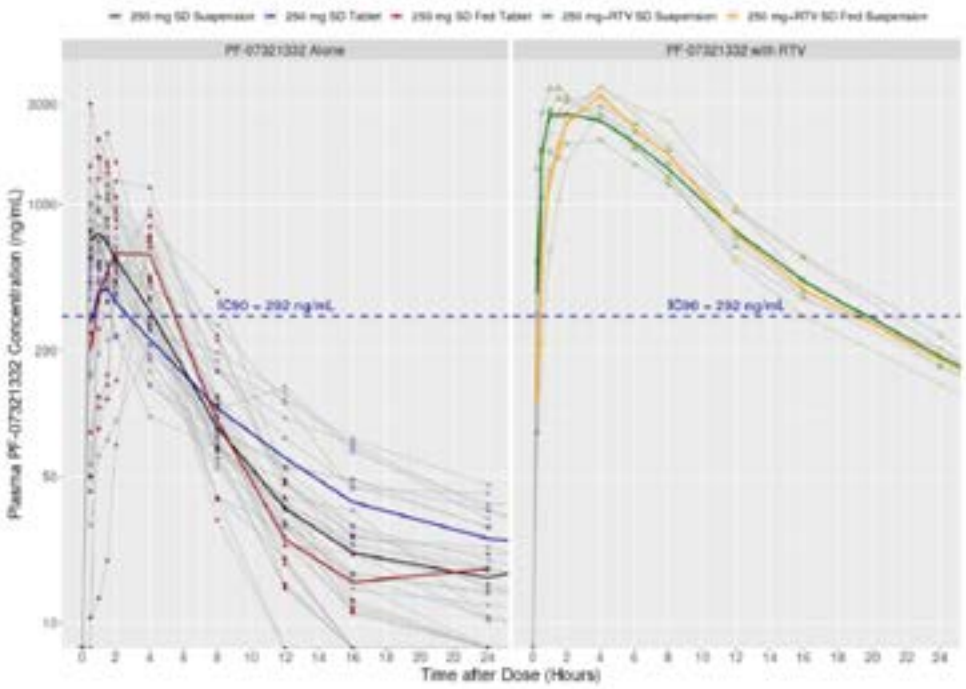
Ritonavir is administered with NIR as a CYP3A inhibitor resulting in higher systemic concentrations of NIR following single dose administration of the oral suspension formulation (Table 18). Pharmacokinetic parameters of NIR following single dose administration of the clinical 150mg tablet formulation (at a single dose of 300 mg NIR/100 mg ritonavir) are shown in Table 19.

Table 18. Single Dose Pharmacokinetics of Nirmatrelvir Alone vs. Nirmatrelvir with Ritonavir in Healthy Subjects

	Geometric Mean (% CV)	
	AUC_{last} (µg.hr/mL)	**C_{max} (µg /mL)**
Nirmatrelvir alone [a]	3.32	0.88
Nirmatrelvir with Ritonavir [b]	27.6	2.88

a. 250 mg (oral suspension formulation)
b. 250 mg (oral suspension formulation with 100 mg ritonavir (tablet formulation) administered together

Figure 4. Observed NIR Plasma Concentration versus Time After Dose for NIR Dose of 250 mg in Study C4671001 Stratified by with and without Co-administration of Ritonavir



Repository artifact ID FI-21466304.
IC_{90} = inhibitory concentration 90%; RTV = ritonavir; SD = single dose.
Symbols represent individual observations; Light grey lines represent individual profiles; Thick colored lines represent group median profiles; Dashed horizontal blue line represents the target exposure IC_{90}.
Excluded observations with time after dose >24 hours.

Table 19. Single Dose Pharmacokinetics of Nirmatrelvir Following Dosing with 300 mg/100 mg Nirmatrelvir/Ritonavir in Healthy Subjects

PK Parameter (units)	Nirmatrelvir (N=12)	Ritonavir (N=12)
C_{max} (µg/mL)	2.21 (33)	0.36 (46)
AUC_{inf} (µg*hr/mL)	23.01 (23)	3.60 (47)
T_{max} (hr)	3.00 (1.02-6.00)	3.98 (1.48-4.20)
$T_{1/2}$ (hr)	6.05 ± 1.79	6.15 ± 2.24

Represents data from 2 x 150 mg tablets of nirmatrelvir co-administered with ritonavir. Values are presented as geometric mean (% CV) except median (range) for T_{max} and arithmetic mean ± SD for $T_{1/2}$.

NIR pharmacokinetic parameters following a supratherapeutic dose of 2250 mg (divided into 3 doses of 750 mg each administered at 0, 2 and 4 h) administered with ritonavir are presented in *Table 20*. The safety data, including AEs, laboratory abnormalities, vital signs, and ECGs indicate that NIR has an acceptable safety and tolerability profile in healthy adult subjects at supratherapeutic exposures (See *Section XI. Human Clinical Safety*).

Table 20. Study 1001 Part 5: Descriptive summary of plasma NIR PK parameters

Parameter	NIR 250mg (suspension)/ritonavir 100mg
N	10

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AUC_{inf} (µg.hr/mL)	188.80 (35)
CL/F (L/hr)	3.970 (35)
Cmax (µg/mL)	15.94 (27)
$T_{1/2}$ (hr)	7.45 ± 2.94
Tmax (hr)	5.0 (3.02 – 6.03)

Source: Study 1001
N = Total number of subjects in the treatment group
Geometric Mean (Geometric %CV) for all except: Median (Range) for Tmax and arithmetic mean ± SD for t1/2

If the patient misses a dose of PAXLOVID within 8 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 8 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose. This recommendation follows what was done in the Phase 2/3 study 1005 and is also confirmed by population PK analysis.

Figure 5 shows the median and 90% prediction interval (PI) of plasma NIR concentration versus time after the first dose. The observed patient data collected in Study 1005 were overlaid on the simulated data. As shown in Figure 5, simulated NIR concentrations remain above the EC_{90} for 12 hours after the first dose.

Figure 5. Mean and 90% prediction intervals for NIR concentrations based on 1000 simulations (NIR/3 300mg/100mg q12h after 1st dose) overlaid with observed data from Study 1005

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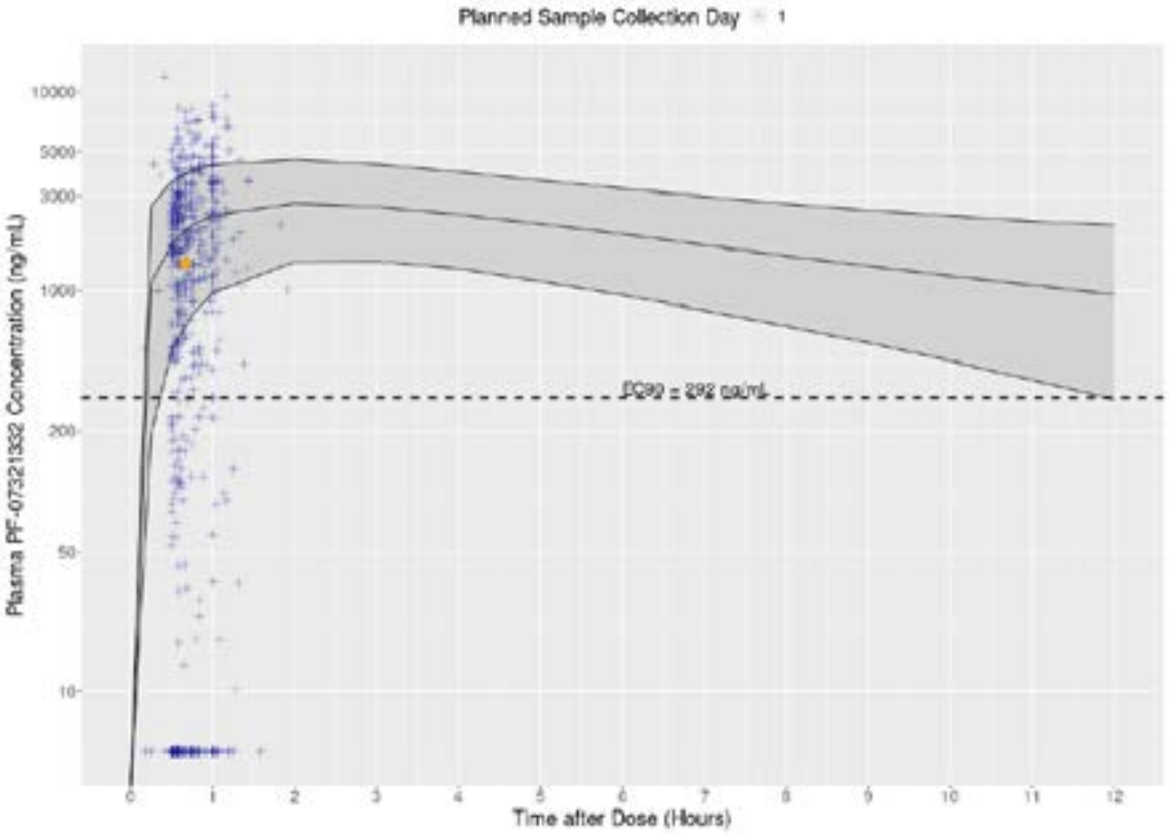

Patients with COVID-19

In the Phase 2/3 EPIC-HR Study, one blood sample was scheduled to be collected on Day 1 (0.5 to 1.5 hr post dose) and on Day 5 (up to 2 hours pre-dose; otherwise, collected anytime post dose) for all subjects when feasible to remain at the study site. Optional PK samples were collected on either Day 2, 3, or 4 via home health visit, in-clinic visits, or self-collected whole blood microsample.

Sparse PK samples were submitted for review in the EUA and included approximately 45% of subjects (planned interim analysis). A total of 1,298 plasma NIR concentrations, including 1,068 evaluable samples and 230 (17.7%) BLQ samples, from 601 subjects with COVID-19 receiving NIR/r 300 mg/100 mg q12h for 5 days from EPIC-HR were available for analysis. There were 46 subjects who did not have any evaluable samples (all observations were BLQs).

Relevant sections of the EUA Fact Sheet will be updated when data from the Phase 2/3 EPIC-HR Study from all randomized patients are provided. Exposure-response analyses are not available.

Cardiac Electrophysiology

The effect of NIR on the QT interval has not been characterized. Ritonavir at a dose of 400 mg twice daily had no clinically relevant effect on QT interval.

Formulation Development of Nirmatrelvir

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An extemporaneously prepared oral suspension and an uncoated 250 mg IR tablet were used in the first in human Study 1001. A 100 mg IR film-coated tablet was developed and was used in Phase 1 Study 1011 and in the sentinel cohort of 68 subjects in Phase 2/3 EPIC-HR Study.

The relative bioavailability of the 250 mg tablet versus 250 mg dose of the oral suspension was evaluated in Study 1001 in 12 healthy subjects. NIR plasma exposure for the tablet treatment was lower compared to the suspension. The test/reference ratios of the adjusted geometric means (90% CI) for NIR AUC_{last} and C_{max} were 81.21% (69.21%, 95.28%) and 56.38% (43.42%, 73.19%), respectively, for the tablet treatment (Test) compared to the suspension treatment (Reference).

A 150 mg IR film-coated tablet was subsequently developed and used in the pivotal Phase 2/3 EPIC-HR Study and other Phase 2/3 studies (Studies 1002 and 1006) as well as in Phase 1 Study 1014. The 150 mg tablet is the final formulation.

There are insufficient data to make a meaningful comparison between the 100 mg and 150 mg NIR tablets. A comparison of the concentrations between patients who received the 100 mg tablet used in the sentinel cohort of the Phase 2/3 study and the remaining patients who received the 150 mg tablet could not be accurately conducted given the sparse PK data submitted for EUA review.

Food Effect

Food effect was evaluated using an oral suspension formulation administered with ritonavir and a 250 mg tablet without ritonavir. In subjects administered the oral suspension with ritonavir, food did not significantly impact the exposure of NIR with an approximately 1.5% increase in AUC and 15% increase in C_{max} of NIR in the fed state as compared to fasted. In subjects administered the 250 mg tablet without ritonavir, AUC and Cmax were approximately 1.5 and 2.4-fold higher compared to the fasted treatment, respectively.

Since NIR is intended for administration with ritonavir, food effect data using the oral suspension was used to inform dosing recommendations in Phase 2/3 studies. Paxlovid is recommended to be given without regard to food similar to how the clinical 150 mg tablet formulation was administered to patients with COVID-19 in the pivotal Phase 2/3 study. A dedicated food effect study using the final 150 mg NIR tablet formulation is planned.

Drug-Drug Interactions

Effect of NIR/r on Other Drugs

Potential drug-drug interaction liability of NIR as a perpetrator (effect of NIR on the absorption and disposition of other drugs) is based on *in vitro* studies of NIR alone.

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The inhibitory potency of NIR was determined by measuring the activity of each CYP enzyme (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5) in pooled human liver microsomes at a concentration range from 0.01 to 300 µM for all CYPs.

NIR reversibly and time-dependently inhibited CYP3A4 and did not reversibly inhibit CYP2D6, CYP2C9, CYP2C19, CYP2C8, or CYP1A2 in vitro at clinically relevant concentrations (Table 21).

Table 21. Assessment of Risk for CYP Inhibition In Vitro Between NIR and Co-administered Substrates

Model	CYP	IC50 (µM)	R Value
Basic (R1) Reversible	CYP1A2	>300	<1.02
	CYP2B6	>300	<1.02
	CYP2C8	>300	<1.02
	CYP2C9	>300	<1.02
	CYP2C19	>300	<1.02
	CYP2D6	>300	<1.02
	CYP2A4/5 Midazolam	58.3	1.09
	CYP3A4/5 Testosterone	106	1.05
	CYP3A4/5 Nifedipine	45.1	1.12
Basic (R1,gut) Reversible	CYP2A4/5 Midazolam	58.3	83.2
	CYP3A4/5 Testosterone	106	46.3
	CYP3A4/5 Nifedipine	45.1	107
Basic (R2) TDI		Ki,u (µM)	
	CYP2A4/5 Midazolam	15.5	26.4
	CYP3A4/5 Testosterone	13.9	30.8

The *in vitro* induction effect of NIR on CYP3A4, CYP2B6, CYP1A2, CYP2C9 and CYP2C19 was evaluated in cultured human hepatocytes at NIR concentrations of 0.01 to 200 µM. NIR exhibited less than a 2-fold induction of enzyme activity at clinically relevant concentrations in all hepatocytes evaluated.

In a mechanistic model, the predicted net effect of NIR on CYP3A was inhibition with no inhibition noted for the other enzymes (Table 22).

Table 22. Mechanistic Model of CYP Mediated DDI Risk Assessment of NIR

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	Reversible Inhibition		TDI		Induction		AUC_{R1}	AUC_{R2}	AUC_{R3}	$AUC_{R1,2}$	$AUC_{R1,2,3}$
	Intestinal	Hepatic	Intestinal	Hepatic	Intestinal	Hepatic					
CYP	Ag (≤0.8)	Ah (≤0.8)	Bg (≤0.8)	Bh (≤0.8)	Cg (≥1.25)	Ch (≥1.25)	Rev	Tdi	Ind	Rev,tdi	Rev,tdi,ind
1A2	--	0.99	--	--	--	--	1.01	--	--	--	--
2B6	--	0.99	--	--	--	1.54	1.00	--	0.82	--	--
2C8	--	0.99	--	--	--	1.73	1.00	--	0.75	--	--
2C9	0.94	0.99	--	--	2.05	1.30	1.01	--	0.77	--	--
2C19	0.94	0.99	--	--	1.70	1.28	1.01	--	0.77	--	--
2D6	0.94	0.99	--	--	--	--	1.01	--	--	--	--
3A	0.46	0.82	0.04	0.10	8.76	3.74	1.56	11.87	0.06	13.83	4.36
3Ahepatic	1	0.82	1	0.10	1	3.74	1.20	7.11	0.28	8.14	2.86
3Aintestinal	0.46	1	0.04	1	8.76	1	1.29	1.67	0.23	1.70	1.53

Ag = 1 / (1 + [I]g/Ki); Ah = 1 / (1 + [I]h/Ki); Bg = kdeg,g / (kdeg,g + [I]g•kinact/([I]g + KI)); Bh = kdeg,h / (kdeg,h + [I]h•kinact/([I]h + KI)); Cg = 1 + d•Emax•[I]g /([I]g + EC50); Ch = 1 + d•Emax•[I]h / ([I]h + EC50); AUCR = 1 / (Ag•Bg•Cg•(1 − fg) + fg) • 1 / (Ah•Bh•Ch•fm + (1 − fm)) ind = induction,rev = reversible; TDI or tdi = time-dependent inhibi ion.

In vitro transporter inhibition studies demonstrated that NIR inhibits P-gp ([I]/IC50=34) and OATP1B1(R_1=1.11). A clinical drug interaction study to assess the effect of NIR/r on dabigatran as a P-gp substrate (Study 1012) is currently ongoing. In vitro inhibition was not observed for BCRP, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1 or MATE2K transporters.

Ritonavir is a potent inhibitor of CYP3A4 and P-gp.

A clinical drug interaction study to assess the effect of NIR/r on the CYP3A substrate midazolam (Study 1013) is currently ongoing. DDI recommendations in the EUA Factsheet are generally aligned with the ritonavir and other ritonavir containing drug labels. An additional interaction was added to the Paxlovid EUA Fact Sheet for BIKTARVY (bictegravir, emtricitabine, tenofovir alafenamide) and clinical recommendations were revised for immunosuppressant drugs and HMG-CoA reductase inhibitors.

Concomitant use of a strong CYP3A inhibitor such as ritonavir can increase the risk of toxicities associated with immunosuppressants that have a narrow therapeutic index (e.g., cyclosporine, tacrolimus and sirolimus). Therapeutic concentration monitoring is recommended for patients on these drugs, although the frequency varies and decreases once the patient is on stable treatment. Therefore, language was added in the factsheet to avoid concomitant use of Paxlovid in patients who are unable to undergo close monitoring of cyclosporine or tacrolimus serum concentrations. Concomitant use of sirolimus and a strong

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CYP3A inhibitor is not recommended even with the option of therapeutic concentration monitoring, consistent with the sirolimus labeling.

Due to the potential for myopathy including rhabdomyolysis, lovastatin and simvastatin are both contraindicated with concomitant use of Paxlovid. However, forgoing an efficacious outpatient treatment of COVID-19 has a greater clinical consequence than pausing the concomitant use of simvastatin or lovastatin for a 5 day treatment duration. Given simvastatin and lovastatin are taken in the evening and have a short half-life, a clinical comment was added to include a timeframe in which patients on simvastatin or lovastatin are eligible for Paxlovid therapy. Specifically, patients should discontinue lovastatin and simvastatin at least 12 hours prior to initiation of Paxlovid.

Effect of other drugs on NIR/r

Despite being co-administered with ritonavir (a potent CYP3A inhibitor), there is potential for strong inhibitors and inducers to alter the pharmacokinetics of NIR. Therefore, clinical drug interaction studies were conducted with itraconazole as strong CYP3A inhibitor and with carbamazepine as a strong CYP3A inducer (see below).

In vitro transporter assays indicated that NIR was a substrate for human MDR1 (P gp), but was not a substrate for human BCRP, MATE1, MATE2K, NTCP, OAT1, OAT2, OAT3, OCT1, OCT2, PEPT1, OATPs 1B1, 1B3, 2B1, or 4C1.

Study 1015 – Itraconazole DDI

Study 1015 was a Phase 1, open-label, fixed sequence, 2-period crossover study to estimate the effect of a strong CYP3A4 inhibitor, itraconazole, on the PK of NIR/r. In Period 1, subjects received NIR/r 300/100 mg orally q12h for a total of 5 doses, with the last dose administered on the morning of Day 3. In Period 2, subjects received itraconazole 200 mg orally q24h for 8 days. On Days 4 through 6 of Period 2, subjects received NIR/r 300/100 mg orally q12h for a total of 5 doses.

Overall, NIR mean AUC_{tau} and C_{max} increased by approximately 39% and 19% respectively, when NIR/r was co-administered with itraconazole compared of NIR/r administered alone **Table 23**. Itraconazole had minimum effect on the overall systemic exposure of ritonavir with a 21% and 15% increase in ritonavir exposure (AUC_{tau} and C_{max}, respectively) observed in the presence of itraconazole. Mean $t_{½}$ values for ritonavir were 5.72 hours when NIR/r administered alone versus 7.65 hours when co-administered with itraconazole.

Table 23. Study 1015 Plasma Nirmatrelvir and Ritonavir Plasma PK Parameters

	NIR (suspension)/r 300/100 mg BID	Itraconazole 200 mg QD + NIR(suspension)/r 300/100mg BID
Nirmatrelvir Plasma PK Parameters		
AUC_{tau} (µg.hr/mL)	33.35 (20)	46.29 (18)

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AUC_{last} (µg.hr/mL)	41.84 (21)	74.43 (21)
C_{max} (µg/mL)	4.68 (17)	5.55 (15)
$t_{1/2}$ (hr)	8.26 ±1.95	7.80 ± 0.89
Tmax (hr)	1.02 (0.50-2.08)	1.70 (0.50-4.00)
Ritonavir Plasma PK Parameters		
AUC_{tau} (µg.hr/mL)	7.19 (30)	8.69 (31)
AUC_{last} (µg.hr/mL)	7.84 (33)	10.23 (37)
Cmax (µg/mL)	1.44 (23)	1.65 (29)
$t_{1/2}$ (hr)	5.72 ± 1.24	7.65 ± 1.63
Tmax (hr)	1.57 (1.47-3.98)	1.98 (1.47-3.98)

This increase in NIR exposure is not expected to result in additional safety concerns given NIR was well tolerated in healthy adult subjects at supratherapeutic exposures (See *Section XI. Human Clinical Safety*). Thus, no dose adjustment is recommended when Paxlovid is used concomitantly with strong CYP3A4 inhibitors.

Study 1014 – Carbamazepine DDI
Study 1014 was a Phase-1, open label, fixed sequence, 2 period crossover study to estimate the effect of a strong CYP3A4 inducer, carbamazepine, on the PK of NIR and ritonavir in healthy subjects.

In Period 1, subjects received a single oral dose of NIR/r 300/100 mg. In Period 2, subjects received carbamazepine in a titrated schedule as follows: On Days 1-3 carbamazepine 100 mg BID, Days 4-7 carbamazepine 200 mg BID, and on Days 8-15 carbamazepine 300 mg BID. On Day 14, a single dose of NIR/r 300/100 mg was administered.

The effect of multiple dose carbamazepine was significantly greater on ritonavir PK as compared to NIR . Following multiple dose co-administration with carbamazepine as compared to dosing of NIR/r alone, NIR mean AUC_{inf} and C_{max} values decreased by approximately 55% and 43% respectively while ritonavir AUC_{inf} and C_{max} values decreased approximately 83% and 74%, respectively.

Table 24. Study 1014: Plasma Nirmatrelvir and Ritonavir Plasma PK Parameters

	NIR 300/ritonavir 100 mg	Carbamazepine + NIR 300/ritonavir 100 mg
Nirmatrelvir Plasma PK Parameters		
AUC_{inf} (µg.hr/mL)	23.01 (23)	10.28 (58)
AUC_{last} (µg.hr/mL)	22.45 (23)	10.05 (58)
C_{max} (µg/mL)	2.21 (33)	1.30 (43)
$t_{1/2}$ (hr)	6.05 ± 1.79	3.85 ± 0.99
Tmax (hr)	3.0 (1.02 – 6.00)	1.50 (0.50 - 4.00)
Ritonavir Plasma PK Parameters		
AUC_{inf} (µg.hr/mL)	3.60 (47)	0.68 (61)
AUC_{last} (µg.hr/mL)	3.41 (47)	0.47 (104)

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C_{max} (µg/mL)	0.36 (46)	0.10 (71)
$t_{1/2}$ (hr)	6.15 ± 2.24	3.35 ± 0.80
Tmax (hr)	3.98 (1.48 -4.20)	1.98 (0.98 – 4.00)

Based on these study results, Paxlovid is contraindicated with potent CYP3A4 inducers like carbamazepine where significantly reduced NIR/r plasma concentrations may be associated with the potential for loss of virologic response and possible resistance.

Due to the delayed offset of induction, additional language was added in the factsheet to alert prescribers against the immediate use of Paxlovid following discontinuation of contraindicated CYP3A inducers. The time course for CYP3A enzymes to return to normal activity precludes the use of Paxlovid in these patients.

Patients on ritonavir- or cobicistat-containing HIV or HCV regimens

In Study 1015, NIR geometric mean AUC_{tau} increased 39% when NIR was coadministered with RTV vs itraconazole plus RTV. Based on the results of this study, no significant increase in NIR exposures are expected when additional CYP3A inhibitors (such as cobicistat or additional doses of ritonavir) are co-administered with NIR/r. This increase in exposure is well below what was noted with the supratherapeutic NIR dose (administered with ritonavir) that was well tolerated in Study 1001. Therefore, no dose adjustments are needed when Paxlovid is given to patients who are also on a ritonavir- or cobicistat-containing regimen.

XII. Nonclinical Data to Support Safety

Genotoxicity studies with nirmatrelvir

Nirmatrelvir was negative for mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the *in vitro* micronucleus assay using human lymphoblastoid TK6 cells, and the *in vivo* rat micronucleus assays.

Safety pharmacology findings with nirmatrelvir

Safety pharmacology studies with NIR were conducted to assess potential pharmacodynamic effects on vital organ systems (central nervous, cardiovascular, and respiratory). Oral administration of up to 1000 mg/kg of NIR to male rats produced no effects on functional observatory behavior (FOB) parameters, but NIR (at 1000 mg/kg) administration resulted in transient locomotor effects, as evidenced by lower number of mean vertical movement counts during the first 5-minute period and a higher number of mean horizontal and vertical movement

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counts during the last 30-minute period. Administration of 1000 mg/kg of NIR also resulted in transient respiratory effects (higher respiratory rate and minute volume) compared to vehicle control animals. These central nervous system (CNS) and respiratory effects occurred at systemic exposures approximately 12 times higher than clinical exposure at the authorized human dose of Paxlovid.

Several in vitro assays were conducted to assess for potential effects of NIR on cardiovascular function. In a hERG assay, the IC_{50} for NIR on hERG potassium current was estimated to be greater than 300 µM. In a guinea pig isolated Langendorff-perfused heart model, NIR did not produce a statistically significant change in cardiac function (+dP/dT, LVP, CPP) or cardiac conduction (PR, QRS, QT intervals) at any of the concentrations tested (0.03 µM-100 µM). NIR did not produce a vasoconstriction response in the rat isolated aorta tissue bath preparation (EC_{50} value >100 µM).

In a cardiovascular safety pharmacology study in cynomolgus monkeys, small transient effects such as increased systolic, diastolic, and mean blood pressure (BP), heart rate (HR) decreases, and associated RR, PR, and QT interval increases were observed following oral administration of 150 (75 BID) mg/kg/day NIR. When the QT interval was corrected for HR (QTc), there was a test article-related decrease. No arrhythmias were noted. NIR at 150 (75 BID) mg/kg/day also produced slight decreases in cardiac contractility. All measures returned to vehicle control levels within 24 HPD (hours post first dose). NIR-related cardiovascular findings in monkeys were observed at systemic exposure about 2 times higher than clinical exposure at the authorized human dose of Paxlovid.

The potential effects on CNS, cardiovascular and respiratory safety pharmacology parameters are monitorable in the clinic and had no correlating clinical signs or histopathological findings in the 14-day or 15-day repeat dose toxicity studies in rats or monkeys. ECG data were also collected in the 15-day monkey study and there were no test article-related changes in ECG parameters (HR, RR-, PR-, QRS-, QT-, QTc intervals) or ECG morphology in that study.

Hematology findings in rats and monkeys with nirmatrelvir

In an oral 14-day repeat dose toxicology study with NIR in rats, there were dose-dependent prolongations in prothrombin time (PT) in males at ≥60 mg/kg/day (16-150%) and females at 1000 mg/kg/day (40%), and prolongations in activated partial thromboplastin time (APTT) in males at ≥200 mg/kg/day (9-19%) and females at 1000 mg/kg/day (11%) with no clinical or microscopic correlates. The mechanism for the prolongations in PT and APTT is unclear but indicates alterations in the coagulation pathway. Platelet counts were also higher (22-25%) at 1000 mg/kg/day in both sexes. In females administered 1000 mg/kg/day, reduced red blood cell (RBC) counts, hematocrit (HCT) and hemoglobin (HGB) (4-5%) and higher (10%) fibrinogen (FIB) were observed. At 200 mg/kg/day, where NIR-related PT and APTT prolongation were noted, the systemic NIR exposure in rats was about 1.2 times higher than clinical exposure at the authorized human

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dose of Paxlovid. All of the hematology and coagulation findings had no clinical or microscopic correlations, and all findings were completely recovered at the end of the recovery phase. Therefore, these findings are not considered adverse, and the No-Observed-Adverse-Effect-Level (NOAEL) was the high dose of 1000 mg/kg/day, resulting in systemic exposure (AUC_{24}) in rats about 4 times higher than clinical exposure at the authorized human dose of Paxlovid.

In an oral 15-day repeat dose toxicology study with NIR in cynomolgus monkeys, an increase (72-109%) in FIB, compared with baseline, was observed in 2 of 3 males and 1 of 3 females administered 600 (300 BID) mg/kg/day. Since no relevant clinical or histopathological findings correlated to the increase in FIB, the NOAEL was the high dose of 600 (300 BID) mg/kg/day. At this dose level, the systemic exposure in monkeys was about 18 times higher than clinical exposure at the authorized human dose of Paxlovid.

Liver and thyroid findings in rats with nirmatrelvir

In the oral 14-day repeat dose toxicology study in rats, minimal to mild periportal hepatocellular hypertrophy in females at ≥200 mg/kg/day and in males at 1000 mg/kg/day with concomitant increased incidence and severity (minimal to mild) of periportal hepatocyte vacuolation in females at 1000 mg/kg/day were noted in the liver and were associated with higher (35-59%) mean liver weights and macroscopic liver finding of abnormal size (enlarged) in males and females at 1000 mg/kg/day. The hepatocellular hypertrophy was consistent with microsomal enzyme induction. In addition, thyroid follicular cell hypertrophy (minimal to mild) was noted in males and females at 1000 mg/kg/day and was characterized by increased size of follicular cells. Effects in thyroid was most likely due to increased thyroid hormone clearance secondary to hepatocellular enzyme induction, a mechanism that rats are known to be particularly sensitive to relative to humans.

In the recovery phase, there were no test article-related organ weight differences in the liver in males and/or females. Microscopic changes had completely recovered as there were no test article-related microscopic findings in the liver and/or thyroid gland at ≥200 mg/kg/day indicating full recovery of the effects on these organs at 1000 mg/kg/day.

Both the liver and thyroid findings were considered non-adverse based on their low severity and the absence of microscopic evidence of associated tissue damage or correlating alterations in clinical pathology parameters. The dose level of 200 mg/kg/day, at which minimal hepatocellular hypertrophy was noted, resulted in systemic exposure in rats about 1.2 times higher than the clinical exposure at the authorized human dose of Paxlovid. The highest dose of 1000 mg/kg/day is considered NOAEL. At this dose level, the systemic exposure in rats was about 4 times higher than clinical exposure at the authorized human dose of Paxlovid.

Developmental and Reproductive effects with nirmatrelvir

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- Fertility and early embryo developmental study in rats

In a fertility and early embryo developmental (FEED) study, male and female rats were orally administered 60, 200, or 1000 mg/kg/day of NIR beginning 14 days prior to mating (i.e., treated males and females were mated together), throughout the mating phase, and continued through gestation day (GD) 6 for females and for a total of 32 doses for males. No NIR-related effects on male systemic toxicity or NIR-related mortality, clinical observations, or effects on food consumption in females were observed. Although epididymal sperm maturation was not reported, no drug-related abnormalities were observed on male reproductive organs upon macroscopic examination. In females, non-adverse increase in body weights (compared to control animals) were observed at 1000 mg/kg/day prior to mating. No NIR-related effects on estrous cyclicity, days to mating, reproductive indices (mating, fecundity, and fertility), or cesarean section observations were observed. Based on the lack of NIR-related adverse effects, the NOAEL for male and female fertility (and systemic toxicity) was 1000 mg/kg/day. At this dose level, the systemic exposure in rats was approximately 4 times higher than clinical exposure at the authorized human dose of Paxlovid. (AUC values in this FEED study were not reported. AUC_{24} was estimated based on the 14-day repeat dose toxicology study.

- Embryo and fetal developmental effects in rats and rabbits

In an embryo-fetal developmental study (EFD) in rats, NIR was administered orally at doses up to 1,000 mg/kg/day during organogenesis (on GD 6 through 17). No NIR-related maternal effects were observed. In addition, no NIR-related effects on fetal body weights or fetal external, visceral, or skeletal morphology were observed. Based on the lack of NIR-related adverse effects in this study, the maternal and developmental NOAEL was the high dose of 1000 mg/kg/day. At this dose level, the systemic exposure in rats was about 8 times higher than clinical exposure at the authorized human dose of Paxlovid.

In an EFD study in rabbits, NIR was administered orally at doses up to 1,000 mg/kg/day during organogenesis (on GD 6 through 19). NIR-related lower (9%) fetal body weight was observed at the high dose (1000 mg/kg/day). No NIR-related maternal macroscopic observations, effects on ovarian and uterine parameters, fetal viability, fetal external, visceral, or skeletal morphology were observed. Based on the lack of NIR-related adverse maternal toxicity, the maternal NOAEL was 1000 mg/kg/day. There were also no NIR-related effects on fetal viability or morphological development in the study. However, the NOAEL for developmental toxicity was 300 mg/kg/day based on lower fetal body weights at 1000 mg/kg/day. At 1,000 mg/kg/day, the systemic exposure (AUC_{24}) in rabbits was approximately 10 times higher than clinical exposures at the authorized human dose of Paxlovid. At 300 mg/kg/day, the systemic exposure in rabbits was about 3 times higher than the clinical exposure at the authorized human dose of Paxlovid.

- Pre- and postnatal developmental study in rats (unaudited interim study report)

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An interim report of an ongoing pre- and postnatal developmental (PPND) study in rats including data up to postnatal day (PND) 56 of the F1 offspring was reviewed. In this study, rats were administered NIR orally at doses of up to 1,000 mg/kg/day from GD 6 through Lactation Day (LD) 20. No adverse effects were observed in pregnant rats and F1 offspring at all dose levels. Body weight gain was decreased from PND 10 to 17 in the offspring at the highest dose of 1000 mg/kg/day, resulting in a decrease (8% in both males and females compared to controls) of body weight at PND 17. No significant difference in body weight was noted at PND 28 (males) or PND 22 (females) to PND 56 (both sexes). Based on this preliminary data, the NOAEL was identified at 1000 mg/kg/day. The maternal systemic exposure (AUC_{24}) at 1,000 mg/kg/day was approximately 8 times higher than clinical exposures at the authorized human dose of Paxlovid (PK data are not available in this interim report. Drug concentrations in maternal and offspring plasma and breastmilk were not reported and so exposure multiples were estimated based on rat AUC_{24} in the 28-day repeat dose toxicology study). No body weight changes in the offspring were noted at 300 mg/kg/day, resulting in systemic exposure (AUC_{24}) approximately 5 times higher than clinical exposures at the authorized human dose of Paxlovid.

Developmental and Reproductive effects with ritonavir

Ritonavir was administered orally to pregnant rats (at 0, 15, 35, and 75 mg/kg/day) and rabbits (at 0, 25, 50, and 110 mg/kg/day) during organogenesis (on GD 6 through 17 and 6 through 19, respectively). No evidence of teratogenicity due to ritonavir was observed in rats and rabbits at systemic exposures (AUC) approximately 4 times higher than exposure at the authorized human dose of Paxlovid. Increased incidences of early resorptions, ossification delays, and developmental variations, as well as decreased fetal body weights were observed in rats in the presence of maternal toxicity, at systemic exposures approximately 4 times higher than exposure at the authorized human dose of Paxlovid. A slight increase in the incidence of cryptorchidism was also noted in rats (at a maternally toxic dose) at an exposure approximately 5 times the exposure at the authorized human dose of Paxlovid. In rabbits, resorptions, decreased litter size, and decreased fetal weights were observed at maternally toxic doses approximately 11 times higher than the authorized human dose of Paxlovid, based on a body surface area conversion factor. In pre- and postnatal development study in rats, administration of 0, 15, 35, and 60 mg/kg/day ritonavir from GD 6 through postnatal day 20 resulted in no developmental toxicity, at ritonavir doses 3 times higher than the authorized human dose of Paxlovid, based on a body surface area conversion factor.

XIII. Nonclinical Data to Support Efficacy

Mechanism of Action

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NIR is a reversible competitive inhibitor of the SARS-CoV-2 Main protease (Mpro), also referred to as the 3C-like protease (3CLpro) or nsp5 protease. NIR inhibits the Mpro by binding directly to the active site, forming a covalent bond with the catalytic residue (Cys145) and non-covalent interactions with ten other residues. Mpro inhibition prevents proteolytic processing of the pp1a/pp1ab polyproteins, a critical early step in the viral replication cycle. The mechanism of action of NIR as an Mpro inhibitor is supported by data from biochemical, cell culture, and animal studies.

Summary of Data Reviewed for Nonclinical Virology-Related Studies

Mechanism of Action and Cell Culture Antiviral Activity Studies

- In biochemical assays, NIR inhibited the activity of a recombinant SARS-CoV-2 (Wuhan-Hu-1) Mpro with an IC_{50} value of 19.2 nM and a K_i value of 3.1 nM. NIR also inhibited recombinant Mpro enzymes from other human coronaviruses (SARS-CoV-1, MERS-CoV, HCoV-OC43, HCoV-HKU1, HCoV-229E, and HCoV-NL63), with IC_{50} values ranging from 28.9 to 479 nM.
- NIR was found to bind to the active site of the SARS-CoV-2 (Wuhan-Hu-1) Mpro by X-ray crystallography. The structure shows that NIR covalently binds to the Mpro catalytic residue C145. NIR also forms non-covalent interactions with ten other residues: H41, M49, F140, G143, H163, H164, M165, E166, L167, and P168. Twelve additional residues are located within 5 Å but do not directly contact NIR: Y54, L141, N142, S144, H172, V186, D187, R188, Q189, T190, A191, and Q192.
- These 23 residues of the SARS-CoV-2 Mpro, which directly interact with or are located in close proximity of NIR, were found to be highly conserved in SARS-CoV-2 (GISAID; ~3.8 million sequences; accessed 12/5/2021), with substitution frequencies ≤0.1%.
- In cell culture antiviral activity studies, NIR had anti-SARS-CoV-2 activity in differentiated normal human bronchial epithelial (dHNBE, EC_{50} value: 32.6-61.8 nM), A549-ACE2 (EC_{50} value: 77.9 nM), and Vero E6 (EC_{50} value: 4480 nM) cells. Antiviral activity was weaker in Vero E6 cells due to a high level of P-gp expression. In the presence of a P-gp inhibitor (CP-100356), NIR had an ~60-fold lower EC_{50} value of 74.5 nM in Vero E6 cells, similar to the EC_{50} values observed in the other cell types. The lower level of P-gp expression in A549-ACE2 and dHNBE cells, which are both of respiratory tissue origin, is considered more relevant and predictive of P-gp expression in key tissue sites of SARS-CoV-2 infection, relative to Vero E6 cells (African green monkey kidney cell line).
- NIR retained activity (≤3-fold change in susceptibility) against five SARS-CoV-2 variants: B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.617.2 (Delta), and C.37 (Lambda). No reduction in activity was observed against B.1.617.2 (Delta, EC_{50} fold-change <1). Only B.1.351 (Beta) had reduced susceptibility across all assay formats (2.9-fold higher EC_{50} value on average). No data are available regarding the activity of NIR against the B.1.1.529 (Omicron) variant in cell

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culture. However, in a biochemical assay, the Mpro P132H substitution found in the Omicron variant did not reduce NIR activity (K_i fold change <1) compared to the Wuhan-Hu-1 enzyme.

- NIR also had activity against SARS-CoV-1 in Vero E6 cells (EC_{50} value: 151 nM with P-gp inhibitor), MERS-CoV in Vero 81 cells (EC_{50} value: 166 nM with P-gp inhibitor), and HCoV-229E in MRC-5 cells (EC_{50} value: 190 nM). Thus, NIR appears to have broad anti-CoV activity. NIR did not have activity against enterovirus 71 or human rhinovirus 1B, which encode 3C proteases structurally similar to CoV Mpro. These results indicate that the antiviral activity of NIR is limited to coronaviruses.
- Ritonavir, an HIV-1 protease inhibitor with pharmacokinetic enhancing activity, had no activity against SARS-CoV-2 in cell culture. In addition, ritonavir did not significantly antagonize the activity of NIR against SARS-CoV-2 in cell culture.
- NIR was 69%, 57%, or 52% bound to plasma protein from humans, cynomolgus monkeys, or rats, respectively, across a range of drug concentrations, as measured by equilibrium dialysis.
- The sponsor selected a NIR target plasma exposure (C_{trough}) of 585 nM (292 ng/mL) for clinical studies, which is equivalent to the unbound EC_{90} value against SARS-CoV-2 in dNHBE cells (181 nM).

Assessments of Cytotoxicity and Off-Target Activity

- NIR had low cytotoxicity in A549-ACE2 (CC_{50} value >3 µM), Vero E6 (CC_{50} value >100 µM), Vero 81 (CC_{50} value >100 µM), and MRC-5 (CC_{50} value >100 µM) cells used in antiviral activity studies, reflecting favorable selectivity indices of >22 to >1342 across different experiments.
- In biochemical assays, NIR did not inhibit 8 mammalian proteases (IC_{50} value >100 µM or >10 µM), including 3 cysteine proteases. In addition, NIR did not inhibit HIV-1 protease (IC_{50} value >100 µM).

Resistance Development and Cross-Resistance

- Biochemical assays using recombinant SARS-CoV-2 Mpro identified 10 substitutions that led to reduced activity (≥3-fold higher K_i values) of NIR: G15S (4.4-fold), Y54A (23.6-fold), T135I (3.5-fold), F140A (39.0-fold), S144A (91.9-fold), H164N (6.4-fold), E166A (33.4-fold), H172Y (233-fold), Q189K (65.4-fold), and D248E (3.7-fold). C.37 (Lambda) contains G15S and did not have reduced susceptibility to NIR in cell culture (EC_{50} fold-change <1). The impacts of the other substitutions have not been tested in cell culture.
- Preliminary cell culture resistance selection studies with NIR using mouse hepatitis virus (MHV, a betacoronavirus used as a surrogate) resulted in the emergence of Mpro amino acid substitutions P15A, T50K, P55L, T129M, and/or S144A. The presence of the substitutions P55L and S144A was associated with reduced NIR susceptibility (~4-5-fold higher EC_{50} values);

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these positions correspond to E55 and S144, respectively, in the SARS-CoV-2 Mpro. E55L alone did not affect NIR activity against SARS-CoV-2 Mpro in a biochemical assay, while S144A led to significantly reduced NIR activity (91.9-fold higher K_i value on average). Neither substitution has been tested in SARS-CoV-2 in cell culture.

- Cross-resistance is not expected between NIR and anti-SARS-CoV-2 monoclonal antibodies or remdesivir based on their different mechanisms of action.

Activity in Animal Models of SARS-CoV-2 Infection

NIR was shown to have antiviral activity in 129 or BALB/c mice infected with mouse-adapted (MA) SARS-CoV-2 MA10. In these studies, NIR dosing modeled a post-exposure prophylaxis and not a treatment of symptomatic disease. SARS-CoV-2 MA10 does not encode any Mpro substitutions relative to SARS-CoV-2.

- In 129 mice, NIR was administered PO at 300 or 1000 mg/kg BID, beginning 4 or 12 hours post-infection and continuing until the termination of the study 3 days post-infection. At 1,000 mg/kg, NIR reduced lung virus titers by ~4 $\log_{10}$ and lung histopathology at 3 days post-infection.
- In BALB/c mice, NIR was administered PO at 300 or 1000 mg/kg BID, beginning 4 hours post-infection and continuing until the termination of the study 4 days post-infection. NIR reduced lung virus titers by ~1.4 $\log_{10}$ or ~1.9 $\log_{10}$ at 300 or 1,000 mg/kg, respectively, at 4 days post-infection. NIR also resulted in decreased SARS-CoV-2 N protein staining in lungs. Lastly, NIR prevented weight loss and led to dose-dependent reductions in lung histopathology at 4 days post-infection.

Nonclinical/Clinical Resistance Summary

The following table provides a comprehensive summary of currently available nonclinical and clinical data characterizing potential NIR resistance pathways.

Table 25. Summary of available nonclinical and clinical analyses of potential NIR resistance pathways.

Mpro AA Position (SARS-CoV-2 numbering)	NIR Contact?	Position of Interest (X)[1]	Substitution (Rel. to Wuhan-Hu-1)	FC in Activity Mpro Biochemical Assay	FC in Activity SARS-CoV-2 in Cell Culture	Emerged in NIR-selected MHV in cell culture	Emerged in NIR-selected SARS-CoV-2 in cell culture	Emerged in NIR/r Treated Subjects
15	No	X	G15S	4.36	0.86 (Lambda)[2]	Yes (P15A)		
17	No		G17S	1.55				
41	Yes	X	H41Y					
45	No		T45I	1.97				
49	Yes	X	M49I	<0.86				
50	No	X	L50	Not tested		Yes (T50K)		
54	Yes	X	Y54A	23.6	In progress			
55	No	X	E55L	<0.51	In progress	Yes (P55L)		
70	No		A70T	<0.37				
75	No		L75F	0.63				
83	No		Q83K	1.88				
88	No		K88R	0.47				

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89	No		L89F	1.32				
90	No		K90R	1.13	2.93 (Beta)[2]			
96	No		V96I	<0.74				
108	No		P108S	2.78				
129	No	X	A129	Not tested		Yes (T129M)		
132	No		P132H	0.69	In progress (Omicron)[2]			
			P132L	1.07				
			P132S	0.6				
135	No	X	T135I	3.46				
140	Yes	X	F140A	39	In progress			
141	Yes	X	L141I/F	Not tested				
142	Yes	X	N142L	1.1				
			N142S	<0.72				
143	Yes	X	G143S	2.54				
144	Yes	X	S144A	91.9	In progress	Yes (S144A)		
145	Yes	X	C145F					
			C145I					
163	Yes	X	H163A					
164	Yes	X	H164N	<6.41 (??)				
165	Yes	X	M165I	<1.11				
166	Yes	X	E166A	33.4	In progress			
167	Yes	X	L167I	2.5				
168	Yes	X	P168R	2.59				
			P168S	0.88				
172	Yes	X	H172Y	233	In progress			
186	Yes	X	V186F/I	Not tested				
187	Yes	X	D187Y	Not tested				
188	Yes	X	R188K/S	Not tested				
189	Yes	X	Q189K	65.4	In progress			
190	Yes	X	T190A	0.56				
			T190I	0.64				
191	Yes	X	A191T	<2.84				
			A191V	<1.26				
192	Yes	X	Q192K/L	Not tested				
212	No		V212F	0.72				
213	No		I213L	0.47				
220	No		L220F	<1.66				
234	No		A234V	2.52				
248	No	X	D248E	3.65				
252	No		P252L	<0.84				
253	No		L253V	<0.63				
260	No	X	A260T	Not tested				Yes
			A260V	0.53				Yes
266	No		A266V	2.27				

Footnotes

1. Criteria for flagging: in/near NIR binding site, phenotypic fold-change ≥3, or emerged in nonclinical or clinical studies

2. Substitutions tested in context of authentic virus isolates representative of noted variant.

Color coding for phenotype data

- Fold-change <3 from WT
- Fold-change 3-10x from WT
- Fold-change >10x from WT
- Tested but no data due to inactive enzyme/virus

Color-coding for emergence data

- Emerged in clinical trial C4671005 (in at least 2 NIR/r-treated subjects and relative to PBO-treated subjects), or
- Emerged in NIR-selected MHV or SARS-CoV-2 in cell culture studies

XIV. Supply Information

One treatment course of Paxlovid per individual for the proposed EUA consists of 300 mg NIR (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally twice daily for 5 days. Therefore one treatment course is supplied as 20 NIR tablets and 10 ritonavir tablets. A reduced dosage is recommended for patients with moderate renal impairment (one 150 mg tablet NIR with one 100 mg tablet ritonavir taken together orally twice daily for 5 days).

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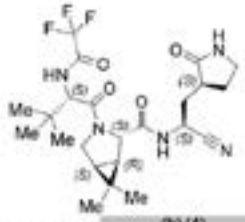
On December 20, 2021 Pfizer provided updated supply projections for Paxlovid to increase the projection for the first half of 2022 from [redacted] – for the global supply. Increases are projected for the more immediate [redacted]) US supply in order to bring forward the target date 10 million doses to the US from [redacted] (table below).

Packs, By Month (k)	Total	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Current US Commitment	10,000							[redacted]						
Changes Needed to Achieve 10M July	-0-													
Revised US Schedule	10,000													

XV. Chemistry, Manufacturing, and Controls Information



Nirmatrelvir contains six stereocenters and has low solubility (0.90-1.21 mg/mL) across the physiologically relevant pH range. Critical stereochemical and solid state characteristics are controlled during the manufacturing process and the drug substance specification. The drug substance manufacturing process has undergone development and two manufacturers were proposed for this EUA: Pfizer Ireland (Ringaskiddy, Ireland) and [redacted]. Pfizer Ringaskiddy manufactured initial EUA supplies using [redacted] and will be using a slightly modified route – [redacted] – moving forward. [redacted] is manufacturing emergency supplies using [redacted] Synthetic [redacted] are comprised of the same [redacted] The batch data for [redacted] and [redacted] drug substance were comparable. The totality of the information provided in the EUA, including the comparability of these batch data, is adequate to support the manufacture of nirmatrelvir drug substance for emergency supply at Pfizer Ringaskiddy using [redacted], and at [redacted] using [redacted] The specifications for [redacted] and [redacted] drug substance are adequate to ensure the identity, strength, and purity of nirmatrelvir drug substance. Adequate safety justification was provided for the specified impurities controlled at levels above the ICH Q3A qualification threshold (per consult with Nonclinical Reviewer Dr. Z. Li). The remaining specified impurities and unspecified impurities are controlled at the ICH Q3A qualification threshold (0.15%) and identification threshold (0.10%), respectively. Sufficient theoretical purge factors were provided to justify ICH M7 Option 4 control of the [redacted] identified potential mutagenic impurities. Data provided supported a 12-month retest period for nirmatrelvir drug substance for emergency supply. The totality of the CMC information provided for nirmatrelvir drug substance in the EUA is adequate to support authorization of the EUA from a drug substance perspective.

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The drug product contains co-packaged 150 mg nirmatrelvir tablets and 100 mg ritonavir tablets. For the EUA supplies, nirmatrelvir tablets and ritonavir tablets are contained within individual cavities of the aluminum foil/foil blisters with a child-resistant PET layer. Each carton contains one blister card for each of the five dosing days, divided into morning and evening doses. CMC information for nirmatrelvir tablets was submitted in EUA 105 and for the ritonavir tablets is referenced to NDA 22417 for Norvir (ritonavir) tablets. Each nirmatrelvir tablet is 8.5 x 17.5 mm oval-shaped debossed (PFE and 3CL), and weighs [(b) (4)] mg. Each tablet contains 150 mg nirmatrelvir, [(b) (4)] mg MCC ([(b) (4)]), [(b) (4)] mg lactose ([(b) (4)]), [(b) (4)] mg croscarmellose sodium ([(b) (4)]), [(b) (4)] mg silicon dioxide ([(b) (4)]), [(b) (4)] mg sodium stearyl fumarate ([(b) (4)]) and [(b) (4)] mg [(b) (4)] (film coat). The proposed emergency use supply for nirmatrelvir tablets will be manufactured using a [(b) (4)] process comprised of [(b) (4)]. The totality of the data from the registration batches, stressed ASAP studies, forced degradation studies and the demonstrated intrinsic stability of the nirmatrelvir drug substance support the proposed 12-month expiry period for nirmatrelvir tablets. Ritonavir tablets have a marketing history of storage in less protective containers, therefore a 12-month expiry for the co-package drug product was found acceptable.

Initially Pfizer proposed that all labeling refer to nirmatrelvir tablets as PF-07321332 tablets. Nomenclature updated as 'nirmatrelvir' was adopted by USAN on November 24, 2021.

XVI. Manufacturing Site Inspections

Table 26: Manufacturing Sites

Manufacturing Site Identifier	Drug Substances / Intermediates/ Drug Product / Testing /Labeler / Packager	Location (U.S. and Non-U.S.)	Inspection Dates	GMP Status (if Known)
Pfizer Ireland Pharmaceuticals, FEI 3002807852	Nirmatrelvir drug substance (DS) manufacturing and testing	Cork, Ireland	Aug2018[1]	Acceptable
[(b) (4)]	Nirmatrelvir drug substance (DS) manufacturing and testing	[(b) (4)]		Acceptable
Pfizer Manufacturing Deutschland GmbH, FEI 3002807097	Nirmatrelvir drug product (DP) manufacturing and testing, Co-packaging of Nirmatrelvir DP and Ritonavir DP	Freiburg, Germany	Feb2020	Acceptable

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(b) (4)	Co-packaging of Nirmatrelvir DP and Ritonavir DP	(b) (4)		Acceptable
Pfizer Inc., FEI 3003836868	DP Stability testing	NJ, U.S.	Jun2016[3]	Acceptable
(b) (4)	Ritonavir DS manufacturing	(b) (4)		Acceptable
	Ritonavir DP manufacturing			Acceptable

[1] FDA evaluated an inspection of Pfizer Ireland Pharmaceuticals, FEI 3002807852 conducted by the The Health Products Regulatory Authority of Ireland from August 13, 2018 to August 17, 2018 under the Mutual Recognition Agreement and determined the inspection classification of this facility is VAI. This facility was last inspected by the FDA from January 22, 2018 to January 26, 2018 and the inspection classification of this facility was VAI.

[2] (b) (4) was last inspected by FDA from (b) (4) and the inspection classification of this facility was NAI. Subsequently, the FDA conducted a remote regulatory assessment from (b) (4) and did not find any significant issues.

[3] Pfizer Inc., FEI 3003836868 was last inspected by FDA from June 1, 2016 to June 2, 2016 and the inspection classification of this facility was NAI. Subsequently, the FDA conducted a remote regulatory assessment from January 8, 2021 to March 31, 2021 and did not find any significant issues.

[4] (b) (4) was last inspected by FDA from (b) (4) and the inspection classification of this facility was VAI. Subsequently, the FDA conducted a remote regulatory assessment from (b) (4) and did not find any significant issues.

Abbreviations: DP, drug product; DS, drug substance; EUA, emergency use authorization; GMP, good manufacturing practice; OAI, official action indicated; U.S., United States

Based on FDA's evaluation of the manufacturing process and control strategy, and the listed facilities, FDA considers the following conditions to the authorization as necessary to product the public health[7]:

- The Sponsor will manufacture Paxlovid to meet all quality standards and per the manufacturing process and control strategy as detailed in the Sponsor's EUA request. The Sponsor will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product, without notification to and concurrence by the Agency as described under condition D.

- All manufacturing, packaging, and testing sites for both drug substance and drug product will comply with current good manufacturing practice requirements of the Federal Food, Drug, and Cosmetic Act Section 501(a)(2)(B).

- The Sponsor will submit information to the Agency within three working days of receipt concerning significant quality problems with distributed drug product of Paxlovid that includes the following:
  - Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; or

[7] See the evaluation documented in OMQ's Authorization Recommendation Memo for Emergency Use Authorization in CMS Case #622919, as well as OPQ's Chemistry, Manufacturing, and Controls EUA Assessment Memo, dated December 20, 2021, associated with EUA 105.

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- Information concerning any microbiological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet established specifications.

If a significant quality problem affects unreleased product and may also impact product(s) previously released and distributed, then information must be submitted for all potentially impacted lots.

Pfizer will include in its notification to the Agency whether the batch, or batches, in question will be recalled. If FDA requests that these, or any other batches, at any time, be recalled, Pfizer must recall them.

If not included in its initial notification, Pfizer must submit information confirming that Pfizer has identified the root cause of the significant quality problems, taken corrective action, and provide a justification confirming that the corrective action is appropriate and effective. Pfizer must submit this information as soon as possible but no later than 45 calendar days from the initial notification.

- The Sponsor will list Paxlovid (NIR tablets co-packaged with ritonavir tablets) with a unique product National Drug Code under the marketing category of Emergency Use Authorization. Further, the listing will include each establishment where manufacturing is performed for the drug and the type of operation performed at each such establishment.

XVII. Clinical Trial Site Inspections

Clinical trial site inspections were not conducted for this EUA.

XVIII. Animal Study Site Inspections (Efficacy and PK/PD)

Nonclinical site inspections were not conducted for this EUA.

XIX. Recommendations From Treatment Guidelines and Other Sources

The following COVID-19 treatment guidelines recommend using SARS-CoV-2 spike protein-directed attachment inhibitors bamlanivimab plus etesevimab, casirivimab plus imdevimab, or sotrovimab (alone) for the treatment of patients with mild-to-moderate COVID-19 who are at high risk of progression to severe COVID-19:

- The National Institutes of Health (NIH) COVID-19 Treatment guidelines (https://www.covid19treatmentguidelines.nih.gov/outpatient-management/; updated October 19, 2021). The rating of the recommendation and the rating of evidence vary based on the population from AIIa (strong recommendation based on other randomized trials or subgroup analyses of randomized trials) to BIII (moderate recommendation based on expert opinion).
- The Infectious Diseases Society of America (IDSA) Guidelines on the Treatment and Management of Patients with COVID-19 (https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-

management/; updated November 18, 2021). The strength of recommendation is rated weak or conditional. The certainty of evidence is rated moderate.

Paxlovid is not currently included in COVID-19 treatment guidelines as it is currently not approved nor authorized for emergency use in the United States.

XX. Risk-Benefit Assessment and Recommendations for Emergency Use

Paxlovid (NIR/r) is an oral antiviral medication developed for the treatment of COVID-19. Paxlovid is comprised of NIR, a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor, co-packaged with ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor. Ritonavir, which has no activity against SARS-CoV-2 on its own, is included to inhibit the CYP3A-mediated metabolism of NIR and consequently increase NIR plasma concentrations to levels anticipated to inhibit SARS-CoV-2 replication. Paxlovid will be administered as two 150 mg tablets of NIR and one 100 mg tablet of ritonavir all given orally twice a day for five days in most authorized populations (a lower dose will be recommended for patients with moderate renal impairment).

Based on FDA's review of the totality of scientific evidence available, including data from EPIC-HR (NCT04960202), a randomized, double-blind, placebo-controlled Phase 2/3 trial of Paxlovid administered to symptomatic non-hospitalized adults with documented SARS-CoV-2 infection who were at high risk for progression to severe COVID-19, it is reasonable to believe that Paxlovid may be effective for use as treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. FDA has also determined that the known and potential benefits of Paxlovid, when used for the treatment of mild-to-moderate COVID-19 as described in *Section III* of this memorandum, outweigh the known and potential risks of the product.

The primary endpoint for EPIC-HR was the proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28. The primary analysis population included only subjects who were dosed within 3 days of symptom onset and who had not received or were not expected to receive COVID-19 monoclonal antibody products.

EPIC-HR Interim Analysis

The initial EUA submission contained data from the interim analysis (n=1,361) where event rates for the primary endpoint in the primary analysis population were 0.8% in the Paxlovid group versus 7.0% in the placebo group. Paxlovid treatment resulted in a 6.3% (95% CI: -9.0% to -3.6%; p<0.0001) absolute reduction, or 89.1% relative reduction, compared to placebo for COVID-19 related hospitalization or death from any cause through Day 28. The difference was highly statistically significant and met the pre-specified stopping boundary leading to the E-DMC's recommendation to stop enrollment.

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Secondary and supportive analyses also demonstrated a benefit with Paxlovid treatment in the interim analysis. A secondary analysis in the population which included subjects who were dosed within 5 days of symptom onset and who had not received or were not expected to receive COVID-19 mAb products, showed similar results to the primary analysis: event rates were 1.0% in the Paxlovid group versus 6.6% in the placebo group. In this population, Paxlovid treatment resulted in a 5. 7% (95% CI: -7.9% to -3.6%; p<0.0001) absolute reduction, or 85.3% relative reduction, compared to placebo for COVID-19 related hospitalization or death from any cause through Day 28. Results were also similar in the population which included subjects who were dosed within 5 days of symptom onset regardless of mAb antibody treatment, with event rates of 1.0% in the Paxlovid group versus 6.4% in the placebo group (83.6% relative reduction). In addition, all 10 deaths in the interim analysis occurred in the placebo group. Change from baseline in SARS-CoV-2 viral RNA shedding at Day 5 also favored the Paxlovid group, with an additional average reduction of approximately 0.9 $\log_{10}$ copies/mL in the Paxlovid group versus the placebo group among subjects dosed within 5 days of symptom onset who had not received or were not expected to receive COVID-19 monoclonal antibody products.

EPIC-HR Full Topline Analysis
Topline efficacy data from all enrolled and dosed subjects in EPIC-HR (n= 2,246), submitted at the end of the EUA review cycle, support the findings from the interim analysis. Treatment with Paxlovid resulted in 88.9%, 87.8%, and 86.7% relative risk reductions for COVID-19 hospitalization or all cause death through Day 28 in subjects dosed within 3 days of symptom onset who did not receive COVID-19 mAb products (mITT population), subjects dosed within 5 days of symptom onset who did not receive COVID-19 mAb products (mITT1 population), and subjects dosed within 5 days of symptom onset regardless of COVID-19 mAb product receipt (mITT2 population), respectively. The EUA Paxlovid treatment course recommended for authorization, which should be initiated as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset, is supported by the EPIC-HR efficacy data in the mITT1 population; these mITT1 efficacy data should be included in the EUA Fact Sheet.

Regarding assessment of the known and potential risks of Paxlovid, the most concerning potential risk involves drug-drug interactions. Paxlovid is both a strong CYP3A inhibitor and also a CYP3A substrate. Consequently, drugs that are extensively metabolized by CYP3A may have large increases in exposure when coadministered with Paxlovid, and drugs that induce CYP3A may decrease NIR and ritonavir plasma concentrations and reduce Paxlovid therapeutic effect. To mitigate this risk, the fact sheet for healthcare providers should include a list of drugs that are contraindicated with Paxlovid, as well as a warning and precaution about the risk of severe or serious adverse reactions due to drug interactions, and

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Section 7 should include a table of drugs that are contraindicated with Paxlovid or which may have other potentially significant drug interactions with Paxlovid.

The overall safety database for Paxlovid is comprised of 1,116 adult subjects who were randomized to receive Paxlovid at or above the proposed dose and duration: 1,109 from EPIC-HR (672 from the interim analysis) and 7 from the Phase 1 study C4671001. These clinical trials excluded subjects taking concomitant medications that could interact with Paxlovid. Overall, serious or severe adverse events were more common among placebo recipients versus Paxlovid recipients. Adverse events seen more commonly among Paxlovid versus placebo recipients included dysgeusia, diarrhea, hypertension, and myalgia; these adverse events were each reported by ≤6% of Paxlovid recipients and should be included in the fact sheets.

The warnings and precautions should also include hepatoxicity and the risk of HIV-1 resistance development. Hepatoxicity is included because hepatoxicity has been seen with ritonavir use; however, hepatoxicity was not reported at higher rates among Paxlovid versus placebo recipients in EPIC-HR. The risk of HIV-1 resistance development in individuals with uncontrolled or undiagnosed HIV-1 infection relates to ritonavir being an HIV-1 protease inhibitor as well as a potent CYP3A inhibitor; consequently, Paxlovid use in the absence of other HIV-1 antiretrovirals could serve as functional monotherapy and theoretically lead to development of resistance to HIV-1 protease inhibitors. Other warnings and precautions included in the ritonavir label, which were seen with ritonavir dosed at 600 mg bid for long durations (months to years), should not be included in the Paxlovid fact sheets as these safety signals were not observed with Paxlovid use in EPIC-HR and are considered unlikely with the lower 100 mg bid x 5 days ritonavir dosing regimen used with Paxlovid.

Paxlovid (specifically NIR) is expected to retain antiviral activity against SARS-CoV-2 Variants Being Monitored, including Alpha (B.1.1.7), Beta (B.1.351), and Gamma (P.1),and the Variant of Concern Delta (B.1.617.2 and AY), based on cell culture antiviral activity assays using authentic SARS-CoV-2 isolates. The susceptibility of the recently identified and rapidly expanding Variant of Concern Omicron (B.1.1.529) to NIR has not yet been determined in a cell culture antiviral activity assay. However, preliminary biochemical data using recombinant Mpro enzymes indicate that NIR is likely to retain activity against the Omicron (B.1.1.529) variant.

Nonclinical virology studies indicate NIR may have a low barrier to resistance, with multiple potential resistance pathways. Certain amino acid changes engineered in Mpro positions near the NIR binding site were shown to confer large reductions in NIR susceptibility in biochemical assays. One such change (S144A, conferring a 92-fold reduction in NIR susceptibility) emerged in mouse hepatitis virus (surrogate coronavirus) selected for resistance to NIR in cell culture. Currently the known potential resistance-associated positions in Mpro are highly conserved in published SARS-CoV-2 sequences and FDA is not aware of any circulating variants that may

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be resistant to NIR. Furthermore, the FDA review of preliminary viral sequencing data from EPIC-HR did not identify any clear signals of baseline or treatment-emergent resistance in Paxlovid-treated subjects. Nevertheless, the potential for SARS-CoV-2 to develop resistance to Paxlovid must continue to be assessed and carefully monitored at the population level.

In selecting the authorized use, the FDA carefully considered the available clinical data. EPIC-HR, the only efficacy trial for which data are currently available, evaluated a 5-day course of Paxlovid for the treatment of mild-to-moderate COVID-19 in adult patients at high risk for progression to severe COVID-19. However, as the pharmacokinetics of Paxlovid in adolescents (12 years of age and older weighing at least 40 kg) are expected to be similar to those of adults, and as adolescents are also at risk of severe COVID-19, the authorization was expanded to include the adolescent population. Paxlovid has not been studied for treatment of severe or critical COVID-19 in hospitalized patients or for pre-exposure prophylaxis of COVID-19, and no clinical data are available for Paxlovid used as post-exposure prophylaxis. Consequently, Paxlovid should not be authorized for those uses as the benefit of Paxlovid for those uses is unknown. In addition, Paxlovid is not recommended in patients with severe renal impairment or in patients with severe hepatic impairment due to a lack of data on a safe and effective dose in these populations. Because the recommendations based on renal and hepatic function and the extensive list of Paxlovid drug interactions may necessitate complex benefit/risk assessments and medical management decisions, the review team has determined that Paxlovid may only be prescribed by physicians, advanced practice registered nurses, and physician assistants who are licensed or authorized under state law to prescribe drugs in the therapeutic class to which PAXLOVID belongs (i.e., anti-infectives).

Based on FDA's review of the totality of scientific evidence available, including data from EPIC-HR (NCT04960202), a randomized, double-blind, placebo-controlled Phase 2/3 trial of Paxlovid administered to symptomatic non-hospitalized adults with documented SARS-CoV-2 infection who were at high risk for progression to severe COVID-19, it is reasonable to believe that Paxlovid may be effective for use as treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. FDA has also determined that the known and potential benefits of Paxlovid, when used for the treatment of mild-to-moderate COVID-19 as described in *Section III* of this memorandum, outweigh the known and potential risks of the product. Therefore, the Review Division and the Office of Infectious Diseases conclude that the statutory criteria under section 564(c) of the Federal Food, Drug, and Cosmetic Act are met and recommend authorization of an EUA for Paxlovid as described above.

XXI. Considerations for Adverse Event (AE) Monitoring

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This product will either be used in clinical trials or in clinical practice under EUA. Investigational product will be used in clinical trials conducted under IND. FDA IND safety reporting regulations will apply.

EUA-labeled product will be made available under the EUA. In the setting of a pandemic where practicing physicians will have competing priorities, adverse event reporting under this EUA will be streamlined through the MEDWATCH system. The prescribing health care provider and/or the provider's designee will be responsible for mandatory reporting of all medication errors and all serious adverse events occurring during Paxlovid use and considered potentially related to Paxlovid within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words "PAXLOVID use for COVID-19 under Emergency Use Authorization (EUA)."

XXII. Mandatory and Discretionary Requirements for Use of the Product Under the EUA

Refer to the Letter of Authorization and the authorized Fact Sheet for Health Care Providers.

XXIII. Information to Be Conveyed to Health Care Providers and Recipients of the Product

The Sponsor's plan for distribution of the Fact Sheet for Health Care Providers and Fact Sheet for Patients, Parents, and Caregivers is as follows:

- Each carton contains a sufficient quantity of PAXLOVID to complete one treatment course.
- The carton has a QR code on it, which directs users to the URL www.COVID19oralRX.com, which will contain a copy of the Letter of Authorization, the authorized Fact Sheets, and any other documents associated with the emergency use of PAXLOVID (e.g., Dear Healthcare Provider Instructions, Dispensing Instructions).
- The fact sheets will include the global URL www.COVID19oralRX.com.

FDA agrees with the plan for dissemination of the Fact Sheets.

- Fact Sheet for Health Care Providers (See *Section XXVI. Appendices*)
- Fact Sheet for Patients and Parents/Caregivers (*See Section XXVI. Appendices*)

XXIV. Outstanding Issues/Data Gaps

The EUA for Paxlovid is primarily based on safety and efficacy data through Day 34 from the ongoing study EPIC-HR. The initial data submitted to support the EUA were based on an interim analysis; topline data from all enrolled subjects were submitted at the end of the review period and support the results of the interim

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analysis. However, final full results from EPIC-HR remain critical to confirm the initial benefit-risk assessment. Furthermore, an imbalance in adverse events was seen in the renal impairment study, with more adverse events seen in subjects with severe renal impairment, and so additional clinical data on the safe and appropriate Paxlovid dose in patients with severe renal impairment are needed. In addition, final reports from several nonclinical studies are outstanding and further data to evaluate for potential baseline or treatment-emergent NIR virologic resistance are needed. As such, we are requiring that the Sponsor submit the following information as conditions of authorization:

1. Pfizer must conduct cell culture phenotypic analyses of recombinant SARS-CoV-2 viruses or replicons carrying specific amino acid changes potentially associated with reduced nirmatrelvir susceptibility in nonclinical or clinical studies, or polymorphisms emerging in novel SARS-CoV-2 variants. Specific amino acid changes that should be characterized include the following:
    - amino acid changes associated with reduced nirmatrelvir susceptibility in biochemical assays,
    - natural amino acid polymorphisms in Mpro that come in contact with or in close proximity (<5 Å) to bound nirmatrelvir,
    - amino acid changes associated with nirmatrelvir/ritonavir treatment emergence, treatment failure, or prolonged virologic shedding or rebound in clinical trials, and
    - amino acid polymorphisms identified in resistance surveillance analyses.

    Amino acid changes in both Mpro and Mpro cleavage sites should be considered in these analyses. Specific amino acid changes of interest for phenotypic characterization in cell culture assays currently include Mpro substitutions Y54A, E55L, F140A, S144A, E166A, H172Y, Q189K, and A260V. When warranted due to technical challenges, alternative approaches to the requested cell culture assays will be considered on a case-by-case basis. Pfizer must submit a preliminary summary report no later than February 28, 2022 for any currently ongoing studies, and at least every 6 months thereafter as additional data accumulate.

2. Pfizer must evaluate the cell culture antiviral activity of nirmatrelvir against an authentic SARS-CoV-2 isolate representative of the Omicron variant. Pfizer must submit a summary report no later than February 28, 2022.

3. Pfizer must conduct studies characterizing potential nirmatrelvir resistance mechanisms in SARS-CoV-2 in cell culture, including selection and genotypic and phenotypic characterization of nirmatrelvir-resistant virus. Pfizer must submit a brief monthly progress report on these studies, a preliminary summary report no later than April 30, 2022, and a final report within 30 days of study completion.

4. Pfizer must complete analyses of SARS-CoV-2 shedding and nucleotide sequencing from the EPIC-HR clinical trial. Viral sequencing analyses should

be conducted for all clinical samples with sufficient viral RNA levels, including samples collected at baseline, on-treatment and post-treatment, to identify and characterize the potential emergence or persistence of amino acid changes associated with PAXLOVID treatment. Pfizer must submit a summary of available data (including analysis-ready datasets) no later than February 28, 2022, and a final report and associated datasets (including analysis-ready datasets and raw fastq NGS data) no later than April 30, 2022.

5. Pfizer will submit the clinical study report containing data from all enrolled subjects in the EPIC-HR clinical trial no later than January 15, 2022.

6. Pfizer will provide results from a safety and pharmacokinetic study evaluating PAXLOVID as treatment of mild-to-moderate COVID-19 in patients with severe renal impairment (for both patients requiring and not requiring hemodialysis), with the study protocol submitted no later than March 31, 2022.

7. Pfizer will provide the audited final report of the rat PPND study, *An Oral (Gavage) Study of the Effects of PF-07321332 on Pre- and Postnatal Development, Including Maternal Function in Rats*, no later than April 30, 2022.

XXV. References

Götzinger F, Santiago-García B, Noguera-Julián A, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. Lancet Child Adolesc Health. 2020 Sep;4(9):653-661. doi: 10.1016/S2352-4642(20)30177-2.

XXVI. Appendices

1. Pharmacometrics Review
2. Fact Sheet for Health Care Providers
3. Fact Sheet for Patients and Parent/Caregivers
4. Dear Health Care Provider Letter

Pharmacometrics Review

1. Population PK analysis

1.1 Review Summary

In general, the applicant's population PK analysis is considered acceptable for the purpose of dose evaluation in adults and adolescent patients. The applicant's population PK analyses were verified by the reviewer, with no significant discordance identified.

1.2 Introduction

The primary objectives of applicant's analysis were to:

- Characterize the PK of NIR (PF-07321332) in healthy adults;
- Evaluate time- and dose-dependent change in PK; and
- Perform PK simulations to support dose recommendation in patients with COVID-19

1.3 Model development

Data

The analyses were based on PK data from the Phase 1 trial C4671001 that evaluated single and multiple dose escalation in healthy adults. Brief descriptions of the study included are presented in ***Table 1***. The final NONMEM data file for analysis contained 536 PK observations from 20 subjects with co-administration of NIR oral suspension and ritonavir. The baseline demographics are presented in ***Table 2***.

Table 1. Summary of PK Sampling Included in Population PK Analysis

Protocol	Design	N	PF-07321332 Dose Regimen	Plasma PK Sampling
C4671001[2]	A Phase 1 randomized, double-blind, sponsor-open, placebo controlled, single- and multiple-dose escalation study to evaluate the safety, tolerability, and pharmacokinetics of PF-07321332 in healthy adult participants	Up to 78 planned	PART-1 SAD Suspension[a] • Cohort 1: 150 mg[b], 1500 mg[b], 750 mg/RTV • Cohort 2: 500 mg[b], 250 mg/RTV, 250 mg/RTV (fed)[c] PART-2 MAD Suspension • Cohort 3: 75 mg/RTV q12h • Cohort 4: 250 mg/RTV q12h • Cohorts 5 & 6: 500 mg/RTV q12h PART-3 relative bioavailability/food effect[b] • SD: 250 mg suspension, 250 mg tablet, 250 mg tablet (fed)[c] PART-4 metabolism & excretion[d] • SD 300 mg/RTV PART-5 supratherapeutic exposures[d] • 750 mg/RTV at 0, 2, & 4 hours	PART-1 SAD: predose, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 48, & 72 hours PART-2 MAD: predose only on Days 2, 3, 6, & 8; predose, 0.5, 1, 1.5, 2, 4, 6, 8, &12 hours post-dose on Days 1, 5, & 10; and 16, 24, & 48 hours post-dose on Day 10 PART-3: predose, 0.5, 1, 1.5, 2, 4, 8, 12, 16, 24, & 48 hours PART-4: predose, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 48, & 72 hours PART-5: predose, 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 12, 24, 48, 72, & 96 hours

PK = pharmacokinetics; MAD = multiple ascending dose; N = number of subjects; q12h = every 12 hours; RTV = ritonavir 100 mg; SAD = single ascending dose; SD = single-dose.
[a]In SAD cohorts requiring co-administration of PF-07321332/placebo with ritonavir, all participants (active and placebo) received 3 doses of 100 mg of ritonavir at -12, 0, and 12 hours on Day 1.
[b]Excluded from Pop PK analysis.
[c]High-fat, high-calorie meal.
[d]Data not yet available.

(Source: Applicant's Population PK Report, Table 1)

Table 27. Summary of Baseline Demographics

	NIR/r (n=20)
Male, n (%)	16 (44%)
Body weight (kg), median [range]	70.8 [58.5-99.4]
Age (years), median [range]	34.5 [21.0-56.0]
Baseline creatinine clearance (mL/min), median [range]	100 [69.9-141]

(Source: Applicant's Population PK Report, Table 5)

Data visualization

Doe-dependent (less than proportional) absorption was observed (75 to 750 mg) in subjects administered NIR/r (***Figure 1***).

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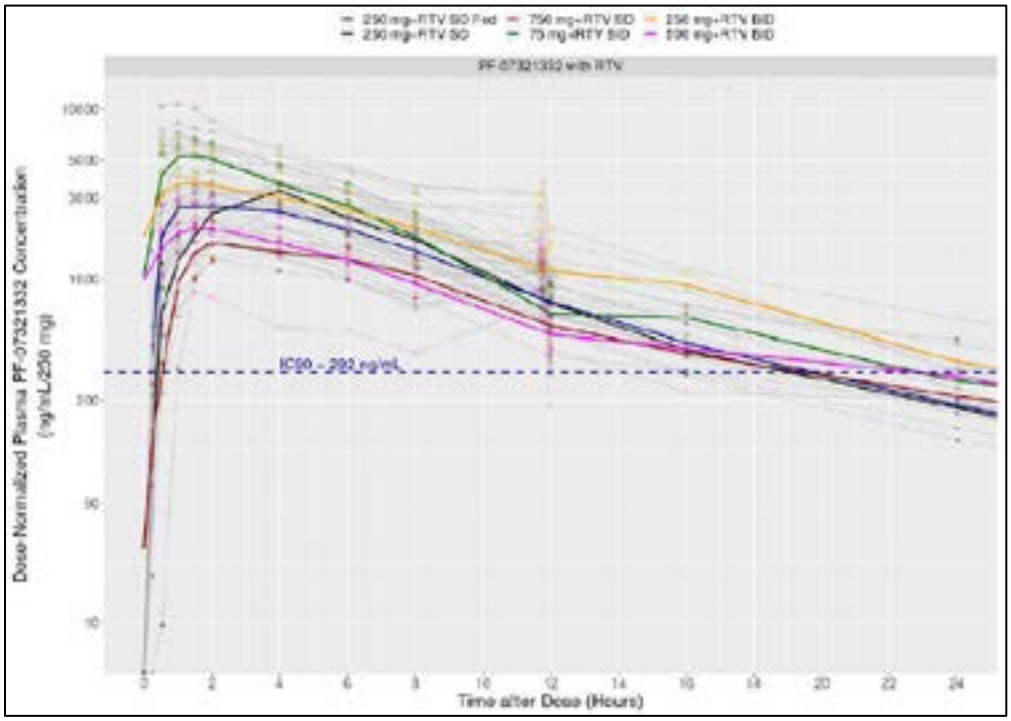
Figure 1. Dose-Normalized NIR Concentration versus Time After Dose for Subjects on NIR/r



BID = twice daily; IC90 = inh bitory concentration 90%; RTV = ritonavir; SD = single dose. Symbols represent individual observations; Light grey lines represent individual profiles; Thick colored lines represent group median profiles; Dashed horizontal blue line represents the target exposure IC90. Excluded observations with time after dose >24 hours.

(Source: Applicant's Population PK Report, Figure 2)

Covariate analysis

Covariate modeling at this stage primarily focused on evaluating dose and food effect on absorption constant (ka) and relative bioavailability (F1), and time effect on clearance (CL). Weight was factored using a standard weight allometry (exponent of 0.75 for CL, 1 for V).

Final Model

The PK following oral administration of NIR oral suspension and ritonavir was adequately characterized by a two-compartment disposition model with first-order absorption. The parameter estimates for the final covariate model are listed in ***Table 3***.

Table 3. Parameter Estimates (RSE) and Median (95% CI) for the Final Model

.	Estimate	% RSE	Shrinkage (%)
CL/F (L/h)	1.02	18.9	
V2/F (L)	8.20	20.8	
Q/F (L/h)	0.444	8.91	
V3 (L)	5.65	20.2	
Weight on CL and Q	0.75 FIX		
Weight on V2 and V3	1 FIX		
ka_{1mg} (1/h)	22.7	4.15	
ka_{power}	-0.533	6.25	
$F1_{1mg}$	1.06	30.5	
$F1_{power}$	-0.375	16.7	
IIV-CL (% CV)	26.4	29.2	1e-10

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COV_{CL-V2}	0.0684	36.0	
IIV-V2 (% CV)	30.7	41.9	5.73
COV_{CL-ka}	0.0582	73.2	
COV_{V2-ka}	0.138	41.4	
IIV-ka (% CV)	54.3	33.6	15.5
COV_{CL-V3}	0.125	58.6	
COV_{V2-V3}	0.0393	152	
COV_{ka-V3}	-0.151	90.5	
IIV-V3 (% CV)	69.9	73.0	7.89
IOV-ka (% CV)	60.7	15.6	38.1; 51.6; 5.23
Proportional error (%)	3.36	111	5.58
Additive error (ng/mL)	399	11.5	5.58

CL = apparent clearance of NIR; Weight effect is parameterized as (Weight/70 kg)^0.75 on CL and Q, and (Weight/70 kg)^1 on V2 and V3; COV = covariance; $F1_{1mg}$ = F1 at 1 mg; $F1_{power}$ = exponent of power function for dose effect on F1; IIV = inter-individual variability; IOV = inter-occasion variability; ka = first-order absorption rate constant; ka_{1mg} = ka at 1 mg; ka_{power} = exponent of power function for dose effect on ka; Q = inter-compartmental clearance; %RSE = percent relative standard error; V2 = central volume of distribution; V3 = peripheral volume of distribution

(Source: Applicant's Population PK Report, Table 7)

Reviewer's Comments: *The applicant's model is developed using PK data of 20 subjects co-administered NIR oral suspension and ritonavir, fasted or on high fat diet, under various dose scenarios (single dose, multiple doses, dose ranging from 75 to 750 mg). Given that subjects in each combination of the factors are limited, the model is not stable with a large unexplained variability. Because PK data for the final 150 mg IR film-coated tablet formulation from Phase 1 Study 1014 became available late in the review cycle, a comprehensive covariate analysis (for example assessing the effect of formulation [oral suspension vs tablet] on the PK of NIR could not be conducted). While the model is considered preliminary, it identified the impact of dose on bioavailability and absorption rate, which is in accordance with the less than dose proportionality observed. Therefore, the model is acceptable to be used to simulate exposure for COVID-19 patients in the early disease stage, who are assumed to similar to healthy subjects, for assessing dose in adults and pediatrics 12 years and older.*

1.4 Simulation

Dose of NIR/r 300/100 mg BID in adults

The applicant applied the population PK model and an inflated IIV in clearance of 60% to simulate exposures for NIR doses of 100 to 500 mg with ritonavir given as BID over 5 days. The C12h and the percentage of subjects achieving a concentration at C12h above EC90 of 292 ng/mL (calculated with in vitro EC90 of 0.181 uM and $f_{u,human}$ of 0.31) are summarized in ***Table 4***. The dose of NIR/r 300/100 mg BID results in median Day 1 and steady-state C12 unbound trough concentrations ~3x and ~6x in vitro EC90, respectively.

Table 4. Predicted C12h and Percentage of Simulated Subjects Achieving C12h > EC90

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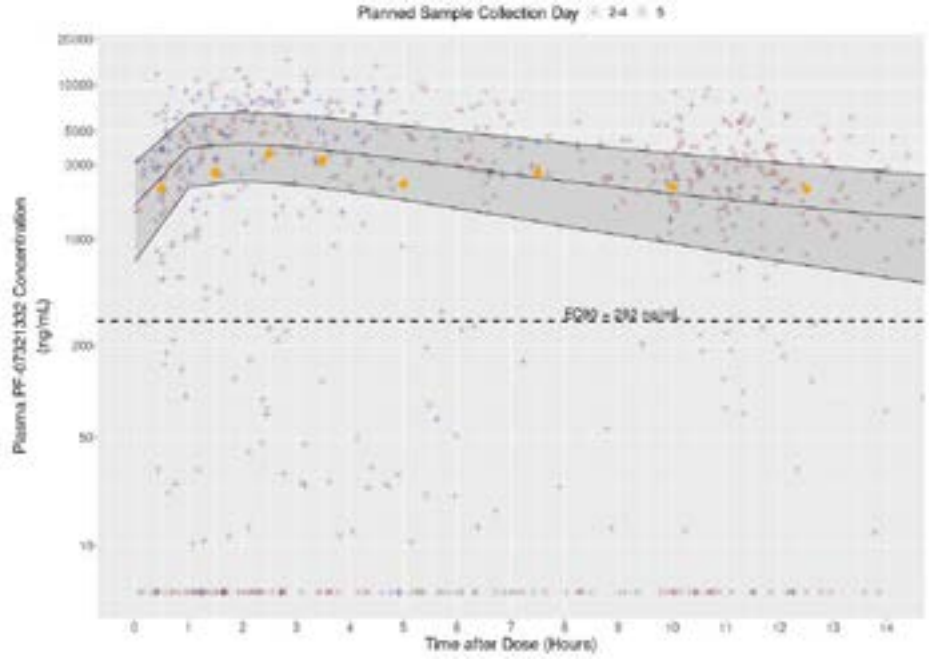
Dose (mg) + RTV[a]	Dose Number	C_{12h} (ng/mL) Median	10^{th} percentile	90^{th} percentile	% Subjects Achieved $C_{12h} \geq IC_{90}$
100	1st (Day 1)	458	141	1018	71.5
	2nd (Day 1)	631	175	1546	79.2
	9th (Day 5)	852	238	2276	85.3
200	1st (Day 1)	743	228	1608	85.0
	2nd (Day 1)	1012	281	2443	89.2
	9th (Day 5)	1361	383	3575	93.4
300	1st (Day 1)	987	307	2124	90.7
	2nd (Day 1)	1347	378	3202	93.6
	9th (Day 5)	1800	498	4670	95.7
400	1st (Day 1)	1209	378	2565	94.0
	2nd (Day 1)	1657	468	3879	95.3
	9th (Day 5)	2197	605	5679	97.4
500	1st (Day 1)	1417	449	2979	95.5
	2nd (Day 1)	1952	552	4516	96.5
	9th (Day 5)	2563	704	6640	97.8

(Source: Applicant's Population PK Report, Table 9)

As shown in ***Figure 2***, the predicted PK profile of NIR/r 300/100 mg q12h) based on the applicant's population PK model generally agreed with the observed data from the ongoing Phase 2/3 EPIC-HR study (data cutoff date 28 Oct 2021).

Figure 2. Median and 90% Prediction Intervals for NIR Concentration Overlaid with Observed Data from EPIC-HR Study (C4671005)



Symbols represent individual observations; Orange diamonds represent median of Day 5 observations binned by intervals (0,1,2,3,4,6,9,11,14 hours post-dose); Dashed horizontal line represents the target exposure EC90. Excluded observations with time after dose >14 hours. EC90 = concentration required for 90% of maximum effect. Samples below limit of quantification are shown below the LLOQ of 10 ng/mL.

(Source: Applicant's Population PK Evaluation of Interim data from Study C4671005, Figure 4)

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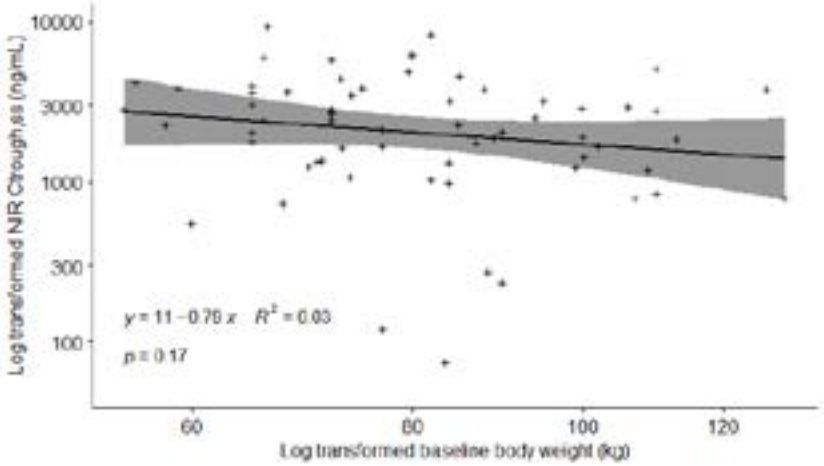
Reviewer's Comments: *The preliminary population PK model appears reasonably unbiased based on the overlay with the observed PK data in adult patients with COVID-19. The selection of NIR/r 300/100 mg BID dose based on the predicted C12h above EC90 was further supported by efficacy data (Section VIII Human Clinical Efficacy).*

Dose of NIR/r 300/100 mg BID in pediatrics 12 years and older

The applicant used the population PK model (standard weight allometry) to predict pediatric exposures. Due to the less than dose proportional increase in NIR exposures, half of the adult dose (taking one 150 mg NIR tablet instead of two with one 100 mg ritonavir tablet) is expected to have less than 50% reduction in exposure, and was evaluated in parallel with the adult dose. A dose of NIR/r 150/100 mg BID in adolescents provides lower AUC, Cmax, and Cmin, by 14%, 6%, and 22%, respectively, as compared to adults. In comparison, a dose of NIR/r 300/100 mg BID in adolescents provides higher NIR AUC, Cmax and Cmin by 32%, 37% and 25%, respectively, as compared to adults receiving the same dose. Overall, both doses are considered comparable to adults. To maintain Cmin comparable to adults in consideration of efficacy, the adult dose was proposed for pediatrics 12 years and older.

Considering that the standard weight allometry was applied, which was not evaluated in the current population PK modeling (the estimated effect of weight has a large uncertainty given the narrow weight range explored), the impact was graphically explored by the reviewer using the available sparse PK data from the Phase 2/3 EPIC-HR study submitted at the time of the review. As steady state Ctrough (C12h) is highly correlated with CL, the Ctrough ∝ 1/CL=1/(weight/70 kg)^theta can be log transformed and expressed as Log(Ctrough) ∝ -theta*Log(weight/70 kg). Therefore, the slope of the linear regression between Log(Ctrough) and Log(weight) corresponds to the negative theta which is the exponent of the weight allometry if it is estimated. As shown in the ***Figure 3***, theta is approximately 0.79 (slope of -0.79) which is very close to 0.75, indicating the standard weight allometry is appropriate to account for the impact of weight on clearance.

Figure 3. Relationship Between Log(Ctrough) and Log(weight)



Ctrough: PK observations >100 hours since 1st dose, and between 10 and 14 hours (range for C12h) after the last dose. Linear regression line and confidence interval are represented by the solid line and grey band. The linear reregression formula, R^2, and p-value are indicated on the plot..

(Source: Reviewer's independent analysis)

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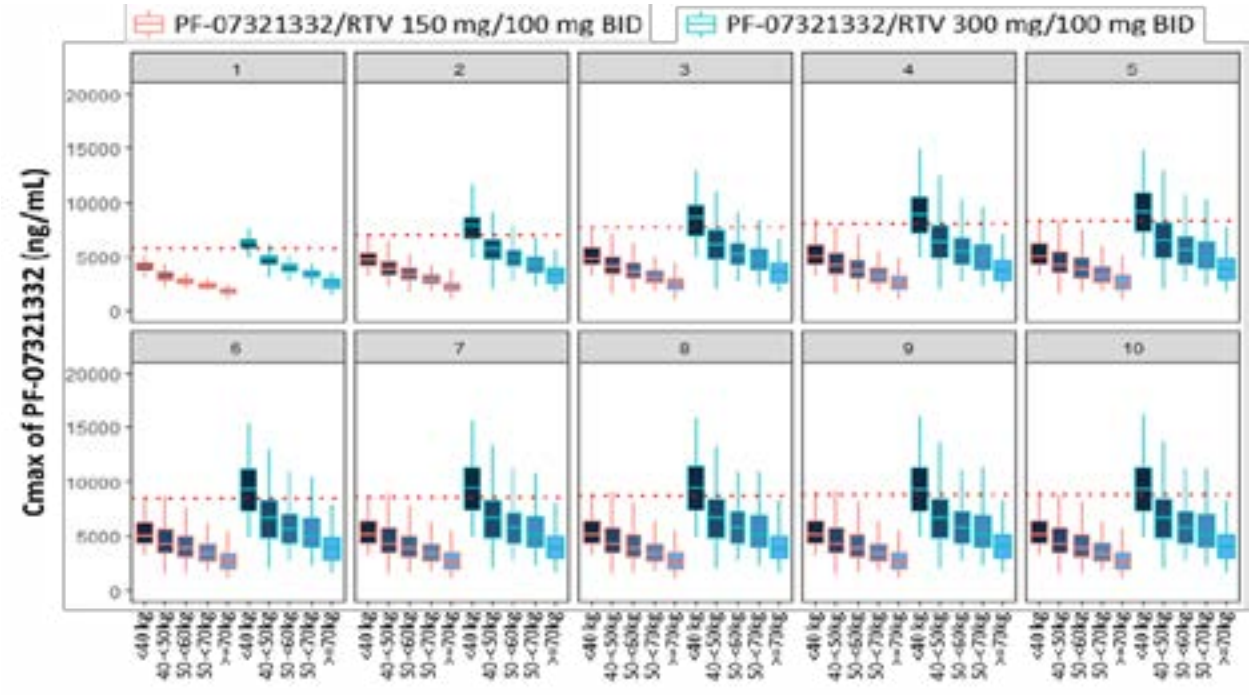
In evaluation of the adult dose in pediatrics with a lower weight, especially under 40 kg which is not covered by the adult body weight range (42-158 kg) in the Phase 2/3 Study C4671005, the reviewer simulated Cmax using the population PK model and NHANES data (2017-2020 pre-pandemic) for pediatrics 12 years and older by weight band as well as adults. The 95th percentile of predicted Cmax in adults was used as the safety margin to check the appropriateness of the dose. For pediatrics under 40 kg receiving NIR/r 300/100 mg BID, about 50% of the subjects are expected to achieve Cmax over the safety margin (***Figure 4)***, which is not acceptable for the lack of safety data.

Figure 4. Predicted Cmax Grouped by Weight Band for Pediatrics for 5 Days of BID Doses



Red dashed lines indicate 95th percentile of the predicted Cmax of adults for the dose number indicated in the panel label.
(Source: Reviewer's independent analysis)

Reviewer's Comments:
Gender or age effect has not been assessed in adults and no pediatric data are available for evaluation. Generally, it is reasonable to apply weight allometry to predict exposure in adolescents and assess the exposure comparability to adults [Momper et al. JAMA Pediatr. 2013; Leong et al. CPT, 2021]. Based on the applicant's assessment, the adult dose was proposed for pediatrics 12 years and older weighing at least 40 kg. The reviewer's independent assessment further suggests that the adult dose might not be appropriate given the expected higher Cmax in the low body weight pediatrics (<40 kg). NIR/r 150/100 mg BID could potentially provide comparable exposure for pediatrics 12 years and older weighing less than 40 kg to that in adults. However, the PK/efficacy/safety for adults <40 kg has not been not established.

Reviewer's independent analysis: *Potential dose of NIR/r which could be evaluated in future clinical trials in patients with severe renal impairment*

NIR/r in patients with severe renal impairment is not recommended and needs to be further assessed in clinical studies (*See contents for the safety and condition of authorization in Section IX Human Clinical Safety Study C4671011*). To streamline the development process, the reviewer applied the population PK model and the relative change in CL resulted from renal impairment (Study C4671011) to propose a dose that can be further tested in clinical studies (***Table 5***).

Table 5. Relative CL in Renal Impairment to Normal Renal Function

	Normal (eGFR ≥90 mL/min)	Mild (eGFR 60-<90 mL/min)	Moderate (eGFR 30-<60 mL/min)	Severe (eGFR <30 mL/min and not requiring dialysis)
CL/F	6.913	5.581	3.689	2.27
% relative to normal	100%	80.7%	53.4%	32.8%
Proposed dose (NIR/r)	300/100 mg BID	300/100 mg BID	150/100 mg BID	300/100 mg on Day 1* 150/100 mg QD on Day2-5*

*Dose proposed for future evaluation only.

(Source: EUA request Table 20 and reviewer's independent analysis)

Simulation was carried out for all grades of renal impairment, with mild and moderate as a proof-of-concept for dose evaluation based on NHANES adult data grouped by renal function category defined by eGFR (Cockcroft-Gault formula). The median of the simulated AUCs for mild and moderate renal impairment receiving NIR/r 100/100 mg, and the relative ratio to that of normal renal function, align with the exposure reported in Study C4671011. At the recommended doses (***Table 5***) for subjects with mild and moderate renal impairment, as shown in ***Figure 5***, the PK profiles are slightly higher (7% and 12% higher in Cmax and AUC0-24h on day 5, but not expect to be clinically relevant) than that of normal renal function. For severe renal impairment, the potential dose (NIR/r 300/100mg on Day 1 followed by 150/100 mg QD on Day 2-5 of treatment) is predicted to achieve the highest Cmax on Day 1, which is covered by the Cmax of subjects with normal renal function from Day 2-5. The dose of 150/100 mg QD on Day 2-5 in the severe patients is expected to provide similar Cmax, higher Ctrough, and comparable Cavg to those for subjects with normal renal function. Therefore, this potential dose is anticipated to provide comparable efficacy for subjects with severe renal impairment. However, given the current safety concerns for subjects with severe renal impairment at the 100/100 mg single dose (*Section IX Human Clinical Safety* Study C4671011), this dose needs to be further evaluated in future clinical trials.

Overall, pending the safety data of this patient cohort from additional clinical studies, the proposed dose at the current stage only reflects our assessment from PK matching perspective with adults of normal renal function, and no recommendation of usage in patients with severe renal impairment should be made at this stage.

Figure 5. Predicted PK profile Grouped by Renal Function Category at the Proposed Dose

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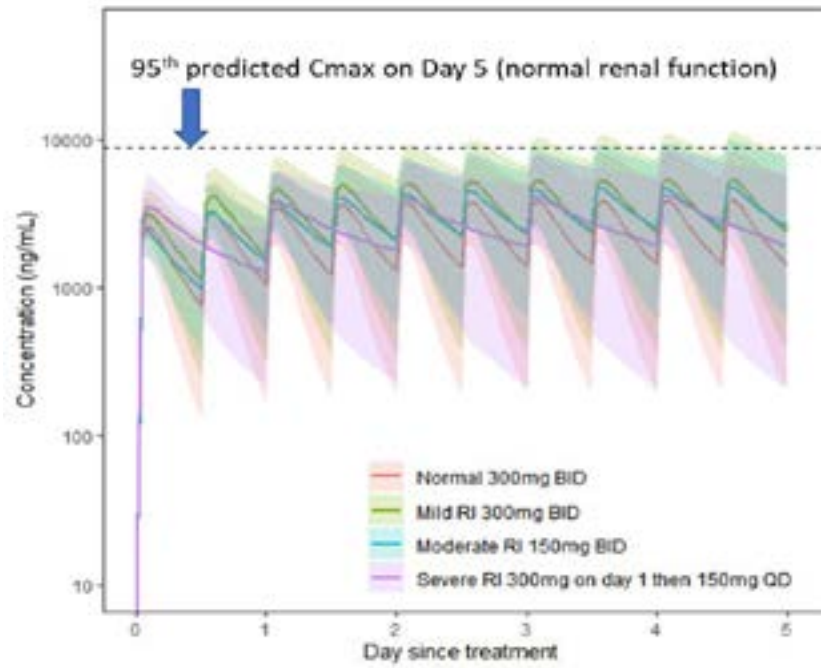

The color line and r bbon represent the median and 90% prediction interval respectively for each renal function category receiving the proposed dose

(Source: Reviewer's independent analysis)

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FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR PAXLOVID™

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)
These highlights of the EUA do not include all the information needed to use PAXLOVID™ under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for PAXLOVID.

PAXLOVID (nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use
Original EUA Authorized Date: 12/2021

EUA FOR PAXLOVID

The U.S. Food and Drug Administration has issued an EUA for the emergency use of the unapproved PAXLOVID which includes nirmatrelvir, a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor, and ritonavir, an HIV-1 protease inh bitor and CYP3A inhibitor, for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

LIMITATIONS OF AUTHORIZED USE

- PAXLOVID is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19.
- PAXLOVID is not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.
- PAXLOVID is not authorized for use longer than 5 consecutive days.

PAXLOVID may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which PAXLOVID belongs (i.e., anti-infectives).

PAXLOVID is not approved for any use, including for use as treatment of COVID-19. (1)

PAXLOVID is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of PAXLOVID under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

See Full Fact Sheet for Healthcare Providers for the justification for emergency use of drugs during the COVID-19 pandemic, information on available alternatives, and additional information on COVID-19.

DOSAGE AND ADMINISTRATION

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. (2.1)
Nirmatrelvir must be co-administered with ritonavir. (2.1)

- Initiate PAXLOVID treatment as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset. (2.1)
- Administer orally with or without food. (2.1)
- Dosage: 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all three tablets taken together twice daily for 5 days. (2.1)
- **Dose reduction for moderate renal impairment (eGFR ≥30 to <60 mL/min)**: 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet), with both tablets taken together twice daily for 5 days. (2.2)
- PAXLOVID is not recommended in patients with severe renal impairment (eGFR <30 mL/min). (2.2, 8.6)
- PAXLOVID is not recommend in patients with severe hepatic impairment (Child-Pugh Class C). (2.3, 8.7)

DOSAGE FORMS AND STRENGTHS

- Tablets: nirmatrelvir 150 mg (3)
- Tablets: ritonavir 100 mg (3)

CONTRAINDICATIONS

- History of clinically significant hypersensitivity reactions to the active ingredients (nirmatrelvir or ritonavir) or any other components. (4)
- Co-administration with drugs highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions. (4, 7.3)
- Co-administration with potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. (4)

WARNINGS AND PRECAUTIONS

- The concomitant use of PAXLOVID and certain other drugs may result in potentially significant drug interactions. Consult the full prescribing information prior to and during treatment for potential drug interactions. (5.1, 7)
- Hepatotoxicity: Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir. (5.2)
- HIV-1 Drug Resistance: PAXLOVID use may lead to a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection. (5.3)

ADVERSE REACTIONS

Adverse events (incidence ≥1% and ≥5 subject difference) were dysgeusia, diarrhea, hypertension, and myalgia. (6.1)

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to PAXLOVID (1) by submitting FDA Form 3500 online, (2) by downloading this form and then submitting by mail or fax, or (3) contacting the FDA at 1-800-FDA-1088 to request this form. Please also provide a copy of this form to Pfizer Inc. at fax number: 1-866-635-8337. (6.4)

DRUG INTERACTIONS

Co-administration of PAXLOVID can alter the plasma concentrations of other drugs and other drugs may alter the plasma concentrations of PAXLOVID. Consider the potential for drug interactions prior to and during PAXLOVID therapy and review concomitant medications during PAXLOVID therapy. (2.4, 4, 5.1, 7, 12.3)

See FACT SHEET FOR PATIENTS, PARENTS, AND CAREGIVERS.

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* Sections or subsections omitted from the EUA are not listed.

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FULL FACT SHEET FOR HEALTHCARE PROVIDERS

1 EMERGENCY USE AUTHORIZATION

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of the unapproved product PAXLOVID for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk[1] for progression to severe COVID-19, including hospitalization or death.

LIMITATIONS OF AUTHORIZED USE

- PAXLOVID is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19 *[see Dosage and Administration (2.1)]*.[2]
- PAXLOVID is not authorized for use as pre-exposure or post-exposure prophylaxis for prevention of COVID-19.
- PAXLOVID is not authorized for use for longer than 5 consecutive days.

PAXLOVID may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which PAXLOVID belongs (i.e., anti-infectives).

PAXLOVID is not approved for any use, including for use for the treatment of COVID-19.

PAXLOVID is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of PAXLOVID under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Justification for Emergency Use of Drugs During the COVID-19 Pandemic

There is currently an outbreak of COVID-19 caused by SARS-CoV-2, a novel coronavirus. The Secretary of Health and Human Services (HHS) has declared that:

- A public health emergency related to COVID-19 has existed since January 27, 2020.
- Circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic (March 27, 2020 declaration).

An EUA is a U.S. Food and Drug Administration authorization for the emergency use of an unapproved product or unapproved use of an approved product (i.e., drug, biological product, or device) in the United States under certain circumstances including, but not limited to, when the Secretary of HHS declares that there is a public health emergency that affects the national security or the health and security of United States citizens living abroad, and that involves biological agent(s) or a disease or condition that may be attributable to such agent(s). Criteria for issuing an EUA include:

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[1] For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

[2] Patients requiring hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID may complete the full 5-day treatment course per the healthcare provider's discretion.

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- The biological agent(s) can cause a serious or life-threatening disease or condition;
- Based on the totality of the available scientific evidence (including data from adequate and well-controlled clinical trials, if available), it is reasonable to believe that
    - the product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition; and
    - the known and potential benefits of the product—when used to diagnose, prevent, or treat such disease or condition—outweigh the known and potential risks of the product, taking into consideration the material threat posed by the biological agent(s);
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the serious or life-threatening disease or condition.

Information Regarding Available Alternatives for the EUA Authorized Use

There are no approved alternatives to PAXLOVID for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Other therapeutics are currently authorized for the same use as PAXLOVID. For additional information on all products authorized for treatment or prevention of COVID-19, please see https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.

For information on clinical studies that are testing the use of PAXLOVID in COVID-19, please see www.clinicaltrials.gov.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Emergency Use of PAXLOVID

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets.

Nirmatrelvir must be co-administered with ritonavir. Failure to correctly co-administer nirmatrelvir with ritonavir may result in plasma levels of nirmatrelvir that are insufficient to achieve the desired therapeutic effect.

The dosage for PAXLOVID is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) with all three tablets taken together orally twice daily for 5 days. *Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID.* Completion of the full 5-day treatment course and continued isolation in accordance with public health recommendations are important to maximize viral clearance and minimize transmission of SARS-CoV-2.

The 5-day treatment course of PAXLOVID should be initiated as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset. Should a patient require hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID, the patient should complete the full 5-day treatment course per the healthcare provider's discretion.

If the patient misses a dose of PAXLOVID within 8 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 8 hours, the patient should not take the missed dose and instead take the next

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dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose.

PAXLOVID (both nirmatrelvir and ritonavir tablets) can be taken with or without food *[see Clinical Pharmacology (12.3)]*. The tablets should be swallowed whole and not chewed, broken, or crushed.

2.2 Important Dosing Information in Patients with Renal Impairment

No dosage adjustment is needed in patients with mild renal impairment (eGFR ≥60 to <90 mL/min). In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), the dosage of PAXLOVID is 150 mg nirmatrelvir and 100 mg ritonavir twice daily for 5 days. *Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID.* Providers should counsel patients about renal dosing instructions *[see Patient Counseling Information (17)].*

PAXLOVID is not recommended in patients with severe renal impairment (eGFR <30 mL/min) until more data are available; the appropriate dosage for patients with severe renal impairment has not been determined *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].*

2.3 Use in Patients with Hepatic Impairment

No dosage adjustment is needed in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic or safety data are available regarding the use of nirmatrelvir or ritonavir in subjects with severe hepatic impairment (Child-Pugh Class C); therefore, PAXLOVID is not recommended for use in patients with severe hepatic impairment *[see Use in Specific Populations (8.7)]*.

2.4 Important Drug Interactions with PAXLOVID

No dosage adjustment is required when co-administered with other products containing ritonavir or cobicistat.

Patients on ritonavir- or cobicistat-containing HIV or HCV regimens should continue their treatment as indicated.

Refer to other sections of the Fact Sheet for important drug interactions with PAXLOVID. Consider the potential for drug interactions prior to and during PAXLOVID therapy and review concomitant medications during PAXLOVID therapy *[see Contraindications (4), Warnings and Precautions (5.1), and Drug Interactions (7)].*

3 DOSAGE FORMS AND STRENGTHS

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets.

- Nirmatrelvir is supplied as oval, pink immediate-release, film-coated tablets debossed with “PFE” on one side and “3CL” on the other side. Each tablet contains 150 mg of nirmatrelvir.

- Ritonavir is supplied as white film-coated ovaloid tablets debossed with the "a" logo and the code NK. Each tablet contains 100 mg of ritonavir.

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4 CONTRAINDICATIONS

PAXLOVID is contraindicated in patients with a history of clinically significant hypersensitivity reactions [e.g., toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome] to its active ingredients (nirmatrelvir or ritonavir) or any other components of the product.

PAXLOVID is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions *[see Drug Interactions (7.3)]*:

- $Alpha_1$-adrenoreceptor antagonist: alfuzosin
- Analgesics: pethidine, piroxicam, propoxyphene
- Antianginal: ranolazine
- Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
- Anti-gout: colchicine
- Antipsychotics: lurasidone, pimozide, clozapine
- Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
- HMG-CoA reductase inhibitors: lovastatin, simvastatin
- PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH)
- Sedative/hypnotics: triazolam, oral midazolam

PAXLOVID is contraindicated with drugs that are potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. PAXLOVID cannot be started immediately after discontinuation of any of the following medications due to the delayed offset of the recently discontinued CYP3A inducer *[see Drug Interactions (7.3)]*:

- Anticancer drugs: apalutamide
- Anticonvulsant: carbamazepine, phenobarbital, phenytoin
- Antimycobacterials: rifampin
- Herbal products: St. John's Wort (*hypericum perforatum*)

5 WARNINGS AND PRECAUTIONS

There are limited clinical data available for PAXLOVID. Serious and unexpected adverse events may occur that have not been previously reported with PAXLOVID use.

5.1 Risk of Serious Adverse Reactions Due to Drug Interactions

Initiation of PAXLOVID, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving PAXLOVID, may increase plasma concentrations of medications metabolized by CYP3A.

Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of PAXLOVID, respectively.

These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medications.

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- Clinically significant adverse reactions from greater exposures of PAXLOVID.
- Loss of therapeutic effect of PAXLOVID and possible development of viral resistance.

See Table 1 for clinically significant drug interactions, including contraindicated drugs. Consider the potential for drug interactions prior to and during PAXLOVID therapy; review concomitant medications during PAXLOVID therapy and monitor for the adverse reactions associated with the concomitant medications *[see Contraindications (4) and Drug Interactions (7)]*.

5.2 Hepatotoxicity

Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir. Therefore, caution should be exercised when administering PAXLOVID to patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis.

5.3 Risk of HIV-1 Resistance Development

Because nirmatrelvir is co-administered with ritonavir, there may be a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection *[see Dosage and Administration (2.4), Contraindications (4), and Drug Interactions (7)]*.

6 ADVERSE REACTIONS

6.1 Adverse Reactions from Clinical Studies

The following adverse reactions have been observed in the clinical studies of PAXLOVID that supported the EUA. The adverse reaction rates observed in these clinical studies cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice. Additional adverse events associated with PAXLOVID may become apparent with more widespread use.

The safety of PAXLOVID is based on data from Study C4671005 (EPIC-HR), a Phase 2/3 randomized, placebo-controlled trial in non-hospitalized adult subjects with a laboratory confirmed diagnosis of SARS-CoV-2 infection *[see Clinical Studies (14.1)]*. A total of 2,224 symptomatic adult subjects 18 years of age and older who are at high risk of developing severe COVID-19 illness received at least one dose of either PAXLOVID (n=1,109) or placebo (n=1,115). Adverse events were those reported while subjects were on study medication and through Day 34 after initiating study treatment. PAXLOVID [300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir] or matching placebo were to be taken twice daily for 5 days.

Adverse events (all grades regardless of causality) in the PAXLOVID group (≥1%) that occurred at a greater frequency (≥5 subject difference) than in the placebo group were dysgeusia (6% and <1%, respectively), diarrhea (3% and 2%), hypertension (1% and <1%), and myalgia (1% and <1%).

The proportions of subjects who discontinued treatment due to an adverse event were 2% in the PAXLOVID group and 4% in the placebo group.

6.4 Required Reporting for Serious Adverse Events and Medication Errors

The prescribing healthcare provider and/or the provider's designee are/is responsible for mandatory reporting of all serious adverse events* and medication errors potentially related to PAXLOVID within 7 calendar days from the onset of the event, using FDA Form 3500 (for information on how to access

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this form, see below). The FDA recommends that such reports, using FDA Form 3500, include the following:

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race).
- A statement " PAXLOVID use for COVID-19 under Emergency Use Authorization (EUA)" under the "**Describe Event, Problem, or Product Use/Medication Error**" heading.
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes).
- Patient's pre-existing medical conditions and use of concomitant products.
- Information about the product (e.g., dosage, route of administration, NDC #).

Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:

- Complete and submit the report online: https://www.fda.gov/medwatch/report.htm
- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - Fax to 1-800-FDA-0178, or
- Call 1-800-FDA-1088 to request a reporting form

In addition, please provide a copy of all FDA MedWatch forms to:

Website	Fax number	Telephone number
www.pfizersafetyreporting.com	1-866-635-8337	1-800-438-1985

The prescribing healthcare provider and/or the provider's designee is/are to provide mandatory responses to requests from FDA for information about adverse events and medication errors associated with PAXLOVID.

*Serious adverse events are defined as:

- Death or a life-threatening adverse event;
- A medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
- A congenital anomaly/birth defect.

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7 DRUG INTERACTIONS

7.1 Potential for PAXLOVID to Affect Other Drugs

PAXLOVID (nirmatrelvir co-packaged with ritonavir) is an inhibitor of CYP3A and may increase plasma concentrations of drugs that are primarily metabolized by CYP3A. Co-administration of PAXLOVID with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated *[see Contraindications (4) and Table 1]*. Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring as shown in Table 1.

7.2 Potential for Other Drugs to Affect PAXLOVID

Nirmatrelvir and ritonavir are CYP3A substrates; therefore, drugs that induce CYP3A may decrease nirmatrelvir and ritonavir plasma concentrations and reduce PAXLOVID therapeutic effect.

7.3 Established and Other Potentially Significant Drug Interactions

Table 1 provides listing of clinically significant drug interactions, including contraindicated drugs. Drugs listed in Table 1 are a guide and not considered a comprehensive list of all possible drugs that may interact with PAXLOVID. The healthcare provider should consult appropriate references for comprehensive information *[see Contraindications (4)]*.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Alpha 1-adrenoreceptor antagonist	alfuzosin	↑ alfuzosin	Co-administration contraindicated due to potential hypotension *[see Contraindications (4)]*.
Analgesics	pethidine, piroxicam, propoxyphene	↑ pethidine ↑ piroxicam ↑ propoxyphene	Co-administration contraindicated due to potential for serious respiratory depression or hematologic abnormalities *[see Contraindications (4)]*.
Antianginal	ranolazine	↑ ranolazine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions *[see Contraindications (4)]*.
Antiarrhythmics	amiodarone, dronedarone, flecainide, propafenone, quinidine	↑ antiarrhythmic	Co-administration contraindicated due to potential for cardiac arrhythmias *[see Contraindications (4)]*.
Antiarrhythmics	bepridil, lidocaine (systemic)	↑ antiarrhythmic	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics if available.
Anticancer drugs	apalutamide	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Anticancer drugs	abemaciclib, ceritinib, dasatinib, encorafenib, ibrutinib, ivosidenib, neratinib, nilotinib, venetoclax, vinblastine, vincristine	↑ anticancer drug	Avoid co-administration of encorafenib or ivosidenib due to potential risk of serious adverse events such as QT interval prolongation. Avoid use of neratinib, venetoclax or ibrutinib. Co-administration of vincristine and vinblastine may lead to significant hematologic or gastrointestinal side effects. For further information, refer to individual product label for anticancer drug.
Anticoagulants	warfarin rivaroxaban	↑↓ warfarin ↑ rivaroxaban	Closely monitor INR if co-administration with warfarin is necessary. Increased bleeding risk with rivaroxaban. Avoid concomitant use.
Anticonvulsants	carbamazepine[a], phenobarbital, phenytoin	↓ nirmatrelvir/ritonavir ↑ carbamazepine ↓ phenobarbital ↓ phenytoin	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.
Antidepressants	bupropion trazodone	↓ bupropion and active metabolite hydroxy-bupropion ↑ trazodone	Monitor for an adequate clinical response to bupropion. Adverse reactions of nausea, dizziness, hypotension, and syncope have been observed following co-administration of trazodone and ritonavir. A lower dose of trazodone should be considered. Refer to trazadone product label for further information.
Antifungals	voriconazole, ketoconazole, isavuconazonium sulfate itraconazole[a]	↓ voriconazole ↑ ketoconazole ↑ isavuconazonium sulfate ↑ itraconazole ↑ nirmatrelvir/ritonavir	Avoid concomitant use of voriconazole. Refer to ketoconazole, isavuconazonium sulfate, and itraconazole product labels for further information.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Anti-gout	colchicine	↑ colchicine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment *[see Contraindications (4)]*.
Anti-HIV protease inhibitors	amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, saquinavir, tipranavir	↑ protease Inhibitor	For further information, refer to the respective protease inhibitors' prescribing information. Patients on ritonavir- or cobicistat-containing HIV regimens should continue their treatment as indicated. Monitor for increased PAXLOVID or protease inhibitor adverse events with concomitant use of these protease inhibitors *[see Dosage and Administration (2.4)]*.
Anti-HIV	didanosine, delavirdine, efavirenz, maraviroc, nevirapine, raltegravir, zidovudine bictegravir/ emtricitabine/ tenofovir	↑ didanosine ↑ efavirenz ↑ maraviroc ↓ raltegravir ↓ zidovudine ↑ bictegravir ↔ emtricitabine ↑ tenofovir	For further information, refer to the respective anti-HIV drugs prescribing information.
Anti-infective	clarithromycin, erythromycin	↑ clarithromycin ↑ erythromycin	Refer to the respective prescribing information for anti-infective dose adjustment.
Antimycobacterial	rifampin	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance. Alternate antimycobacterial drugs such as rifabutin should be considered *[see Contraindications (4)]*.
Antimycobacterial	bedaquiline rifabutin	↑ bedaquiline ↑ rifabutin	Refer to the bedaquiline product label for further information. Refer to rifabutin product label for further information on rifabutin dose reduction.
Antipsychotics	lurasidone, pimozide, clozapine	↑ lurasidone ↑ pimozide ↑ clozapine	Co-administration contraindicated due to serious and/or life-threatening reactions such as cardiac arrhythmias *[see Contraindications (4)]*.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Antipsychotics	quetiapine	↑ quetiapine	If co-administration is necessary, reduce quetiapine dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations.
Calcium channel blockers	amlodipine, diltiazem, felodipine, nicardipine, nifedipine	↑ calcium channel blocker	Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with PAXLOVID. If co-administered, refer to individual product label for calcium channel blocker for further information.
Cardiac glycosides	digoxin	↑ digoxin	Caution should be exercised when co-administering PAXLOVID with digoxin, with appropriate monitoring of serum digoxin levels. Refer to the digoxin product label for further information.
Endothelin receptor Antagonists	bosentan	↑ bosentan	Discontinue use of bosentan at least 36 hours prior to initiation of PAXLOVID. Refer to the bosentan product label for further information.
Ergot derivatives	dihydroergotamine, ergotamine, methylergonovine	↑ dihydroergotamine ↑ ergotamine ↑ methylergonovine	Co-administration contraindicated due to potential for acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system *[see Contraindications (4)]*.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Hepatitis C direct acting antivirals	elbasvir/grazoprevir, glecaprevir/pibrentasvir	↑ antiviral	Increased grazoprevir concentrations can result in ALT elevations. It is not recommended to co-administer ritonavir with glecaprevir/pibrentasvir.
	ombitasvir/paritaprevir/ritonavir and dasabuvir		Refer to the ombitasvir/paritaprevir/ritonavir and dasabuvir label for further information.
	sofosbuvir/velpatasvir/voxilaprevir		Refer to the sofosbuvir/velpatasvir/voxilaprevir product label for further information. Patients on ritonavir-containing HCV regimens should continue their treatment as indicated. Monitor for increased PAXLOVID or HCV drug adverse events with concomitant use *[see Dosage and Administration (2.4)]*.
Herbal products	St. John's Wort (*hypericum perforatum*)	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.
HMG-CoA reductase inhibitors	lovastatin, simvastatin	↑ lovastatin ↑ simvastatin	Co-administration contraindicated due to potential for myopathy including rhabdomyolysis *[see Contraindications (4)]*. Discontinue use of lovastatin and simvastatin at least 12 hours prior to initiation of PAXLOVID.
HMG-CoA reductase inhibitors	atorvastatin, rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Consider temporary discontinuation of atorvastatin and rosuvastatin during treatment with PAXLOVID.
Hormonal contraceptive	ethinyl estradiol	↓ ethinyl estradiol	An additional, non-hormonal method of contraception should be considered.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Immunosuppressants	cyclosporine, tacrolimus, sirolimus	↑ cyclosporine ↑ tacrolimus ↑ sirolimus	Therapeutic concentration monitoring is recommended for immunosuppressants. Avoid use of PAXLOVID when close monitoring of immunosuppressant serum concentrations is not feasible. Avoid concomitant use of sirolimus and PAXLOVID. If co-administered, refer to individual product label for immunosuppressant for further information.
Long-acting beta-adrenoceptor agonist	salmeterol	↑ salmeterol	Co-administration is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Narcotic analgesics	fentanyl methadone	↑ fentanyl ↓ methadone	Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl is concomitantly administered with PAXLOVID. Monitor methadone-maintained patients closely for evidence of withdrawal effects and adjust the methadone dose accordingly.
PDE5 inhibitor	sildenafil (Revatio®) when used for pulmonary arterial hypertension	↑ sildenafil	Co-administration contraindicated due to the potential for sildenafil associated adverse events, including visual abnormalities hypotension, prolonged erection, and syncope *[see Contraindications (4)]*.
Sedative/hypnotics	triazolam, oral midazolam	↑ triazolam ↑ midazolam	Co-administration contraindicated due to potential for extreme sedation and respiratory depression *[see Contraindications (4)]*.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Sedative/hypnotics	midazolam (administered parenterally)	↑ midazolam	Co-administration of midazolam (parenteral) should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered. Refer to the midazolam product label for further information.
Systemic corticosteroids	betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, methylprednisolone, mometasone, prednisone, triamcinolone	↑ corticosteroid	Increased risk for Cushing's syndrome and adrenal suppression. Alternative corticosteroids including beclomethasone and prednisolone should be considered.

a. See Pharmacokinetics, Drug Interaction Studies Conducted with Nirmatrelvir and Ritonavir (12.3).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available human data on the use of nirmatrelvir during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Published observational studies on ritonavir use in pregnant women have not identified an increase in the risk of major birth defects. Published studies with ritonavir are insufficient to identify a drug-associated risk of miscarriage *(see Data).* There are maternal and fetal risks associated with untreated COVID-19 in pregnancy *(see Clinical Considerations).*

In an embryo-fetal development study with nirmatrelvir, reduced fetal body weights following oral administration of nirmatrelvir to pregnant rabbits were observed at systemic exposures (AUC) approximately 10 times higher than clinical exposure at the authorized human dose of PAXLOVID. No other adverse developmental outcomes were observed in animal reproduction studies with nirmatrelvir at systemic exposures (AUC) greater than or equal to 3 times higher than clinical exposure at the authorized human dose of PAXLOVID *(see Data)*.

In animal reproduction studies with ritonavir, no evidence of adverse developmental outcomes was observed following oral administration of ritonavir to pregnant rats and rabbits at doses (based on body surface area conversions) or systemic exposures (AUC) greater than or equal to 3 times higher than clinical doses or exposure at the authorized human dose of PAXLOVID *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S.

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general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated Maternal and/or Embryo-fetal Risk
COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

Data

Human Data

Ritonavir
Based on prospective reports to the antiretroviral pregnancy registry of live births following exposure to ritonavir-containing regimens (including over 3,400 live births exposed in the first-trimester and over 3,500 live births exposed in the second and third trimesters), there was no difference in the rate of overall birth defects for ritonavir compared with the background birth defect rate of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The prevalence of birth defects in live births was 2.3% (95% confidence interval [CI]: 1.9%-2.9%) following first-trimester exposure to ritonavir-containing regimens and 2.9% (95% CI: 2.4%-3.6%) following second and third trimester exposure to ritonavir-containing regimens. While placental transfer of ritonavir and fetal ritonavir concentrations are generally low, detectable levels have been observed in cord blood samples and neonate hair.

Animal Data

Nirmatrelvir
Embryo-fetal developmental (EFD) toxicity studies were conducted in pregnant rats and rabbits administered oral nirmatrelvir doses of up to 1,000 mg/kg/day during organogenesis [on Gestation Days (GD) 6 through 17 in rats and 6 through 19 in rabbits]. No biologically significant developmental effects were observed in the rat EFD study. At the highest dose of 1,000 mg/kg/day, the systemic nirmatrelvir exposure (AUC_{24}) in rats was approximately 8 times higher than clinical exposures at the authorized human dose of PAXLOVID. In the rabbit EFD study, lower fetal body weights (9% decrease) were observed at 1,000 mg/kg/day in the absence of significant maternal toxicity findings. At 1,000 mg/kg/day, the systemic exposure (AUC_{24}) in rabbits was approximately 10 times higher than clinical exposures at the authorized human dose of PAXLOVID. No other significant developmental toxicities (malformations and embryo-fetal lethality) were observed at up to the highest dose tested, 1,000 mg/kg/day. No developmental effects were observed in rabbits at 300 mg/kg/day resulting in systemic exposure (AUC_{24}) approximately 3 times higher than clinical exposures at the authorized human dose of PAXLOVID. A pre- and postnatal developmental (PPND) study in pregnant rats administered oral nirmatrelvir doses of up to 1,000 mg/kg/day from GD 6 through Lactation Day (LD) 20 is ongoing and only interim data through postnatal day (PND) 56 are currently available. Although no difference in body weight was noted at birth when comparing offspring born to nirmatrelvir treated versus control animals, a decrease (8% in males and females) in the body weight of offspring was observed at PND 17. No significant differences in offspring body weight were observed from PND 28 to PND 56. The maternal systemic exposure (AUC_{24}) at 1,000 mg/kg/day was approximately 8 times higher than clinical exposures at the authorized human dose of PAXLOVID. No body weight changes in the offspring were noted at 300 mg/kg/day, resulting in systemic exposure

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(AUC_{24}) approximately 5 times higher than clinical exposures at the authorized human dose of PAXLOVID.

Ritonavir
Ritonavir was administered orally to pregnant rats (at 0, 15, 35, and 75 mg/kg/day) and rabbits (at 0, 25, 50, and 110 mg/kg/day) during organogenesis (on GD 6 through 17 and 6 through 19, respectively). No evidence of teratogenicity due to ritonavir was observed in rats and rabbits at systemic exposures (AUC) approximately 4 times higher than exposure at the authorized human dose of PAXLOVID. Increased incidences of early resorptions, ossification delays, and developmental variations, as well as decreased fetal body weights were observed in rats in the presence of maternal toxicity, at systemic exposures approximately 4 times higher than exposure at the authorized human dose of PAXLOVID. A slight increase in the incidence of cryptorchidism was also noted in rats (at a maternally toxic dose) at an exposure approximately 5 times the exposure at the authorized human dose of PAXLOVID. In rabbits, resorptions, decreased litter size, and decreased fetal weights were observed at maternally toxic doses approximately 11 times higher than the authorized human dose of PAXLOVID, based on a body surface area conversion factor. In a pre- and postnatal development study in rats, administration of 0, 15, 35, and 60 mg/kg/day ritonavir from GD 6 through postnatal day 20 resulted in no developmental toxicity, at ritonavir doses 3 times higher than the authorized human dose of PAXLOVID, based on a body surface area conversion factor.

8.2 Lactation

Risk Summary

There are no available data on the presence of nirmatrelvir in human or animal milk, the effects on the breastfed infant, or the effects on milk production. A transient decrease in body weight was observed in the nursing offspring of rats administered nirmatrelvir *(see Data)*. Limited published data reports that ritonavir is present in human milk. There is no information on the effects of ritonavir on the breastfed infant or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PAXLOVID and any potential adverse effects on the breastfed infant from PAXLOVID or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

Data
In the pre- and postnatal developmental study, body weight decreases (up to 8%) were observed in the offspring of pregnant rats administered nirmatrelvir at maternal systemic exposure (AUC_{24}) approximately 8 times higher than clinical exposures at the authorized human dose of PAXLOVID. No body weight changes in the offspring were noted at maternal systemic exposure (AUC_{24}) approximately 5 times higher than clinical exposures at the authorized human dose of PAXLOVID.

8.3 Females and Males of Reproductive Potential

Contraception

Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Advise patients using combined hormonal contraceptives to use an effective alternative contraceptive method or an additional barrier method of contraception *[see Drug Interactions (7.3)]*.

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8.4 Pediatric Use

PAXLOVID is not authorized for use in pediatric patients younger than 12 years of age or weighing less than 40 kg. The safety and effectiveness of PAXLOVID have not been established in pediatric patients. The authorized adult dosing regimen is expected to result in comparable serum exposures of nirmatrelvir and ritonavir in patients 12 years of age and older and weighing at least 40 kg as observed in adults, and adults with similar body weight were included in the trial EPIC-HR *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

8.5 Geriatric Use

Clinical studies of PAXLOVID include subjects 65 years of age and older and their data contributes to the overall assessment of safety and efficacy *[see Adverse Reactions (6.1) and Clinical Studies (14.1)]*. Of the total number of subjects in EPIC-HR randomized to receive PAXLOVID (N=1,120), 13% were 65 years of age and older and 3% were 75 years of age and older.

8.6 Renal Impairment

Systemic exposure of nirmatrelvir increases in renally impaired patients with increase in the severity of renal impairment *[see Clinical Pharmacology (12.3)].*

No dosage adjustment is needed in patients with mild renal impairment. In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), reduce the dose of PAXLOVID to 150 mg nirmatrelvir and 100 mg ritonavir twice daily for 5 days. *Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID.* Providers should counsel patients about renal dosing instructions *[see Patient Counseling Information (17)].*

PAXLOVID is not recommended in patients with severe renal impairment (eGFR <30 mL/min based on CKD-EPI formula) until more data are available; the appropriate dosage for patients with severe renal impairment has not been determined.

8.7 Hepatic Impairment

No dosage adjustment of PAXLOVID is needed for patients with either mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic or safety data are available regarding the use of nirmatrelvir or ritonavir in subjects with severe hepatic impairment (Child-Pugh Class C), therefore, PAXLOVID is not recommended for use in patients with severe hepatic impairment *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Treatment of overdose with PAXLOVID should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with PAXLOVID.

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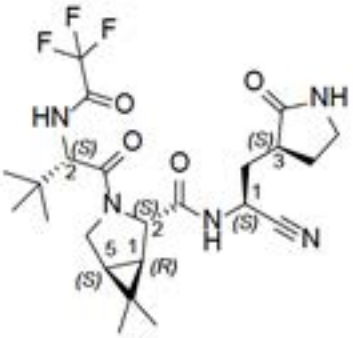
11 DESCRIPTION

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. Nirmatrelvir is a SARS-CoV-2 main protease (Mpro) inhibitor, and ritonavir is an HIV-1 protease inhibitor and CYP3A inhibitor.

Nirmatrelvir

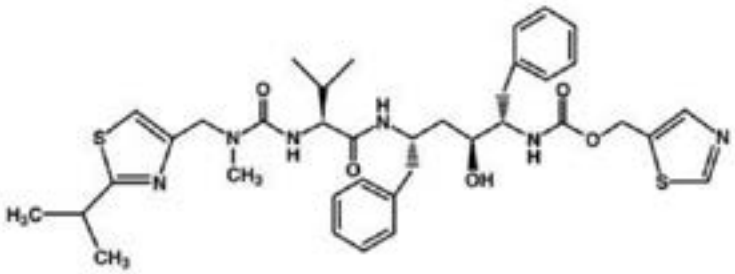
The chemical name of active ingredient of nirmatrelvir is (1*R*,2*S*,5*S*)-*N*-((1*S*)-1-Cyano-2-((3*S*)-2-oxopyrrolidin-3-yl)ethyl)-3-((2*S*)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide]. It has a molecular formula of $C_{23}H_{32}F_3N_5O_4$ and a molecular weight of 499.54. Nirmatrelvir has the following structural formula:



Nirmatrelvir is available as immediate-release, film-coated tablets. Each tablet contains 150 mg nirmatrelvir with the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, and sodium stearyl fumarate. The following are the ingredients in the film coating: hydroxy propyl methylcellulose, iron oxide red, polyethylene glycol, and titanium dioxide.

Ritonavir

Ritonavir is chemically designated as 10-Hydroxy-2-methyl-5-(1-methylethyl)-1- [2-(1 methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12- tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]. Its molecular formula is $C_{37}H_{48}N_6O_5S_2$, and its molecular weight is 720.95. Ritonavir has the following structural formula:



Ritonavir is available as film-coated tablets. Each tablet contains 100 mg ritonavir with the following inactive ingredients: anhydrous dibasic calcium phosphate, colloidal silicon dioxide, copovidone, sodium stearyl fumarate, and sorbitan monolaurate. The following are the ingredients in the film coating: colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, polyethylene glycol 400, polyethylene glycol 3350, polysorbate 80, talc, and titanium dioxide.

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12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (Mpro), also referred to as 3C-like protease (3CLpro) or nsp5 protease. Inhibition of SARS-CoV-2 Mpro renders it incapable of processing polyprotein precursors, preventing viral replication. Nirmatrelvir inhibited the activity of recombinant SARS-CoV-2 Mpro in a biochemical assay with a K_i value of 3.1 nM and an IC_{50} value of 19.2 nM. Nirmatrelvir was found to bind directly to the SARS-CoV-2 Mpro active site by X-ray crystallography.

Ritonavir is an HIV-1 protease inhibitor but is not active against SARS-CoV-2 Mpro. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir.

12.3 Pharmacokinetics

The pharmacokinetics of nirmatrelvir/ritonavir have been studied in healthy subjects.

Ritonavir is administered with nirmatrelvir as a pharmacokinetic enhancer resulting in higher systemic concentrations and longer half-life of nirmatrelvir, thereby supporting a twice daily administration regimen.

Upon oral administration of nirmatrelvir/ritonavir, the increase in systemic exposure appears to be less than dose proportional up to 750 mg as a single dose and up to 500 mg twice daily as multiple doses. Twice daily dosing over 10 days achieved steady-state on Day 2 with approximately 2-fold accumulation. The pharmacokinetic properties of nirmatrelvir/ritonavir are displayed in Table 2.

Table 2: Pharmacokinetic Properties of Nirmatrelvir and Ritonavir in Healthy Subjects

	Nirmatrelvir (When Given With Ritonavir)	Ritonavir
Absorption		
T_{max} (h), median	3.00[a]	3.98[a]
Distribution		
% bound to human plasma proteins	69%	98-99%
Blood-to-plasma ratio	0.60	0.14[c]
V_z/F (L), mean	104.7[b]	112.4[b]
Elimination		
Major route of elimination	Renal elimination[d]	Hepatic metabolism
Half-life ($t_{1/2}$) (hr), mean	6.05[a]	6.15[a]
Oral clearance (CL/F), mean	8.99[b]	13.92[b]
Metabolism		
Metabolic pathways	Minimal[d]	Major CYP3A4, Minor CYP2D6
Excretion		
% drug-related material in feces	49.6%[e]	86.4%[f]
% drug-related material in urine	35.3%[e]	11.3%[f]

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Table 2: Pharmacokinetic Properties of Nirmatrelvir and Ritonavir in Healthy Subjects

a. Represents data after a single dose of 300 mg nirmatrelvir (2 x 150 mg tablet formulation) administered together with 100 mg ritonavir tablet in healthy subjects.
b. 300 mg nirmatrelvir (oral suspension formulation) and 100 mg ritonavir (tablet formulation) administered together twice a day for 3 days.
c. Red blood cell to plasma ratio.
d. Nirmatrelvir is a CYP3A4 substrate but when dosed with ritonavir metabolic clearance is minimal.
e. Determined by ^{19}F-NMR analysis following 300 mg oral suspension enhanced with 100 mg ritonavir at -12 hours, 0 hours, 12 hours, and 24 hours.
f. Determined by ^{14}C analysis following 600 mg ^{14}C-ritonavir oral solution.

Single dose pharmacokinetic data of PAXLOVID in healthy subjects is depicted below (Table 3).

Table 3: Single Dose Pharmacokinetics of Nirmatrelvir Following Dosing with 300 mg/100 mg Nirmatrelvir/Ritonavir in Healthy Subjects

PK Parameter (units)	Nirmatrelvir (N=12)
C_{max} (µg/mL)	2.21 (33)
AUC_{inf} (µg*hr/mL)	23.01 (23)
T_{max} (hr)	3.00 (1.02-6.00)
$T_{1/2}$ (hr)	6.05 ± 1.79

Represents data from 2 x 150 mg tablets of nirmatrelvir. Values are presented as geometric mean (geometric % CV) except median (range) for T_{max} and arithmetic mean ± SD for $T_{1/2}$.

Effect of Food on Oral Absorption of Nirmatrelvir
Dosing with a high fat meal modestly increased the exposure of nirmatrelvir (approximately 15% increase in mean C_{max} and 1.6% increase in mean AUC_{last}) relative to fasting conditions following administration of a suspension formulation of nirmatrelvir co-administered with ritonavir tablets.

Specific Populations

The pharmacokinetics of nirmatrelvir/ritonavir based on age and gender have not been evaluated.

Pediatric Patients
The pharmacokinetics of nirmatrelvir/ritonavir in patients less than 18 years of age have not been evaluated.

Using a population PK model, the dosing regimen is expected to result in comparable steady-state plasma exposure of nirmatrelvir in patients 12 years of age and older and weighing at least 40 kg to those observed in adults after adjusting for body weight.

Racial or Ethnic Groups
Systemic exposure in Japanese subjects was numerically lower but not clinically meaningfully different than those in Western subjects.

Patients with Renal Impairment
An open-label study compared nirmatrelvir/ritonavir pharmacokinetics in healthy adult subjects and subjects with mild (eGFR ≥60 to <90 mL/min), moderate (eGFR ≥30 to <60 mL/min), and severe (eGFR <30 mL/min) renal impairment following administration of a single oral dose of nirmatrelvir 100 mg enhanced with ritonavir 100 mg administered at -12, 0, 12, and 24 hours. Compared to healthy controls with no renal impairment, the C_{max} and AUC of nirmatrelvir in patients with mild renal impairment was 30% and 24% higher, in patients with moderate renal impairment was 38% and 87%

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higher, and in patients with severe renal impairment was 48% and 204% higher, respectively (Table 4).

Table 4: Impact of Renal Impairment on Nirmatrelvir/Ritonavir Pharmacokinetics

	Normal Renal Function (n=8)	Mild Renal Impairment (n=8)	Moderate Renal Impairment (n=8)	Severe Renal Impairment (n=8)
C_{max} (µg/mL)	1.60 (31)	2.08 (29)	2.21 (17)	2.37 (38)
AUC_{inf} (µg*hr/mL)	14.46 (20)	17.91 (30)	27.11 (27)	44.04 (33)
T_{max} (hr)	2.0 (1.0 - 4.0)	2.0 (1.0 – 3.0)	2.50 (1.0 – 6.0)	3.0 (1.0 - 6.1)
$T_{1/2}$ (hr)	7.73 ± 1.82	6.60 ± 1.53	9.95 ± 3.42	13.37 ± 3.32

Values are presented as geometric mean (geometric % CV) except median (range) for T_{max} and arithmetic mean ± SD for $t_{1/2}$.

Patients with Hepatic Impairment

A single oral dose of 100 mg nirmatrelvir enhanced with 100 mg ritonavir at -12 hours, 0 hours, 12 hours and 24 hours in subjects with moderate hepatic impairment resulted in similar exposures compared to subjects with normal hepatic function (Table 5).

Table 5: Impact of Hepatic Impairment on Nirmatrelvir/Ritonavir Pharmacokinetics

	Normal Hepatic Function (n=8)	Moderate Hepatic Impairment (n=8)
C_{max} (µg/mL)	1.89 (20)	1.92 (48)
AUC_{inf} (µg*hr/mL)	15.24 (36)	15.06 (43)
T_{max} (hr)	2.0 (0.6 - 2.1)	1.5 (1.0 - 2.0)
$T_{1/2}$ (hr)	7.21 ± 2.10	5.45 ± 1.57

Values are presented as geometric mean (geometric % CV) except median (range) for T_{max} and arithmetic mean ± SD for $t_{1/2}$.

Nirmatrelvir/ritonavir has not been studied in patients with severe hepatic impairment.

Drug Interaction Studies Conducted with Nirmatrelvir

In vitro data indicates that nirmatrelvir is a substrate for human MDR1 (P-gp) and 3A4, but not a substrate for human BCRP, MATE1, MATE2K, NTCP, OAT1, OAT2, OAT3, OCT1, OCT2, PEPT1, OATPs 1B1, 1B3, 2B1, or 4C1.

Nirmatrelvir does not reversibly inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 *in vitro* at clinically relevant concentrations. Nirmatrelvir has the potential to reversibly and time-dependently inhibit CYP3A4 and inhibit MDR1 (P-gp).

Nirmatrelvir does not induce any CYPs at clinically relevant concentrations.

Drug Interaction Studies Conducted with Ritonavir

In vitro studies indicate that ritonavir is mainly a substrate of CYP3A. Ritonavir also appears to be a substrate of CYP2D6 which contributes to the formation of isopropylthiazole oxidation metabolite M-2.

Ritonavir is an inhibitor of CYP3A and to a lesser extent CYP2D6. Ritonavir appears to induce CYP3A, CYP1A2, CYP2C9, CYP2C19, and CYP2B6 as well as other enzymes, including glucuronosyl transferase.

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The effects of co-administration of PAXLOVID with itraconazole (CYP3A inhibitor) and carbamazepine (CYP3A inducer) on the nirmatrelvir AUC and C_{max} are summarized in Table 6 (effect of other drugs on nirmatrelvir).

Table 6: Drug Interactions: Pharmacokinetic Parameters for Nirmatrelvir in the Presence of the Co-administered Drugs

Co-administered Drug	Dose (Schedule)		N	Ratio (in combination with Co-administered drug/alone) of Nirmatrelvir Pharmacokinetic Parameters (90% CI); No Effect=100	
	Co-administered Drug	Nirmatrelvir/ Ritonavir		C_{max}	AUC[a]
Carbamazepine[b]	300 mg twice daily (16 doses)	300 mg/100 mg twice daily (5 doses)	9	56.82 (47.04, 68.62)	44.50 (33.77, 58.65)
Itraconazole	200 mg once daily (8 doses)	300 mg/100 mg twice daily (5 doses)	11	118.57 (112.50, 124.97)	138.82 (129.25, 149.11)

Abbreviations: AUC=area under the plasma concentration-time curve; CI=confidence interval; C_{max}=maximum plasma concentrations.

a. For carbamazepine, AUC=AUC_{inf}, for itraconazole, AUC=AUC_{tau}.

b. Carbamazepine titrated up to 300 mg twice daily on Day 8 through Day 15 (e.g., 100 mg twice daily on Day 1 through Day 3 and 200 mg twice daily on Day 4 through Day 7).

12.4 Microbiology

Antiviral Activity

Nirmatrelvir exhibited antiviral activity against SARS-CoV-2 (USA-WA1/2020 isolate) infection of differentiated normal human bronchial epithelial (dNHBE) cells with EC_{50} and EC_{90} values of 62 nM and 181 nM, respectively, after 3 days of drug exposure.

Nirmatrelvir had similar cell culture antiviral activity (EC_{50} values ≤3-fold relative to USA-WA1/2020) against SARS-CoV-2 isolates belonging to the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Lambda (C.37) variants. The Beta (B.1.351) variant was the least susceptible tested variant with approximately 3-fold reduced susceptibility relative to the USA-WA1/2020 isolate.

No data are available regarding the activity of nirmatrelvir against the SARS-CoV-2 Omicron (B.1.1.529) variant in cell culture. However, in a biochemical assay, the Mpro P132H substitution found in the Omicron variant did not reduce nirmatrelvir activity (K_i fold change <1) compared to the USA-WA1/2020 enzyme.

Antiviral Activity Against SARS-CoV-2 in Animal Models

Nirmatrelvir showed antiviral activity in BALB/c and 129 mice infected with mouse-adapted SARS-CoV-2. Oral administration of nirmatrelvir at 300 mg/kg or 1,000 mg/kg twice daily initiated 4 hours post-inoculation or 1,000 mg/kg twice daily initiated 12 hours post-inoculation resulted in reduction of lung viral titers and ameliorated indicators of disease (weight loss and lung pathology) compared to placebo-treated animals.

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Antiviral Resistance

Phenotypic assessments were conducted to characterize the impact of naturally occurring SARS-CoV-2 Mpro polymorphisms on the activity of nirmatrelvir in a biochemical assay using recombinant Mpro enzyme. The clinical significance of these polymorphisms is unknown, and it is also unknown if results from the biochemical assay are predictive of antiviral activity in cell culture. The following Mpro amino acid substitutions were associated with reduced nirmatrelvir activity (≥3-fold higher K_i values): G15S (4.4-fold), T135I (3.5-fold), S144A (91.9-fold), H164N (6.4-fold), H172Y (233-fold), Q189K (65.4-fold), and D248E (3.7-fold). G15S is present in the Lambda variant, which did not have reduced susceptibility to nirmatrelvir (relative to USA-WA1/2020) in cell culture.

In addition, three SARS-CoV-2 Mpro amino acid positions where polymorphisms have not been naturally observed were evaluated by substituting alanine at these positions and assessing their impact on activity in biochemical assays. These Mpro amino acid substitutions were associated with reduced nirmatrelvir activity (i.e., higher K_i values): Y54A (23.6-fold), F140A (39.0-fold), and E166A (33.4-fold). The clinical significance of substitutions at these Mpro positions is unknown.

Cell culture resistance selection studies with nirmatrelvir using mouse hepatitis virus (MHV, a betacoronavirus used as a surrogate) resulted in the emergence of Mpro amino acid substitutions P15A, T50K, P55L, T129M, and/or S144A. The clinical relevance of these changes is not known. The presence of the substitutions P55L and S144A was associated with reduced nirmatrelvir susceptibility (~4- to 5-fold higher EC_{50} values). These positions correspond to E55 and S144 in SARS-CoV-2 Mpro, respectively. E55L alone did not affect nirmatrelvir activity against SARS-CoV-2 Mpro in a biochemical assay, while S144A reduced nirmatrelvir activity by 91.9-fold (based on K_i value).

Limited SARS-CoV-2 sequencing data are available to characterize nirmatrelvir resistance in clinical trials. The SARS-CoV-2 Mpro substitutions A260V (n=3) or A260T (n=1) emerged in 4% (4/97) of nirmatrelvir/ritonavir treated subjects in clinical trial EPIC-HR with available sequence analysis data. A260T and A260V substitutions are infrequent natural polymorphisms in publicly available SARS-CoV-2 sequences (as of Dec 5, 2021). In a biochemical assay, the A260V Mpro substitution did not reduce nirmatrelvir activity (K_i fold-change <1).

Cross-resistance is not expected between nirmatrelvir and anti-SARS-CoV-2 monoclonal antibodies or remdesivir based on their different mechanisms of action.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Nirmatrelvir

Carcinogenicity studies have not been conducted with nirmatrelvir.

Nirmatrelvir was negative for mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the *in vitro* micronucleus assay using human lymphoblastoid TK6 cells, and the *in vivo* rat micronucleus assays.

In a fertility and early embryonic development study, nirmatrelvir was administered orally to male and female rats at doses of 60, 200, or 1,000 mg/kg/day once daily beginning 14 days prior to mating, throughout the mating phase, and continued through GD 6 for females and for a total of 32 doses for

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males. There were no effects on fertility, reproductive performance, or early embryonic development at doses up to 1,000 mg/kg/day, resulting in systemic exposure (AUC_{24}) approximately 4 times higher than exposure at the authorized human dose of PAXLOVID.

Ritonavir

Carcinogenicity studies in mice and rats have been conducted on ritonavir. In male mice, at levels of 50, 100, or 200 mg/kg/day, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 2 times higher (in males) than the exposure in humans at the authorized human dose of PAXLOVID. There were no carcinogenic effects seen in females at the dosages tested. The exposure at the high dose was approximately 4 times higher (in females) than the exposure in humans at the authorized human dose of PAXLOVID. In rats dosed at levels of 7, 15, or 30 mg/kg/day, there were no carcinogenic effects. In this study, the exposure at the high dose was approximately 36% that of the exposure in humans at the authorized human dose of PAXLOVID.

Ritonavir was found to be negative for mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Ritonavir produced no effects on fertility in rats at drug exposures approximately 2 (male) and 4 (female) times higher than the exposure in humans at the authorized human dose of PAXLOVID.

13.2 Animal Toxicology and/or Pharmacology

Studies with nirmatrelvir included repeat dose toxicity studies in rats (14 days) and monkeys (15 days). Repeated daily oral dosing in rats at up to 1,000 mg/kg/day resulted in non-adverse hematological, liver, and thyroid effects. All of the hematology and coagulation findings (i.e., increases in PT and APTT) had no clinical or microscopic correlates and all findings completely recovered at the end of the 2-week recovery period. The liver (i.e., minimal to mild periportal hepatocyte hypertrophy and vacuolation) and thyroid gland (i.e., thyroid follicular cell hypertrophy) findings were consistent with secondary adaptive effects related to microsomal enzyme-induced increase in thyroid hormone clearance in the liver, a mechanism that rats are known to be particularly sensitive to relative to humans. All of the findings observed in the liver and thyroid were low severity and occurred in the absence of correlating alterations in clinical pathology parameters, and all of these findings fully recovered. No adverse effects were observed at doses up to 1,000 mg/kg/day, resulting in systemic exposure approximately 4 times higher than exposures at the authorized human dose of PAXLOVID. Nirmatrelvir-related findings following repeat oral dosing in monkeys for 15 days were limited to emesis and increase in fibrinogen. Increased fibrinogen may be attributed to an inflammatory state but lacked a microscopic correlate. At the high dose of 600 mg/kg/day, the systemic exposure in monkeys was about 18 times higher than exposures at the authorized human dose of PAXLOVID.

14 CLINICAL STUDIES

14.1 Efficacy in Subjects at High Risk of Progressing to Severe COVID-19 Illness

The data supporting this EUA are based on the analysis of EPIC-HR (NCT04960202), a Phase 2/3, randomized, double-blind, placebo-controlled study in non-hospitalized symptomatic adult subjects with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Eligible subjects were 18 years of

age and older with at least 1 of the following risk factors for progression to severe disease: diabetes, overweight (BMI >25), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease, hypertension, sickle cell disease, neurodevelopmental disorders, active cancer, medically-related technological dependence, or were 60 years of age and older regardless of comorbidities. Subjects with COVID-19 symptom onset of ≤5 days were included in the study. Subjects were randomized (1:1) to receive PAXLOVID (nirmatrelvir/ritonavir 300 mg/100 mg) or placebo orally every 12 hours for 5 days. The study excluded individuals with a history of prior COVID-19 infection or vaccination. The primary efficacy endpoint was the proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28. The analysis was conducted in the modified intent-to-treat (mITT) analysis set (all treated subjects with onset of symptoms ≤3 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment), the mITT1 analysis set (all treated subjects with onset of symptoms ≤5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment), and the mITT2 analysis set (all treated subjects with onset of symptoms ≤5 days).

A total of 2,246 subjects were randomized to receive either PAXLOVID or placebo. At baseline, mean age was 46 years; 51% were male; 72% were White, 5% were Black, and 14% were Asian; 45% were Hispanic or Latino; 66% of subjects had onset of symptoms ≤3 days from initiation of study treatment; 47% of subjects were serological negative at baseline; the mean (SD) baseline viral load was 4.63 $\log_{10}$ copies/mL (2.87); 26% of subjects had a baseline viral load of >10^7 (units); 6% of subjects either received or were expected to receive COVID-19 therapeutic monoclonal antibody treatment at the time of randomization and were excluded from the mITT and mITT1 analyses.

The baseline demographic and disease characteristics were balanced between the PAXLOVID and placebo groups.

Table 7 provides results of the primary endpoint in mITT1 analysis population. For the primary endpoint, the relative risk reduction in the mITT1 analysis population for PAXLOVID compared to placebo was 88% (95% CI: 75%, 94%).

Table 7: Efficacy Results in Non-Hospitalized Adults with COVID-19 Dosed within 5 Days of Symptom Onset who Did Not Receive COVID-19 Monoclonal Antibody Treatment at Baseline (mITT1 Analysis Set)

	PAXLOVID (N=1,039)	**Placebo** (N=1,046)
COVID-19 related hospitalization or death from any cause through Day 28		
n (%)	8 (0.8%)	66 (6.3%)
Reduction relative to placebo[a] [95% CI], %	-5.62 (-7.21, -4.03)	
All-cause mortality through Day 28, %	0	12 (1.1%)

Abbreviations: CI=confidence interval.
The determination of primary efficacy was based on a planned interim analysis of 780 subjects in mITT population. The estimated risk reduction was -6.3% with a 95% CI of (-9.0%, -3.6%) and 2-sided p-value <0.0001.
a. The estimated cumulative proportion of participants hospitalized or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.

Consistent results were observed in the mITT and mITT2 analysis populations. A total of 1,379 subjects were included in the mITT analysis population. The event rates were 5/697 (0.72%) in the PAXLOVID group, and 44/682 (6.45%) in the placebo group. The primary SARS-CoV-2 variant across both treatment arms was Delta (98%), including clades 21J, 21A, and 21I.

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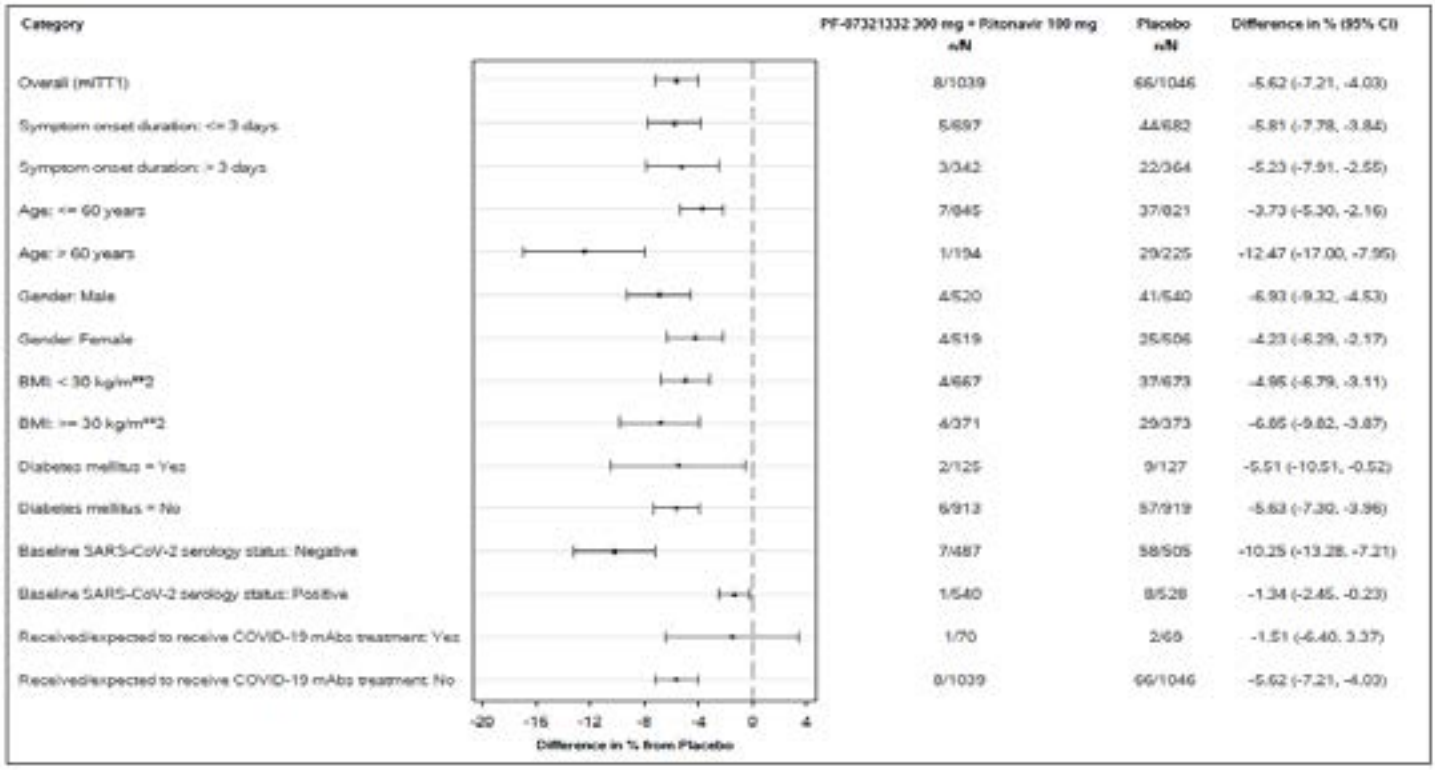
Similar trends have been observed across subgroups of subjects *(see Figure 1)*. These subgroup analyses are considered exploratory.

Figure 1: Adults with COVID-19 Dosed within 5 Days of Symptom Onset with COVID-19-Related Hospitalization or Death from Any Cause Through Day 28 (Protocol C4671005)



N=number of participants in the category of the analysis set.
All categories are based on mITT1 population except for COVID-19 mAb treatment which is based on mITT2 population.
Seropositivity was defined if results were positive in either Elecsys anti-SARS-CoV-2 S or Elecsys anti-SARS-CoV-2 (N) assay.
The difference of the proportions in the 2 treatment groups and its 95% confidence interval based on Normal approximation of the data are presented.

Relative to placebo, PAXLOVID treatment was associated with an approximately 0.9 $\log_{10}$ copies/mL greater decline in viral RNA levels in nasopharyngeal samples through Day 5, with similar results observed in the mITT, mITT1, and mITT2 analysis populations.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets.

- Nirmatrelvir tablets, 150 mg are oval, pink immediate-release, film-coated tablets debossed with “PFE” on one side and “3CL” on the other side.
- Ritonavir tablets, 100 mg are white film-coated ovaloid tablets debossed with the "a" logo and the code NK.

Nirmatrelvir tablets and ritonavir tablets are supplied in separate blister cavities within the same child-resistant blister card.

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Each carton contains 30 tablets divided in 5 daily-dose blister cards (NDC number: 0069-1085-30).

Each daily blister card (NDC number: 0069-1085-06) contains 4 nirmatrelvir tablets (150 mg each) and 2 ritonavir tablets (100 mg each) and indicates which tablets need to be taken in the morning and evening.

Storage and Handling

Store at USP controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

17 PATIENT COUNSELING INFORMATION

As a healthcare practitioner, you must communicate to the patient and/or caregiver information consistent with the "FACT SHEET FOR PATIENTS, PARENTS, AND CAREGIVERS" and provide them with a copy of this Fact Sheet prior to administration of PAXLOVID.

Use in Patients with Renal Impairment

No dose adjustment is needed in patients with mild renal impairment.

To ensure appropriate dosing in patients with moderate renal impairment, instruct such patients that they will be taking one 150 mg nirmatrelvir tablet with one 100 mg ritonavir tablet together twice daily for 5 days. Instruct patients that the pharmacist will alter their daily blister cards to ensure they receive the correct dose.

Pharmacist should refer to the provided instructions entitled "IMPORTANT PAXLOVID™ EUA DISPENSING INFORMATION FOR PATIENTS WITH MODERATE RENAL IMPAIRMENT" for dispensing of PAXLOVID to patients with moderate renal impairment *[see Dosage and Administration (2.2)]*.

Appropriate dosage for patients with severe renal impairment has not been determined *[see Dosage and Administration (2.2), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

Drug Interactions

Inform patients that PAXLOVID may interact with some drugs and is contraindicated for use with some drugs; therefore, patients should be advised to report to their healthcare provider the use of any prescription, non-prescription medication, or herbal products *[see Dosage and Administration (2.4), Contraindications (4), Warnings and Precautions (5.1), and Drug Interactions (7)].*

Administration Instructions

Inform patients to take PAXLOVID with or without food as instructed. Advise patients to swallow all tablets for PAXLOVID whole and not to chew, break, or crush the tablets. Alert the patient of the importance of completing the full 5-day treatment course and to continuing isolation in accordance with public health recommendations to maximize viral clearance and minimize transmission of SARS-CoV-2. If the patient misses a dose of PAXLOVID within 8 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 8 hours, the patient should not take the missed dose and instead take

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the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose *[see Dosage and Administration (2.1)]*.

18 MANUFACTURER INFORMATION

For general questions, visit the website or call the telephone number provided below.

Website	Telephone number
www.COVID19oralRx.com	1-877-219-7225 (1-877-C19-PACK)

For Medical Information about PAXLOVID, please visit www.pfizermedinfo.com or call 1-800-438-1985.

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New York, NY 10017

LAB-1492-0.8

Revised: 22 DEC 2021

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FACT SHEET FOR PATIENTS, PARENTS, AND CAREGIVERS

EMERGENCY USE AUTHORIZATION (EUA) OF PAXLOVID FOR CORONAVIRUS DISEASE 2019 (COVID-19)

You are being given this Fact Sheet because your healthcare provider believes it is necessary to provide you with PAXLOVID for the treatment of mild-to-moderate coronavirus disease (COVID-19) caused by the SARS-CoV-2 virus. This Fact Sheet contains information to help you understand the risks and benefits of taking the PAXLOVID you have received or may receive.

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to make PAXLOVID available during the COVID-19 pandemic (for more details about an EUA please see "**What is an Emergency Use Authorization?**" at the end of this document). PAXLOVID is not an FDA-approved medicine in the United States. Read this Fact Sheet for information about PAXLOVID. Talk to your healthcare provider about your options or if you have any questions. It is your choice to take PAXLOVID.

What is COVID-19?

COVID-19 is caused by a virus called a coronavirus. You can get COVID-19 through close contact with another person who has the virus.

COVID-19 illnesses have ranged from very mild-to-severe, including illness resulting in death. While information so far suggests that most COVID-19 illness is mild, serious illness can happen and may cause some of your other medical conditions to become worse. Older people and people of all ages with severe, long lasting (chronic) medical conditions like heart disease, lung disease, and diabetes, for example seem to be at higher risk of being hospitalized for COVID-19.

What is PAXLOVID?

PAXLOVID is an investigational medicine used to treat mild-to-moderate COVID-19 in adults and children [12 years of age and older weighing at least 88 pounds (40 kg)] with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. PAXLOVID is investigational because it is still being studied. There is limited information about the safety and effectiveness of using PAXLOVID to treat people with mild-to-moderate COVID-19.

The FDA has authorized the emergency use of PAXLOVID for the treatment of mild-to-moderate COVID-19 in adults and children [12 years of age and older weighing at least 88 pounds (40 kg)] with a positive test for the virus that causes COVID-19, and who are at high risk for progression to severe COVID-19, including hospitalization or death, under an EUA.

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What should I tell my healthcare provider before I take PAXLOVID?

Tell your healthcare provider if you:

- Have any allergies
- Have liver or kidney disease
- Are pregnant or plan to become pregnant
- Are breastfeeding a child
- Have any serious illnesses

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some medicines may interact with PAXLOVID and may cause serious side effects. Keep a list of your medicines to show your healthcare provider and pharmacist when you get a new medicine.

You can ask your healthcare provider or pharmacist for a list of medicines that interact with PAXLOVID. **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take PAXLOVID with other medicines.

Tell your healthcare provider if you are taking combined hormonal contraceptive. PAXLOVID may affect how your birth control pills work. Females who are able to become pregnant should use another effective alternative form of contraception or an additional barrier method of contraception. Talk to your healthcare provider if you have any questions about contraceptive methods that might be right for you.

How do I take PAXLOVID?

- PAXLOVID consists of 2 medicines: nirmatrelvir and ritonavir.
  - Take 2 pink tablets of nirmatrelvir with 1 white tablet of ritonavir by mouth 2 times each day (in the morning and in the evening) for 5 days. **For each dose, take all 3 tablets at the same time.**
  - **If you have kidney disease, talk to your healthcare provider. You may need a different dose.**
- Swallow the tablets whole. Do not chew, break, or crush the tablets.
- Take PAXLOVID with or without food.
- Do not stop taking PAXLOVID without talking to your healthcare provider, even if you feel better.
- If you miss a dose of PAXLOVID within 8 hours of the time it is usually taken, take it as soon as you remember. If you miss a dose by more than 8 hours, skip the missed dose and take the next dose at your regular time. Do not take 2 doses of PAXLOVID at the same time.
- If you take too much PAXLOVID, call your healthcare provider or go to the nearest hospital emergency room right away.
- If you are taking a ritonavir- or cobicistat-containing medicine to treat hepatitis C or Human Immunodeficiency Virus (HIV), you should continue to take your medicine as prescribed by your healthcare provider.

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Talk to your healthcare provider if you do not feel better or if you feel worse after 5 days.

Who should generally not take PAXLOVID?

Do not take PAXLOVID if:

- You are allergic to nirmatrelvir, ritonavir, or any of the ingredients in PAXLOVID.
- You are taking any of the following medicines:
  - Alfuzosin
  - Pethidine, piroxicam, propoxyphene
  - Ranolazine
  - Amiodarone, dronedarone, flecainide, propafenone, quinidine
  - Colchicine
  - Lurasidone, pimozide, clozapine
  - Dihydroergotamine, ergotamine, methylergonovine
  - Lovastatin, simvastatin
  - Sildenafil (Revatio®) for pulmonary arterial hypertension (PAH)
  - Triazolam, oral midazolam
  - Apalutamide
  - Carbamazepine, phenobarbital, phenytoin
  - Rifampin
  - St. John's Wort (*hypericum perforatum*)

Taking PAXLOVID with these medicines may cause serious or life-threatening side effects or affect how PAXLOVID works.

These are not the only medicines that may cause serious side effects if taken with PAXLOVID. PAXLOVID may increase or decrease the levels of multiple other medicines. It is very important to tell your healthcare provider about all of the medicines you are taking because additional laboratory tests or changes in the dose of your other medicines may be necessary while you are taking PAXLOVID. Your healthcare provider may also tell you about specific symptoms to watch out for that may indicate that you need to stop or decrease the dose of some of your other medicines.

What are the important possible side effects of PAXLOVID?

Possible side effects of PAXLOVID are:

- **Liver Problems.** Tell your healthcare provider right away if you have any of these signs and symptoms of liver problems: loss of appetite, yellowing of your skin and the whites of eyes (jaundice), dark-colored urine, pale colored stools and itchy skin, stomach area (abdominal) pain.
- **Resistance to HIV Medicines**. If you have untreated HIV infection, PAXLOVID may lead to some HIV medicines not working as well in the future.

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- **Other possible side effects include:**
  - altered sense of taste
  - diarrhea
  - high blood pressure
  - muscle aches

These are not all the possible side effects of PAXLOVID. Not many people have taken PAXLOVID. Serious and unexpected side effects may happen. PAXLOVID is still being studied, so it is possible that all of the risks are not known at this time.

What other treatment choices are there?
Like PAXLOVID, FDA may allow for the emergency use of other medicines to treat people with COVID-19. Go to https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization for information on the emergency use of other medicines that are authorized by FDA to treat people with COVID-19. Your healthcare provider may talk with you about clinical trials for which you may be eligible.

It is your choice to be treated or not to be treated with PAXLOVID. Should you decide not to receive it or for your child not to receive it, it will not change your standard medical care.

What if I am pregnant or breastfeeding?
There is no experience treating pregnant women or breastfeeding mothers with PAXLOVID. For a mother and unborn baby, the benefit of taking PAXLOVID may be greater than the risk from the treatment. If you are pregnant, discuss your options and specific situation with your healthcare provider.

It is recommended that you use effective barrier contraception or do not have sexual activity while taking PAXLOVID.

If you are breastfeeding, discuss your options and specific situation with your healthcare provider.

How do I report side effects with PAXLOVID?
Contact your healthcare provider if you have any side effects that bother you or do not go away.

Report side effects to **FDA MedWatch** at www.fda.gov/medwatch or call 1-800-FDA-1088 or you can report side effects to Pfizer Inc. at the contact information provided below.

Website	Fax number	Telephone number
www.pfizersafetyreporting.com	1-866-635-8337	1-800-438-1985

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How should I store PAXLOVID?
Store PAXLOVID tablets at room temperature, between 68°F to 77°F (20°C to 25°C).

How can I learn more about COVID-19?
- Ask your healthcare provider.
- Visit https://www.cdc.gov/COVID19.
- Contact your local or state public health department.

What is an Emergency Use Authorization (EUA)?
The United States FDA has made PAXLOVID available under an emergency access mechanism called an Emergency Use Authorization (EUA). The EUA is supported by a Secretary of Health and Human Service (HHS) declaration that circumstances exist to justify the emergency use of drugs and biological products during the COVID-19 pandemic.

PAXLOVID for the treatment of mild-to-moderate COVID-19 in adults and children [12 years of age and older weighing at least 88 pounds (40 kg)] with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, has not undergone the same type of review as an FDA-approved product. In issuing an EUA under the COVID-19 public health emergency, the FDA has determined, among other things, that based on the total amount of scientific evidence available including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective for diagnosing, treating, or preventing COVID-19, or a serious or life-threatening disease or condition caused by COVID-19; that the known and potential benefits of the product, when used to diagnose, treat, or prevent such disease or condition, outweigh the known and potential risks of such product; and that there are no adequate, approved, and available alternatives.

All of these criteria must be met to allow for the product to be used in the treatment of patients during the COVID-19 pandemic. The EUA for PAXLOVID is in effect for the duration of the COVID-19 declaration justifying emergency use of this product, unless terminated or revoked (after which the products may no longer be used under the EUA).

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Additional Information
For general questions, visit the website or call the telephone number provided below.

Website	Telephone number
www.COVID19oralRx.com	1-877-219-7225 (1-877-C19-PACK)

You can also go to www.pfizermedinfo.com or call 1-800-438-1985 for more information.

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New York, NY 10017

LAB-1494-0.3

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December 22, 2021

IMPORTANT PRESCRIBING INFORMATION

Subject: PAXLOVID Emergency Use Authorization (EUA) dosing and dispensing in moderate renal impairment, and risk of serious adverse reactions due to drug interactions

Dear Healthcare Provider,

The purpose of this letter is to make you aware of the EUA dosing and dispensing requirements for patients with moderate renal impairment, and the potential for drug-drug interactions associated with PAXLOVID (nirmatrelvir tablets; ritonavir tablets). PAXLOVID contains two different drugs that are co-packaged in a daily blister card for oral use.

The dosage for PAXLOVID is as follows:

eGFR*	**PAXLOVID Dose**
Greater than 60 mL/min (*normal renal function or mild renal impairment*)	300 mg nirmatrelvir with 100 mg ritonavir, taken twice daily for 5 days
≥30 to <60 mL/min (*moderate renal impairment*)	150 mg nirmatrelvir with 100 mg ritonavir, taken twice daily for 5 days
<30 mL/min (*severe renal impairment*)	PAXLOVID is not recommended (the appropriate dose has not been determined).

*eGFR=estimated glomerular filtration rate based on the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula

Each daily blister card contains a morning and evening dose, with each dose consisting of 300 mg nirmatrelvir (two oval, pink 150 mg tablets) and 100 mg ritonavir (one ovaloid, white 100 mg tablet) as shown in Figure A below, which is incongruent with the moderate renal impairment dose.

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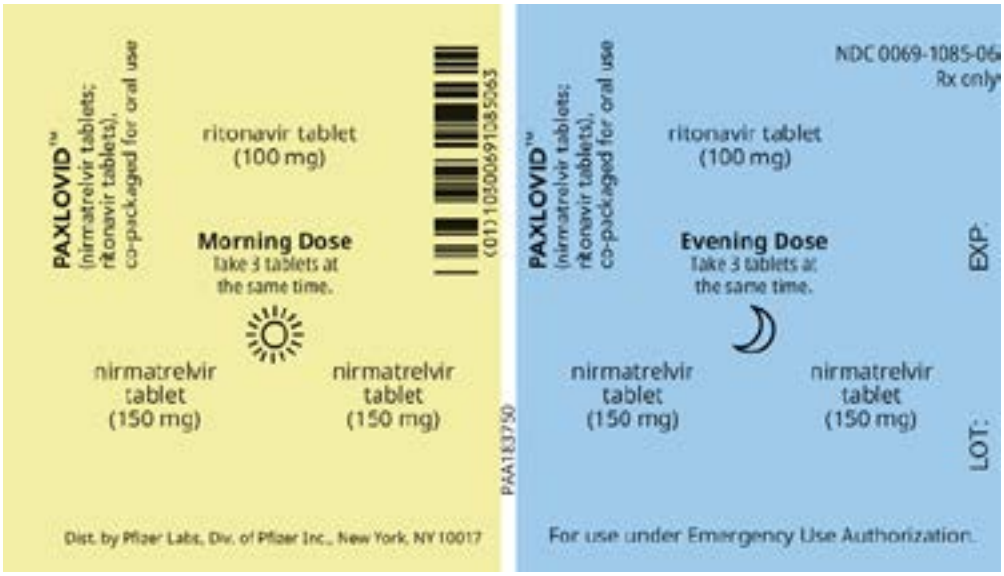

Figure A: Blister card containing morning and evening dose for normal renal function or mild renal impairment

Each daily blister card contains more nirmatrelvir tablets than are needed for dosing in patients with moderate renal impairment. **It is critical that all prescriptions specify the numeric dose for each active ingredient within PAXLOVID as follows:**

- **PAXLOVID 150 mg nirmatrelvir with 100 mg ritonavir for patients with moderate renal impairment, or**
- **PAXLOVID 300 mg nirmatrelvir with 100 mg ritonavir for patients with normal renal function or mild renal impairment**

Dispensing information in patients with moderate renal impairment:

Each shipment of PAXLOVID will be accompanied with **instructions, for pharmacists to remove the unneeded, additional nirmatrelvir tablets, and with stickers to affix to each daily blister card as well as the carton** when dispensing PAXLOVID to patients with moderate renal impairment (see below for image of dispensing instructions).

Pharmacists should ensure that they refer to the instructions entitled "IMPORTANT PAXLOVID™ DISPENSING INFORMATION FOR PATIENTS WITH MODERATE RENAL IMPAIRMENT" regarding specific instructions on tablet removal and proper sticker placement. In addition, **pharmacists should counsel patients** about renal dosing instructions and notify them that their blister cards have been altered at the pharmacy.

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IMPORTANT PAXLOVID™ EUA DISPENSING INFORMATION FOR PATIENTS WITH MODERATE RENAL IMPAIRMENT

To dispense PAXLOVID dose (150 mg nirmatrelvir with 100 mg ritonavir) for moderate renal impairment, pharmacist should:

STEP ONE: Remove one of the 150 mg nirmatrelvir tablets from the morning dose and remove one of the 150 mg nirmatrelvir tablets from the evening dose of the blister card (see figure 1 below). The nirmatrelvir tablets that are removed should be the ones closest to the middle of the blister pack.

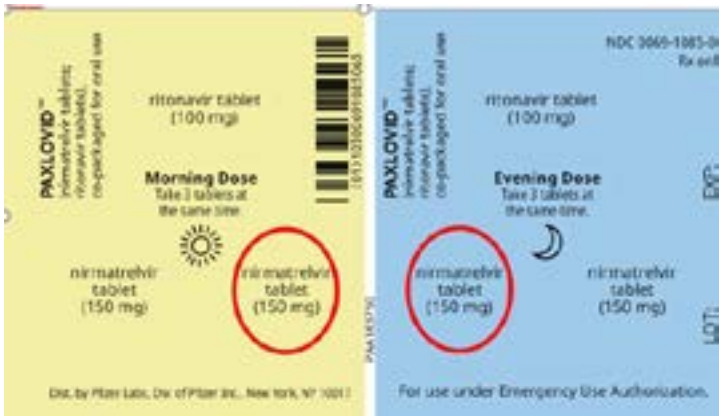

Figure 1: Remove the nirmatrelvir tablets circled in red from the blister card

STEP TWO: Affix the blister card with one sticker from the provided tear pad to carefully cover the empty blister cavities as shown in figure 2 below. The exact placement of this sticker is important to cover the empty blister cavities from the tablets. Ensure the sticker also covers the pre-printed dosing instruction that is on the blister card.

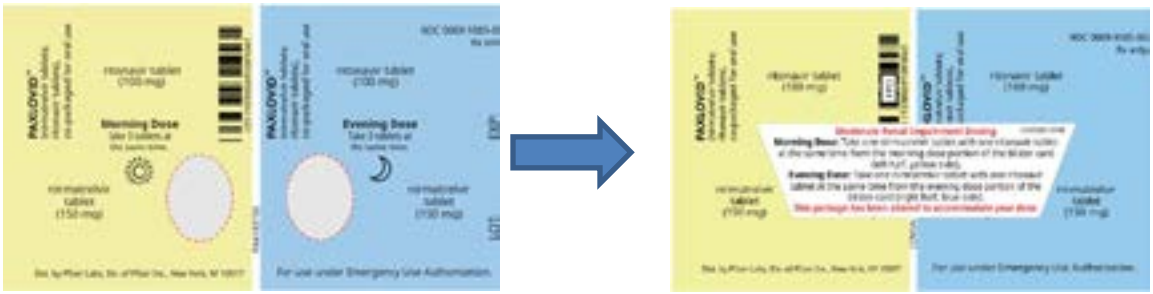

Figure 2: Placement of sticker over empty blister cavities and pre-printed dosing instruction after removal of nirmatrelvir tablets

STEP THREE: Repeat steps one and two for every blister card in the carton (each carton contains five blister cards for a full 5-day dosing regimen).

STEP FOUR: Affix one sticker from the provided tear pad to carefully cover over the pre-printed dosing regimen on the carton as shown in figure 3 below:

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Figure 3: Placement of sticker over pre-printed dosing regimen on carton

Patients with moderate renal impairment should be instructed to take only one 150-mg nirmatrelvir tablet with one 100-mg ritonavir tablet together twice daily for 5 days. **Patients with moderate renal impairment should be notified that their blister cards have been altered by their pharmacist to remove unneeded tablets.**

Risk of Serious Adverse Reactions Due to Drug Interactions:

Use of PAXLOVID, a CYP3A inhibitor, in patients receiving concomitant medications metabolized by CYP3A may increase the plasma concentrations of those concomitant medications.

Use of concomitant medications that inhibit or induce CYP3A may increase or decrease concentrations of PAXLOVID, respectively.

These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medications.
- Clinically significant adverse reactions from greater exposures of PAXLOVID.
- Loss of therapeutic effect of PAXLOVID and possible development of viral resistance.

See the current EUA Fact Sheet for Healthcare Providers for clinically significant drug interactions, including **contraindicated** drugs. Consider the potential for drug interactions prior to and during PAXLOVID therapy; review concomitant medications during PAXLOVID therapy and monitor for the adverse reactions associated with the concomitant medications.

Prescribers and pharmacists should inform patients that PAXLOVID may interact with some drugs and is **contraindicated** for use with some drugs; therefore, patients should be advised to report to their healthcare provider the use of any prescription or non-prescription medication or herbal products.

Indication & Authorized Use:

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of the unapproved product PAXLOVID for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

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For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html.

Healthcare providers should consider the benefit-risk for an individual patient.

Limitations of Authorized Use:

- PAXLOVID is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19.
- PAXLOVID is not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.
- PAXLOVID is not authorized for use for longer than 5 consecutive days.

PAXLOVID may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which PAXLOVID belongs (i.e., anti-infectives).

Patients requiring hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID may complete the full 5-day treatment course per the healthcare provider's discretion.

Reporting Adverse Events and Medication Errors:

Under the EUA, all serious adverse events and all medication errors potentially related to PAXLOVID must be reported.
Serious adverse event reports and medication error reports should be submitted to FDA's MedWatch program using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm, or
- Complete and submit a postage-paid Form FDA 3500 (https://www.fda.gov/media/76299/download) and return by mail (MedWatch, 5600 Fishers Lane, Rockville, MD 208529787, or by fax (1-800-FDA-0178), or
- Call 1-800-FDA-1088 to request a reporting form. Please provide a copy of all FDA MedWatch forms to Pfizer via fax (1-866-635-8337), telephone (1-800-438-1985) or website www.pfizersafetyreporting.com

The PAXLOVID EUA Fact Sheet for Healthcare Providers is available at www.COVID19oralRx.com or by scanning the QR Code below:

Sincerely,

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Eddie G M Power PhD MBA GFMD
Vice President, North America Medical Affairs

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Document 2A.16

U.S. FDA Fact Sheet for Patients, Parents, and Caregivers Emergency Use Authorization (EUA) of Paxlovid for Coronavirus Disease 2019 (COVID-19)

Document URL

https://www.fda.gov/media/155051/download

Reference website URL

https://www.fda.gov/drugs/emergency-preparedness-drugs/emergency-use-authorizations-drugs-and-non-vaccine-biological-products

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FACT SHEET FOR PATIENTS, PARENTS, AND CAREGIVERS

EMERGENCY USE AUTHORIZATION (EUA) OF PAXLOVID FOR CORONAVIRUS DISEASE 2019 (COVID-19)

You are being given this Fact Sheet because your healthcare provider believes it is necessary to provide you with PAXLOVID for the treatment of mild-to-moderate coronavirus disease (COVID-19) caused by the SARS-CoV-2 virus. This Fact Sheet contains information to help you understand the risks and benefits of taking the PAXLOVID you may receive. This Fact Sheet also contains information about how to take PAXLOVID and how to report side effects or problems with the appearance or packaging of PAXLOVID.

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to make PAXLOVID available for the treatment of mild-to-moderate COVID-19 in adults and children 12 years of age and older weighing at least 88 pounds (40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death (for more details about an EUA please see "**What is an Emergency Use Authorization?**" at the end of this document). Read this Fact Sheet for information about PAXLOVID. Talk to your healthcare provider about your options or if you have any questions. It is your choice to take PAXLOVID.

What is COVID-19?

COVID-19 is caused by a virus called a coronavirus. You can get COVID-19 through close contact with another person who has the virus.

COVID-19 illnesses have ranged from very mild-to-severe, including illness resulting in death. While information so far suggests that most COVID-19 illness is mild, serious illness can happen and may cause some of your other medical conditions to become worse. Older people and people of all ages with severe, long lasting (chronic) medical conditions like heart disease, lung disease, and diabetes, for example seem to be at higher risk of being hospitalized for COVID-19.

What is PAXLOVID?

PAXLOVID is a medicine that is available under EUA for the treatment of mild-to-moderate COVID-19 in adults and children 12 years of age and older weighing at least 88 pounds (40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death. Although PAXLOVID is FDA-approved for the treatment of COVID-19 in certain adults (see section **What other treatment choices are there?**), PAXLOVID use in children remains investigational because it is still being studied. *There is limited information about the safety and effectiveness of using PAXLOVID to treat children with mild-to-moderate COVID-19*.

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What is the most important information I should know about PAXLOVID?
PAXLOVID can interact with other medicines causing severe or life-threatening side effects or death. It is important to know the medicines that should not be taken with PAXLOVID.

Do not take PAXLOVID if:

- you are taking any of the following medicines:
  - alfuzosin
  - amiodarone
  - apalutamide
  - carbamazepine
  - colchicine
  - dihydroergotamine
  - dronedarone
  - eletriptan
  - eplerenone
  - ergotamine
  - finerenone
  - flecainide
  - flibanserin
  - ivabradine
  - lomitapide
  - lovastatin
  - lumacaftor/ivacaftor
  - lurasidone
  - methylergonovine
  - midazolam (oral)
  - naloxegol
  - phenobarbital
  - phenytoin
  - pimozide
  - primidone
  - propafenone
  - quinidine
  - ranolazine
  - rifampin
  - rifapentine
  - St. John's Wort (*hypericum perforatum*)
  - sildenafil (Revatio®) for pulmonary arterial hypertension
  - silodosin
  - simvastatin
  - tolvaptan
  - triazolam
  - ubrogepant
  - voclosporin

These are not the only medicines that may cause serious or life-threatening side effects if taken with PAXLOVID. PAXLOVID may increase or decrease the levels of multiple other medicines. It is very important to tell your healthcare provider about all of the medicines you are taking because additional laboratory tests or changes in the dose of your other medicines may be necessary during treatment with PAXLOVID. Your healthcare provider may also tell you about specific symptoms to watch out for that may indicate that you need to stop or decrease the dose of some of your other medicines.

- you are allergic to nirmatrelvir, ritonavir, or any of the ingredients in PAXLOVID. See the end of this leaflet for a complete list of ingredients in PAXLOVID. See **"What are the important possible side effects of PAXLOVID?"** for signs and symptoms of allergic reactions.

What should I tell my healthcare provider before I take PAXLOVID?

Tell your healthcare provider if you:

- have kidney problems. You may need a different dose of PAXLOVID.
- have liver problems, including hepatitis.
- have Human Immunodeficiency Virus 1 (HIV-1) infection. PAXLOVID may lead to some HIV-1 medicines not working as well in the future.
- are pregnant or plan to become pregnant. It is not known if PAXLOVID can harm your unborn baby. Tell your healthcare provider right away if you are or if you become pregnant.

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- are breastfeeding or plan to breastfeed. It is not known if PAXLOVID can pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with PAXLOVID.

Some medicines may interact with PAXLOVID and may cause serious side effects.

- **Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
- Your healthcare provider can tell you if it is safe to take PAXLOVID with other medicines.
- You can ask your healthcare provider or pharmacist for a list of medicines that interact with PAXLOVID.
- Do not start taking a new medicine without telling your healthcare provider.

Tell your healthcare provider if you are taking combined birth control (hormonal contraceptive). PAXLOVID may affect how your hormonal contraceptives work. Females who are able to become pregnant should use another effective alternative form of contraception or an additional barrier method of contraception during treatment with PAXLOVID. Talk to your healthcare provider if you have any questions about contraceptive methods that might be right for you.

How do I take PAXLOVID?

- Take PAXLOVID exactly as your healthcare provider tells you to take it.
- **PAXLOVID consists of 2 medicines: nirmatrelvir tablets and ritonavir tablets. The 2 medicines are taken together 2 times each day for 5 days.**
  - Nirmatrelvir is an oval, pink tablet.
  - Ritonavir is a white or off-white tablet.
- PAXLOVID is available in 2 Dose Packs (see **Figures A and B** below). Your healthcare provider will prescribe the PAXLOVID Dose Pack that is right for you.
- **If you have kidney disease, your healthcare provider may prescribe a lower dose (see Figure B). Talk to your healthcare provider to make sure you receive the correct Dose Pack.**

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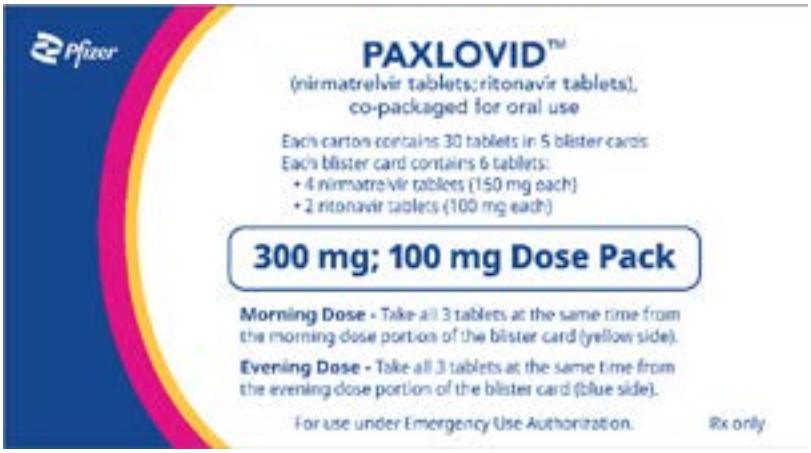
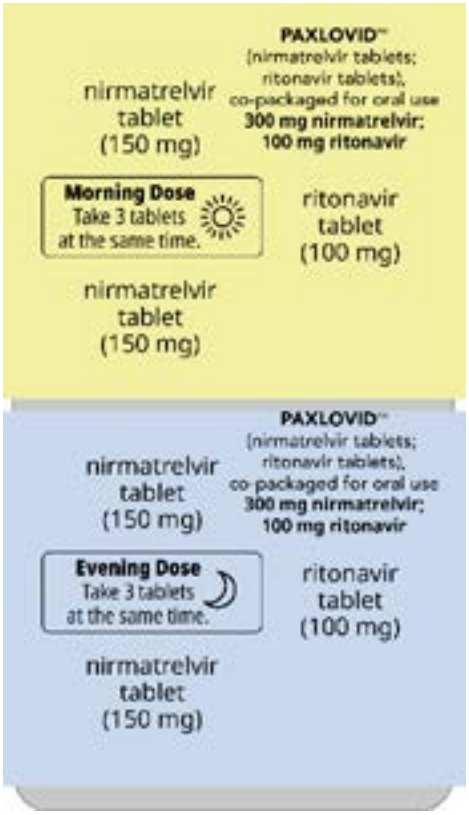
Figure A

If you are prescribed PAXLOVID 300 mg; 100 mg Dose Pack:
each dose contains 3 tablets.



How to take PAXLOVID 300 mg; 100 mg Dose Pack



Morning Dose:
Take the 2 pink nirmatrelvir tablets and
1 white to off-white ritonavir tablet together
at the same time each morning.

Evening Dose:
Take the 2 pink nirmatrelvir tablets and
1 white to off-white ritonavir tablet together
at the same time each evening.

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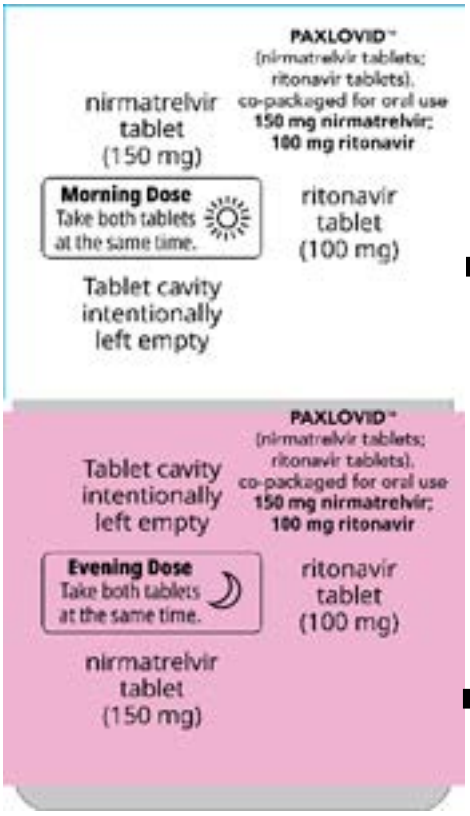
Figure B

If you are prescribed PAXLOVID 150 mg; 100 mg Dose Pack:
each dose contains 2 tablets.

How to take PAXLOVID 150 mg; 100 mg Dose Pack



Morning Dose:
Take the 1 pink nirmatrelvir tablet and
1 white to off-white ritonavir tablet together
at the same time each morning.

Evening Dose:
Take the 1 pink nirmatrelvir tablet and
1 white to off-white ritonavir tablet together
at the same time each evening.

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- Do not remove your PAXLOVID tablets from the blister card before you are ready to take your dose.
    - Take your first dose of PAXLOVID in the morning or evening, depending on when you pick up your prescription, or as your healthcare provider tells you to.
- Swallow the tablets whole. Do not chew, break, or crush the tablets.
- Take PAXLOVID with or without food.
- Do not stop taking PAXLOVID without talking to your healthcare provider, even if you feel better.
- If you miss a dose of PAXLOVID within 8 hours of the time it is usually taken, take it as soon as you remember. If you miss a dose by more than 8 hours, skip the missed dose and take the next dose at your regular time. Do not take 2 doses of PAXLOVID at the same time.
- If you take too much PAXLOVID, call your healthcare provider or go to the nearest hospital emergency room right away.
- If you are taking a ritonavir- or cobicistat-containing medicine to treat hepatitis C or HIV-1 infection, you should continue to take your medicine as prescribed by your healthcare provider.

Talk to your healthcare provider if you do not feel better or if you feel worse after 5 days.

What are the important possible side effects of PAXLOVID?

PAXLOVID may cause serious side effects, including:

- **Allergic reactions, including severe allergic reactions (anaphylaxis) have** happened during treatment with PAXLOVID**.** Stop taking PAXLOVID and get medical help right away if you get any of the following symptoms of an allergic reaction:
    - skin rash, hives, blisters or peeling skin
    - painful sores or ulcers in the mouth, nose, throat or genital area
    - swelling of the mouth, lips, tongue or face
    - trouble swallowing or breathing
    - throat tightness
    - hoarseness
- **Liver Problems.** Tell your healthcare provider right away if you get any of the following signs and symptoms of liver problems during treatment with PAXLOVID:
    - loss of appetite
    - yellowing of your skin and the white of eyes
    - dark-colored urine
    - pale colored stools
    - itchy skin
    - stomach-area (abdominal) pain

The most common side effects of PAXLOVID include: altered sense of taste and diarrhea.

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Other possible side effects include:

- headache
- vomiting
- abdominal pain
- nausea
- high blood pressure
- feeling generally unwell

These are not all the possible side effects of PAXLOVID. For more information, ask your healthcare provider or pharmacist.

What other treatment choices are there?
PAXLOVID is FDA-approved for the treatment of mild-to-moderate COVID-19 in certain adults; however, there are not sufficient quantities of the approved presentations (i.e., dose packs) of PAXLOVID at this time. This EUA continues to authorize the emergency use of PAXLOVID for the approved patient population to ensure continued access in order to meet the public health need.

VEKLURY (remdesivir) is FDA-approved for the treatment of mild-to-moderate COVID-19 in certain adults and children. Talk with your healthcare provider to see if VEKLURY is appropriate for you.

For information on the emergency use of other medicines that are authorized by FDA to treat people with COVID-19, please go to https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization. Your healthcare provider may talk with you about clinical trials for which you may be eligible.

It is your choice to be treated or not to be treated with PAXLOVID. Should you decide not to receive it or for your child not to receive it, it will not change your standard medical care.

What if I am pregnant or breastfeeding?
There is limited experience treating pregnant women or breastfeeding mothers with PAXLOVID. For a mother and unborn baby, the benefit of taking PAXLOVID may be greater than the risk from the treatment. If you are pregnant, discuss your options and specific situation with your healthcare provider.

If you are breastfeeding, discuss your options and specific situation with your healthcare provider.

How do I report side effects or problems with the appearance or packaging of PAXLOVID?
Contact your healthcare provider if you have any side effects that bother you or do not go away.

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Report side effects or problems with the appearance or packaging of PAXLOVID (see Figures A and B above for examples of PAXLOVID Dose Packs) to **FDA MedWatch** at www.fda.gov/medwatch or call 1-800-FDA-1088 or you can report side effects to Pfizer Inc. at the contact information provided below.

Website	Fax number	Telephone number
www.pfizersafetyreporting.com	1-866-635-8337	1-800-438-1985

How should I store PAXLOVID?
Store PAXLOVID tablets at room temperature, between 68°F to 77°F (20°C to 25°C).
Keep PAXLOVID and all medicines out of the reach of children.

What if I have questions about the expiration date for my PAXLOVID?
The FDA has extended the expiration date (shelf-life) for some lots of PAXLOVID. To find the extended expiration date, enter the lot number found on the side of carton or bottom of blister pack at this website: https://www.paxlovidlotexpiry.com/ or talk with your healthcare provider. Information on the authorized shelf-life extensions for PAXLOVID may also be found at https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/expiration-dating-extension.

How can I learn more about COVID-19?
- Ask your healthcare provider.
- Visit https://www.cdc.gov/COVID19.
- Contact your local or state public health department.

What is an Emergency Use Authorization (EUA)?
The United States FDA has made PAXLOVID available under an emergency access mechanism called an Emergency Use Authorization (EUA). The EUA is supported by a Secretary of Health and Human Services (HHS) declaration that circumstances exist to justify the emergency use of drugs and biological products during the COVID-19 pandemic.

In issuing an EUA, the FDA has determined, among other things, that based on the total amount of scientific evidence available including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective for diagnosing, treating, or preventing COVID-19, or a serious or life-threatening disease or condition caused by COVID-19; that the known and potential benefits of the product, when used to diagnose, treat, or prevent such disease or condition, outweigh the known and potential risks of such product; and that there are no adequate, approved, and available alternatives.

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All of these criteria must be met to allow for the product to be available under an EUA. The EUA for PAXLOVID is in effect for the duration of the COVID-19 declaration justifying emergency use of this product, unless the relevant EUA declaration is terminated or the EUA revoked (after which the products may no longer be used under the EUA).

What are the ingredients in PAXLOVID?

Active ingredient: nirmatrelvir and ritonavir
Nirmatrelvir inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, and sodium stearyl fumarate. Film-coating contains: hydroxy propyl methylcellulose, iron oxide red, polyethylene glycol, and titanium dioxide.
Ritonavir inactive ingredients: anhydrous dibasic calcium phosphate, colloidal silicon dioxide, copovidone, sodium stearyl fumarate, and sorbitan monolaurate. The film coating may contain: colloidal anhydrous silica, colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, polyethylene glycol, polysorbate 80, talc, and titanium dioxide.

Additional Information

For general questions, visit the website or call the telephone number provided below.

Website	Telephone number
www.COVID19oralRx.com	1-877-219-7225 (1-877-C19-PACK)

Pfizer

Distributed by
Pfizer Labs
Division of Pfizer Inc.
New York, NY 10001

LAB-1494-9.3b

Revised: 05/2023

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Document 2A.17

U.S. FDA Fact Sheet for Healthcare Providers: Emergency Use Authorization for Paxlovid

Document URL

https://www.fda.gov/media/155050/download

Reference website URL

https://www.fda.gov/drugs/emergency-preparedness-drugs/emergency-use-authorizations-drugs-and-non-vaccine-biological-products

License

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FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR PAXLOVID™

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)
These highlights of the EUA do not include all the information needed to use PAXLOVID™ under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for PAXLOVID.

PAXLOVID (nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use
Original EUA Authorized Date: 12/2021
Revised EUA Authorized Date: 05/2023

WARNING: SIGNIFICANT DRUG INTERACTIONS WITH PAXLOVID
See full prescribing information for complete boxed warning.

- **PAXLOVID includes ritonavir, a strong CYP3A inhibitor, which may lead to greater exposure of certain concomitant medications, resulting in potentially severe, life-threatening, or fatal events. *(4, 5.1, 7)***
- **Prior to prescribing PAXLOVID: 1) Review all medications taken by the patient to assess potential drug-drug interactions with a strong CYP3A inhibitor like PAXLOVID and 2) Determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring. *(7)***
- **Consider the benefit of PAXLOVID treatment in reducing hospitalization and death, and whether the risk of potential drug-drug interactions for an individual patient can be appropriately managed. *(5.1, 7, 14)***

----------RECENT MAJOR CHANGES----------

Boxed Warning: added	05/2023
Limitations of Authorized Use (1): updated	05/2023
Contraindications (4): add rifapentine	05/2023
Warnings and Precautions (5.1, 5.2): updated	05/2023
Adverse Reactions (6.1, 6.2): updated	05/2023
Drug Interactions (7.1, 7.3): updated	05/2023
Use in Specific Populations (8.1, 8.2, 8.5, 8.6): updated	05/2023
Clinical Pharmacology (12.1, 12.2, 12.3, 12.4): updated	05/2023
Nonclinical Toxicology (13.1, 13.2): updated	05/2023
Clinical Studies (14.1, 14.2, 14.3): updated	05/2023
Emergency Use Authorization (1): removal of requirement of SARS-CoV-2 viral testing	02/2023
Warnings and Precautions (5.2, 17): revision to hypersensitivity reactions to PAXLOVID including anaphylaxis	09/2022
Adverse Reactions (6.2): addition of new adverse reactions	09/2022
Microbiology (12.4): addition of Omicron sub-variants, *in vivo*, and resistance data	09/2022
Drug Interactions (7.3): addition of new drug interactions	08/2022
Emergency Use Authorization (1): addition of pharmacist prescribing guidance	07/2022
Contraindications (4): addition of new contraindicated drugs	06/2022
Microbiology (12.4): addition of viral RNA rebound	06/2022

----------EUA FOR PAXLOVID----------

The U.S. Food and Drug Administration has issued an EUA for the emergency use of PAXLOVID which includes nirmatrelvir, a SARS-CoV-2 main protease (M^{pro}: also referred to as 3CLpro or nsp5 protease) inhibitor, and ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor, for the treatment of adults and pediatric patients (12 years of age and older weighing at least 40 kg) with mild-to-moderate coronavirus disease 2019 (COVID-19) and who are at high risk for progression to severe COVID-19, including hospitalization or death.

LIMITATIONS OF AUTHORIZED USE

- PAXLOVID is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19.
- PAXLOVID is not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.
- PAXLOVID is not authorized for use longer than 5 consecutive days.

PAXLOVID may be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs.

PAXLOVID may also be prescribed for an individual patient by a state-licensed pharmacist under the following conditions:

- Sufficient information is available, such as through access to health records less than 12 months old or consultation with a health care provider in an established provider-patient relationship with the individual patient, to assess renal and hepatic function; and
- Sufficient information is available, such as through access to health records, patient reporting of medical history, or consultation with a health care provider in an established provider-patient relationship with the individual patient, to obtain a comprehensive list of medications (prescribed and non-prescribed) that the patient is taking to assess for potential drug interaction.

The state-licensed pharmacist should refer an individual patient for clinical evaluation (e.g., telehealth, in-person visit) with a physician, advanced practice registered nurse, or physician assistant licensed or authorized under state law to prescribe drugs, if any of the following apply:

- Sufficient information is not available to assess renal and hepatic function.
- Sufficient information is not available to assess for a potential drug interaction.
- Modification of other medications is needed due to a potential drug interaction.
- PAXLOVID is not an appropriate therapeutic option based on the authorized Fact Sheet for Healthcare Providers or due to potential drug interactions for which recommended monitoring would not be feasible.

PAXLOVID is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of PAXLOVID under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

See Full Fact Sheet for Healthcare Providers for the justification for emergency use of drugs during the COVID-19 pandemic, information on available alternatives, and additional information on COVID-19.

----------DOSAGE AND ADMINISTRATION----------

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. (2.1)
Nirmatrelvir must be co-administered with ritonavir. (2.1)

- Initiate PAXLOVID treatment as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset. (2.1)
- Administer orally with or without food. (2.1)
- Dosage: 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all three tablets taken together twice daily for 5 days. (2.1, 2.2)
- **Dose reduction for moderate renal impairment (eGFR ≥30 to <60 mL/min)**: 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet), with both tablets taken together twice daily for 5 days. (2.3)
- PAXLOVID is not recommended in patients with severe renal impairment (eGFR <30 mL/min). (2.3, 8.6)
- PAXLOVID is not recommend in patients with severe hepatic impairment (Child-Pugh Class C). (2.4, 8.7)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: nirmatrelvir 150 mg (3)
- Tablets: ritonavir 100 mg (3)

----------CONTRAINDICATIONS----------

- History of clinically significant hypersensitivity reactions to the active ingredients (nirmatrelvir or ritonavir) or any other components. (4)

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- Co-administration with drugs highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions. (4, 7.3)
- Co-administration with potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. (4)

---------- WARNINGS AND PRECAUTIONS----------

- The concomitant use of PAXLOVID and certain other drugs may result in potentially significant drug interactions. Consult the full prescribing information prior to and during treatment for potential drug interactions. (5.1, 7)
- Hypersensitivity Reactions: Anaphylaxis, serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson syndrome), and other hypersensitivity reactions have been reported with PAXLOVID. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue PAXLOVID and initiate appropriate medications and/or supportive care. (5.2)
- Hepatotoxicity: Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir. (5.3)
- HIV-1 Drug Resistance: PAXLOVID use may lead to a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection. (5.4)

---------- ADVERSE REACTIONS ----------

Adverse events (incidence ≥1% and greater incidence than in the placebo group) were dysgeusia and diarrhea. (6.1)

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to PAXLOVID (1) by submitting FDA Form 3500 online, (2) by downloading this form and then submitting by mail or fax, or (3) contacting the FDA at 1-800-FDA-1088 to request this form. Please also provide a copy of this form to Pfizer Inc. at fax number: 1-866-635-8337. (6.4)

----------DRUG INTERACTIONS----------

Co-administration of PAXLOVID can alter the plasma concentrations of other drugs and other drugs may alter the plasma concentrations of PAXLOVID. Consider the potential for drug interactions prior to and during PAXLOVID therapy and review concomitant medications during PAXLOVID therapy. (4, 5.1, 7, 12.3)

See FACT SHEET FOR PATIENTS, PARENTS, AND CAREGIVERS.

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* Sections or subsections omitted from the EUA are not listed.

FULL FACT SHEET FOR HEALTHCARE PROVIDERS

WARNING: SIGNIFICANT DRUG INTERACTIONS WITH PAXLOVID

- **PAXLOVID includes ritonavir, a strong CYP3A inhibitor, which may lead to greater exposure of certain concomitant medications, resulting in potentially severe, life-threatening, or fatal events *[see Contraindications (4), Warnings and Precautions (5.1), and Drug Interactions (7)].***
- **Prior to prescribing PAXLOVID: 1) Review all medications taken by the patient to assess potential drug-drug interactions with a strong CYP3A inhibitor like PAXLOVID and 2) Determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring *[see Drug Interactions (7)].***
- **Consider the benefit of PAXLOVID treatment in reducing hospitalization and death, and whether the risk of potential drug-drug interactions for an individual patient can be appropriately managed *[see Warnings and Precautions (5.1), Drug Interactions (7), and Clinical Studies (14)].***

1 EMERGENCY USE AUTHORIZATION

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of PAXLOVID for the treatment of adults and pediatric patients (12 years of age and older weighing at least 40 kg) with mild-to-moderate coronavirus disease 2019 (COVID-19) and who are at high risk[1] for progression to severe COVID-19, including hospitalization or death.

LIMITATIONS OF AUTHORIZED USE

- PAXLOVID is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19 [see Dosage and Administration (2.1)].[2]
- PAXLOVID is not authorized for use as pre-exposure or post-exposure prophylaxis for prevention of COVID-19 *[see Clinical Studies (14.3)]*.
- PAXLOVID is not authorized for use for longer than 5 consecutive days.

PAXLOVID may be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs.

PAXLOVID may also be prescribed for an individual patient by a state-licensed pharmacist under the following conditions:

- Sufficient information is available, such as through access to health records less than 12 months old or consultation with a health care provider in an established provider-patient relationship with the individual patient, to assess renal and hepatic function; and
- Sufficient information is available, such as through access to health records, patient reporting of medical history, or consultation with a health care provider in an established provider-patient

[1] Determining whether a patient is at high risk for progression to severe COVID-19, including hospitalization or death, is based on the provider's assessment of the individual patient being considered for treatment of COVID-19 and that patient's medical history. For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html.

[2] Patients requiring hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID may complete the full 5-day treatment course per the healthcare provider's discretion.

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relationship with the individual patient, to obtain a comprehensive list of medications (prescribed and non-prescribed) that the patient is taking to assess for potential drug interaction.

The state-licensed pharmacist should refer an individual patient for clinical evaluation (e.g., telehealth, in-person visit) with a physician, advanced practice registered nurse, or physician assistant licensed or authorized under state law to prescribe drugs, if any of the following apply:

- Sufficient information is not available to assess renal and hepatic function.
- Sufficient information is not available to assess for a potential drug interaction.
- Modification of other medications is needed due to a potential drug interaction.
- PAXLOVID is not an appropriate therapeutic option based on the authorized Fact Sheet for Healthcare Providers or due to potential drug interactions for which recommended monitoring would not be feasible.

PAXLOVID is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of PAXLOVID under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Justification for Emergency Use of Drugs During the COVID-19 Pandemic

There is currently an outbreak of COVID-19 caused by SARS-CoV-2, a novel coronavirus. The Secretary of Health and Human Services (HHS) has:

- Determined that there is a public health emergency, or significant potential for a public health emergency.[3]
- Declared that circumstances exist justifying the authorization of emergency use of drugs and biological products for the prevention or treatment of COVID-19.[4]

An EUA is a U.S. Food and Drug Administration authorization for the emergency use of an unapproved product or unapproved use of an approved product (i.e., drug, biological product, or device) in the United States under certain circumstances including, but not limited to, when the Secretary of HHS declares that there is a public health emergency that affects the national security or the health and security of United States citizens living abroad, and that involves biological agent(s) or a disease or condition that may be attributable to such agent(s). Criteria for issuing an EUA include:

[3] *See* U.S. Department of Health and Human Services, Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3. February 4, 2020; https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency. *See also* U.S. Department of Health and Human Services, Amended Determination of a Public Health Emergency or Significant Potential for a Public Health Emergency Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3(b). March 15, 2023 ("Amended Determination"); https://www.federalregister.gov/documents/2023/03/20/2023-05609/covid-19-emergency-use-authorization-declaration.

[4] *See* U.S. Department of Health and Human Services, Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3, 85 FR 18250 (April 1, 2020); https://www.federalregister.gov/documents/2020/04/01/2020-06905/emergency-use-authorization-declaration. *See also* Amended Determination ("The declarations issued pursuant to section 564(b)(1) of the FD&C Act that circumstances exist justifying the authorization of emergency use of certain in vitro diagnostics, personal respiratory protective devices, other medical devices and drugs and biological products, as set forth in those declarations, and that are based on the February 4, 2020 determination, remain in effect until those declarations are terminated in accordance with section 564 of the FD&C Act.").

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- The biological agent(s) can cause a serious or life-threatening disease or condition;
- Based on the totality of the available scientific evidence (including data from adequate and well-controlled clinical trials, if available), it is reasonable to believe that
    - the product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition; and
    - the known and potential benefits of the product—when used to diagnose, prevent, or treat such disease or condition—outweigh the known and potential risks of the product, taking into consideration the material threat posed by the biological agent(s);
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the serious or life-threatening disease or condition.

Information Regarding Approved Alternatives for the EUA Authorized Use[5]

PAXLOVID is FDA-approved for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. Although different presentations of PAXLOVID are now FDA-approved for the treatment of mild-to-moderate COVID-19 in certain adults, there are not currently sufficient supplies of the approved PAXLOVID available for distribution to this patient population in its entirety; therefore, this EUA continues to authorize the emergency use of PAXLOVID[6] for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death, at this time. Apart from this paragraph, all references to the term "PAXLOVID" in this Fact Sheet refer to product that is labelled in accordance with this EUA.

Veklury (remdesivir) is an FDA-approved alternative to PAXLOVID when used for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death. Veklury is administered via intravenous infusion for a total treatment duration of 3 days. Although Veklury is an FDA-approved alternative to PAXLOVID as described above, FDA does not consider Veklury to be an adequate alternative to PAXLOVID for this authorized use because it may not be feasible or practical for certain patients (e.g., it requires an intravenous infusion daily for 3 days).

Other therapeutics are currently authorized for the same use as PAXLOVID. For additional information on all products authorized for treatment or prevention of COVID-19, please see https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.

For information on clinical studies that are testing the use of PAXLOVID in COVID-19, please see www.clinicaltrials.gov.

[5] This section only describes the uses for which an FDA-approved drug is considered to be an alternative to PAXLOVID. For additional information, including the full indications for the FDA-approved drugs referenced within this section, please refer to the relevant Prescribing Information at: Drugs@FDA: FDA-Approved Drugs. As stated in the Letter of Authorization, the emergency use of PAXLOVID must be consistent with the terms and conditions of its authorization.
[6] See the Letter of Authorization and section 16 (HOW SUPPLIED/STORAGE AND HANDLING) in this Fact Sheet for the specific presentations of PAXLOVID authorized under this EUA.

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2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Information for Emergency Use of PAXLOVID

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. There are two different dose packs available:

- PAXLOVID (nirmatrelvir; ritonavir) co-packaged for oral use 300 mg;100 mg *[see Dosage and Administration (2.2)].*
- PAXLOVID (nirmatrelvir; ritonavir) co-packaged for oral use 150 mg;100 mg for patients with moderate renal impairment *[see Dosage and Administration (2.3)].*

Nirmatrelvir must be co-administered with ritonavir. Failure to correctly co-administer nirmatrelvir with ritonavir may result in plasma levels of nirmatrelvir that are insufficient to achieve the desired therapeutic effect.

Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID [see Dosage and Administration (2.2, 2.3)]. Completion of the full 5-day treatment course and continued isolation in accordance with public health recommendations are important to maximize viral clearance and minimize transmission of SARS-CoV-2.

The 5-day treatment course of PAXLOVID should be initiated as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset even if baseline COVID-19 symptoms are mild. Should a patient require hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID, the patient should complete the full 5-day treatment course per the healthcare provider's discretion.

If the patient misses a dose of PAXLOVID within 8 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 8 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose.

PAXLOVID (both nirmatrelvir and ritonavir tablets) can be taken with or without food *[see Clinical Pharmacology (12.3)]*. The tablets should be swallowed whole and not chewed, broken, or crushed.

2.2 Recommended Dosage

The recommended dosage for PAXLOVID is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) with all 3 tablets taken together orally twice daily for 5 days.

2.3 Dosage in Patients with Renal Impairment

No dosage adjustment is recommended in patients with mild renal impairment (eGFR ≥60 to <90 mL/min).

In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), the dosage of PAXLOVID is 150 mg nirmatrelvir (one 150 mg tablet) and 100 mg ritonavir (one 100 mg tablet) with both tablets taken together twice daily for 5 days *[see How Supplied/Storage and Handling (16)]*. *Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID.* Providers should counsel patients about renal dosing instructions *[see Patient Counseling Information (17)].*

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PAXLOVID is not recommended in patients with severe renal impairment (eGFR <30 mL/min) until more data are available; the appropriate dosage for patients with severe renal impairment has not been determined *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].*

2.4 Use in Patients with Hepatic Impairment

No dosage adjustment is needed in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic or safety data are available regarding the use of nirmatrelvir or ritonavir in subjects with severe (Child-Pugh Class C) hepatic impairment; therefore, PAXLOVID is not recommended for use in patients with severe hepatic impairment *[see Use in Specific Populations (8.7)]*.

3 DOSAGE FORMS AND STRENGTHS

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets.

- Nirmatrelvir is supplied as oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Each tablet contains 150 mg of nirmatrelvir.

- Ritonavir is supplied as white or white to off-white film-coated tablets uniquely identified by the color, shape, and debossing *[see How Supplied/Storage and Handling (16)]*. Each tablet contains 100 mg of ritonavir.

4 CONTRAINDICATIONS

PAXLOVID is contraindicated in patients with a history of clinically significant hypersensitivity reactions [e.g., toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome] to its active ingredients (nirmatrelvir or ritonavir) or any other components of the product.

PAXLOVID is contraindicated with drugs that are primarily metabolized by CYP3A and for which elevated concentrations are associated with serious and/or life-threatening reactions and drugs that are strong CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. There are certain other drugs for which concomitant use with PAXLOVID should be avoided and/or dose adjustment, interruption, or therapeutic monitoring is recommended. Drugs listed in this section are a guide and not considered a comprehensive list of all drugs that may be contraindicated with PAXLOVID. The healthcare provider should consult other appropriate resources such as the prescribing information for the interacting drug for comprehensive information on dosing or monitoring with concomitant use of a strong CYP3A inhibitor like PAXLOVID *[see Drug Interactions (7.3)]*:

- Drugs that are primarily metabolized by CYP3A for which elevated concentrations are associated with serious and/or life-threatening reactions *[see Drug Interactions (7.3)]*:

  - Alpha 1-adrenoreceptor antagonist: alfuzosin
  - Antianginal: ranolazine
  - Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
  - Anti-gout: colchicine (in patients with renal and/or hepatic impairment *[see Table 1, Drug Interactions (7.3)]*)
  - Antipsychotics: lurasidone, pimozide

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- Benign prostatic hyperplasia agents: silodosin
- Cardiovascular agents: eplerenone, ivabradine
- Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
- HMG-CoA reductase inhibitors: lovastatin, simvastatin (these drugs can be temporarily discontinued to allow PAXLOVID use *[see Table 1, Drug Interactions (7.3)]*)
- Immunosuppressants: voclosporin
- Microsomal triglyceride transfer protein inhibitor: lomitapide
- Migraine medications: eletriptan, ubrogepant
- Mineralocorticoid receptor antagonists: finerenone
- Opioid antagonists: naloxegol
- PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH)
- Sedative/hypnotics: triazolam, oral midazolam
- Serotonin receptor 1A agonist/serotonin receptor 2A antagonist: flibanserin
- Vasopressin receptor antagonists: tolvaptan

➢ Drugs that are strong CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. PAXLOVID cannot be started immediately after discontinuation of any of the following medications due to the delayed offset of the recently discontinued CYP3A inducer *[see Drug Interactions (7.3)]*:

- Anticancer drugs: apalutamide
- Anticonvulsant: carbamazepine, phenobarbital, primidone, phenytoin
- Antimycobacterials: rifampin, rifapentine
- Cystic fibrosis transmembrane conductance regulator potentiators: lumacaftor/ivacaftor
- Herbal products: St. John's Wort (*hypericum perforatum*)

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Adverse Reactions Due to Drug Interactions

Initiation of PAXLOVID, which contains ritonavir, a strong CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving PAXLOVID, may increase plasma concentrations of medications metabolized by CYP3A. Medications that induce CYP3A may decrease concentrations of PAXLOVID. These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medications.
- Loss of therapeutic effect of PAXLOVID and possible development of viral resistance.

Severe, life-threatening, and/or fatal adverse reactions due to drug interactions have been reported in patients treated with PAXLOVID. The most commonly reported concomitant medications resulting in serious adverse reactions were calcineurin inhibitors (e.g., tacrolimus, cyclosporine), followed by calcium channel blockers.

Prior to prescribing PAXLOVID, review all medications taken by the patient to assess potential drug-drug interactions and determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring (e.g., calcineurin inhibitors) *[see Contraindications (4) and Drug Interactions (7)]*. See Table 1 for clinically significant drug interactions, including contraindicated

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drugs. Drugs listed in Table 1 are a guide and not considered a comprehensive list of all possible drugs that may interact with PAXLOVID.

Consider the benefit of PAXLOVID treatment in reducing hospitalization and death, and whether the risk of potential drug-drug interactions for an individual patient can be appropriately managed *[see Drug Interactions (7) and Clinical Studies (14)]*.

5.2 Hypersensitivity Reactions

Anaphylaxis, serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson syndrome), and other hypersensitivity reactions have been reported with PAXLOVID *[see Adverse Reactions (6.2)]*. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue PAXLOVID and initiate appropriate medications and/or supportive care.

5.3 Hepatotoxicity

Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir. Therefore, caution should be exercised when administering PAXLOVID to patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis.

5.4 Risk of HIV-1 Resistance Development

Because nirmatrelvir is co-administered with ritonavir, there may be a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection *[see Contraindications (4), and Drug Interactions (7)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity reactions *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of PAXLOVID is based on two Phase 2/3 randomized, placebo-controlled trials in symptomatic adult subjects 18 years of age and older with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Subjects in both studies received PAXLOVID (nirmatrelvir/ritonavir 300 mg/100 mg) or placebo every 12 hours for 5 days for the treatment of mild-to-moderate COVID-19 within 5 days of symptom onset *[see Clinical Studies (14)]*:

- Trial C4671005 (EPIC-HR) enrolled subjects who were at high risk for progression to severe disease.
- Trial C4671002 (EPIC-SR) enrolled subjects who were at standard risk for progression to severe disease (previously unvaccinated subjects at standard risk or fully vaccinated subjects with at least 1 risk factor for progression to severe disease).

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Adverse reactions were those reported while subjects were on study medication and through 28 days after the last dose of study treatment.

In Trial C4671005 (EPIC-HR), 1,038 subjects received PAXLOVID and 1,053 subjects received placebo. The most common adverse reactions (≥1% incidence in the PAXLOVID group and occurring at a greater frequency than in the placebo group) were dysgeusia (5% and <1%, respectively) and diarrhea (3% and 2%, respectively).

Among vaccinated or unvaccinated subjects at standard risk or fully vaccinated subjects with at least 1 risk factor for progression to severe disease in Trial C4671002 (EPIC-SR), 540 subjects received PAXLOVID and 528 subjects received placebo. The adverse reactions observed were consistent with those observed in EPIC-HR.

6.2 Post-Authorization Experience

The following adverse reactions have been identified during post-authorization use of PAXLOVID.

Immune System Disorders: Anaphylaxis, hypersensitivity reactions *[see Warnings and Precautions (5.2)]*
Skin and Subcutaneous Tissue Disorders: Toxic epidermal necrolysis, Stevens-Johnson syndrome *[see Warnings and Precautions (5.2)]*
Nervous System Disorders: Headache
Vascular Disorders: Hypertension
Gastrointestinal Disorders: Abdominal pain, nausea, vomiting
General Disorders and Administration Site Conditions: Malaise

6.4 Required Reporting for Serious Adverse Events and Medication Errors

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all serious adverse events* and medication errors potentially related to PAXLOVID within 7 calendar days from the healthcare provider's awareness of the event, using FDA Form 3500 (for information on how to access this form, see below). The FDA requires that such reports, using FDA Form 3500, include the following:

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race).
- A statement " PAXLOVID use for COVID-19 under Emergency Use Authorization (EUA)" under the "**Describe Event, Problem, or Product Use/Medication Error**" heading.
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes).
- Patient's pre-existing medical conditions and use of concomitant products.
- Information about the product (e.g., dosage, route of administration, NDC #).

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Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:

- Complete and submit the report online: https://www.fda.gov/medwatch/report.htm
- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - Fax to 1-800-FDA-0178, or
- Call 1-800-FDA-1088 to request a reporting form

In addition, please provide a copy of all FDA MedWatch forms to:

Website	Fax number	Telephone number
www.pfizersafetyreporting.com	1-866-635-8337	1-800-438-1985

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of PAXLOVID.

*Serious adverse events are defined as:

- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- Other important medical event, which may require a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

6.5 Other Reporting Requirements

Healthcare facilities and providers will report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.

7 DRUG INTERACTIONS

7.1 Potential for PAXLOVID to Affect Other Drugs

PAXLOVID (nirmatrelvir co-packaged with ritonavir) is a strong inhibitor of CYP3A, and an inhibitor of CYP2D6, P-gp and OATP1B1. Co-administration of PAXLOVID with drugs that are primarily metabolized by CYP3A and CYP2D6 or are transported by P-gp or OATP1B1 may result in increased plasma concentrations of such drugs and increase the risk of adverse events. Co-administration of PAXLOVID with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated *[see Contraindications (4) and Drug Interactions (7.3) Table 1]*. Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring as shown in Table 1.

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7.2 Potential for Other Drugs to Affect PAXLOVID

Nirmatrelvir and ritonavir are CYP3A substrates; therefore, drugs that induce CYP3A may decrease nirmatrelvir and ritonavir plasma concentrations and reduce PAXLOVID therapeutic effect *[see Contraindications (4) and Drug Interactions (7.3) Table 1]*.

7.3 Established and Other Potentially Significant Drug Interactions

Table 1 provides a listing of clinically significant drug interactions, including contraindicated drugs *[see Contraindications (4) and Warnings and Precautions (5.1)]*. Drugs listed in Table 1 are a guide and not considered a comprehensive list of all possible drugs that may interact with PAXLOVID. The healthcare provider should consult other appropriate resources such as the prescribing information for the interacting drug for comprehensive information on dosing or monitoring with concomitant use of a strong CYP3A inhibitor such as ritonavir.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Alpha 1-adrenoreceptor antagonist	alfuzosin	↑ alfuzosin	Co-administration contraindicated due to potential hypotension *[see Contraindications (4)]*.
Alpha 1-adrenoreceptor antagonist	tamsulosin	↑ tamsulosin	Avoid concomitant use with PAXLOVID.
Antianginal	ranolazine	↑ ranolazine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions *[see Contraindications (4)]*.
Antiarrhythmics	amiodarone, dronedarone, flecainide, propafenone, quinidine	↑ antiarrhythmic	Co-administration contraindicated due to potential for cardiac arrhythmias *[see Contraindications (4)]*.
Antiarrhythmics	lidocaine (systemic), disopyramide	↑ antiarrhythmic	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics if available.
Anticancer drugs	apalutamide	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Anticancer drugs	abemaciclib, ceritinib, dasatinib, encorafenib, ibrutinib, ivosidenib, neratinib, nilotinib, venetoclax, vinblastine, vincristine	↑ anticancer drugs	Avoid co-administration of encorafenib or ivosidenib due to potential risk of serious adverse events such as QT interval prolongation. Avoid use of neratinib, venetoclax or ibrutinib. Co-administration of vincristine and vinblastine may lead to significant hematologic or gastrointestinal side effects. For further information, refer to individual product label for anticancer drug.
Anticoagulants	warfarin	↑↓ warfarin	Closely monitor international normalized ratio (INR) if co-administration with warfarin is necessary.
	rivaroxaban	↑ rivaroxaban	Increased bleeding risk with rivaroxaban. Avoid concomitant use.
	dabigatran[a]	↑ dabigatran	Increased bleeding risk with dabigatran. Depending on dabigatran indication and renal function, reduce dose of dabigatran or avoid concomitant use. Refer to the dabigatran product label for further information.
	apixaban	↑ apixaban	Combined P-gp and strong CYP3A inhibitors increase blood levels of apixaban and increase the risk of bleeding. Dosing recommendations for co-administration of apixaban with PAXLOVID depend on the apixaban dose. Refer to the apixaban product label for more information.
Anticonvulsants	carbamazepine[a], phenobarbital, primidone, phenytoin	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.
Anticonvulsants	clonazepam	↑ anticonvulsant	A dose decrease may be needed for clonazepam when co-administered with PAXLOVID and clinical monitoring is recommended.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Antidepressants	bupropion	↓ bupropion and active metabolite hydroxy-bupropion	Monitor for an adequate clinical response to bupropion.
	trazodone	↑ trazodone	Adverse reactions of nausea, dizziness, hypotension, and syncope have been observed following co-administration of trazodone and ritonavir. A lower dose of trazodone should be considered. Refer to trazadone product label for further information.
Antifungals	voriconazole	↓ voriconazole	Avoid concomitant use of voriconazole.
	ketoconazole, isavuconazonium sulfate, itraconazole[a]	↑ ketoconazole ↑ isavuconazonium sulfate ↑ itraconazole	Refer to ketoconazole, isavuconazonium sulfate, and itraconazole product labels for further information.
		↑ nirmatrelvir/ritonavir	A nirmatrelvir/ritonavir dose reduction is not needed.
Anti-gout	colchicine	↑ colchicine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment *[see Contraindications (4)]*.
Anti-HIV protease inhibitors	atazanavir, darunavir, tipranavir	↑ protease inhibitor	For further information, refer to the respective protease inhibitors' prescribing information. Patients on ritonavir- or cobicistat-containing HIV regimens should continue their treatment as indicated. Monitor for increased PAXLOVID or protease inhibitor adverse events.
Anti-HIV	efavirenz, maraviroc, nevirapine, zidovudine, bictegravir/ emtricitabine/ tenofovir	↑ efavirenz ↑ maraviroc ↑ nevirapine ↓ zidovudine ↑ bictegravir ↔ emtricitabine ↑ tenofovir	For further information, refer to the respective anti-HIV drugs prescribing information.
Anti-infective	clarithromycin, erythromycin	↑ clarithromycin ↑ erythromycin	Refer to the respective prescribing information for anti-infective dose adjustment.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Antimycobacterial	rifampin, rifapentine	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance. Alternate antimycobacterial drugs such as rifabutin should be considered *[see Contraindications (4)]*.
Antimycobacterial	bedaquiline rifabutin	↑ bedaquiline ↑ rifabutin	Refer to the bedaquiline product label for further information. Refer to rifabutin product label for further information on rifabutin dose reduction.
Antipsychotics	lurasidone, pimozide	↑ lurasidone ↑ pimozide	Co-administration contraindicated due to serious and/or life-threatening reactions such as cardiac arrhythmias *[see Contraindications (4)]*.
Antipsychotics	quetiapine clozapine	↑ quetiapine ↑ clozapine	If co-administration is necessary, reduce quetiapine dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations. If co-administration is necessary, consider reducing the clozapine dose and monitor for adverse reactions.
Benign prostatic hyperplasia agents	silodosin	↑ silodosin	Co-administration contraindicated due to potential for postural hypotension *[see Contraindications (4)]*.
Calcium channel blockers	amlodipine, diltiazem, felodipine, nicardipine, nifedipine, verapamil	↑ calcium channel blocker	Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with PAXLOVID. If co-administered, refer to individual product label for calcium channel blocker for further information.
Cardiac glycosides	digoxin	↑ digoxin	Caution should be exercised when co-administering PAXLOVID with digoxin, with appropriate monitoring of serum digoxin levels. Refer to the digoxin product label for further information.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Cardiovascular agents	eplerenone	↑ eplerenone	Co-administration with eplerenone is contraindicated due to potential for hyperkalemia *[see Contraindications (4)]*.
	ivabradine	↑ ivabradine	Co-administration with ivabradine is contraindicated due to potential for bradycardia or conduction disturbances *[see Contraindications (4)]*.
Cardiovascular agents	aliskiren, ticagrelor, vorapaxar	↑ aliskiren ↑ ticagrelor ↑ vorapaxar	Avoid concomitant use with PAXLOVID.
	clopidogrel	↓ clopidogrel active metabolite	
	cilostazol	↑ cilostazol	Dosage adjustment of cilostazol is recommended. Refer to the cilostazol product label for more information.
Corticosteroids primarily metabolized by CYP3A	betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, methylprednisolone, mometasone, triamcinolone	↑ corticosteroid	Co-administration with corticosteroids (all routes of administration) of which exposures are significantly increased by strong CYP3A inhibitors can increase the risk for Cushing's syndrome and adrenal suppression. However, the risk of Cushing's syndrome and adrenal suppression associated with short-term use of a strong CYP3A inhibitor is low. Alternative corticosteroids including beclomethasone, prednisone, and prednisolone should be considered.
Cystic fibrosis transmembrane conductance regulator potentiators	lumacaftor/ivacaftor	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)].*
Cystic fibrosis transmembrane conductance regulator potentiators	ivacaftor	↑ ivacaftor	Reduce dosage when co-administered with PAXLOVID. Refer to individual product labels for more information.
	elexacaftor/tezacaftor/ivacaftor	↑elexacaftor/tezacaftor/ivacaftor	
	tezacaftor/ivacaftor	↑ tezacaftor/ivacaftor	
Dipeptidyl peptidase 4 (DPP4) inhibitors	saxagliptin	↑ saxagliptin	Dosage adjustment of saxagliptin is recommended. Refer to the saxagliptin product label for more information.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Endothelin receptor antagonists	bosentan	↑ bosentan ↓ nirmatrelvir/ritonavir	Discontinue use of bosentan at least 36 hours prior to initiation of PAXLOVID. Refer to the bosentan product label for further information.
Ergot derivatives	dihydroergotamine, ergotamine, methylergonovine	↑ dihydroergotamine ↑ ergotamine ↑ methylergonovine	Co-administration contraindicated due to potential for acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system *[see Contraindications (4)]*.
Hepatitis C direct acting antivirals	elbasvir/grazoprevir glecaprevir/ pibrentasvir ombitasvir/paritaprevir /ritonavir and dasabuvir sofosbuvir/velpatasvir/ voxilaprevir	↑ antiviral	Increased grazoprevir concentrations can result in alanine transaminase (ALT) elevations. Avoid concomitant use of glecaprevir/pibrentasvir with PAXLOVID. Refer to the ombitasvir/paritaprevir/ritonavir and dasabuvir label for further information. Refer to the sofosbuvir/velpatasvir/voxilaprevir product label for further information. Patients on ritonavir-containing HCV regimens should continue their treatment as indicated. Monitor for increased PAXLOVID or HCV drug adverse events with concomitant use.
Herbal products	St. John's Wort (*hypericum perforatum*)	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
HMG-CoA reductase inhibitors	lovastatin, simvastatin	↑ lovastatin ↑ simvastatin	Co-administration contraindicated due to potential for myopathy including rhabdomyolysis *[see Contraindications (4)]*. If treatment with PAXLOVID is considered medically necessary, discontinue use of lovastatin and simvastatin at least 12 hours prior to initiation of PAXLOVID, during the 5 days of PAXLOVID treatment and for 5 days after completing PAXLOVID.
HMG-CoA reductase inhibitors	atorvastatin, rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Consider temporary discontinuation of atorvastatin and rosuvastatin during treatment with PAXLOVID. Atorvastatin and rosuvastatin do not need to be withheld prior to or after completing PAXLOVID.
Hormonal contraceptive	ethinyl estradiol	↓ ethinyl estradiol	An additional, non-hormonal method of contraception should be considered during the 5 days of PAXLOVID treatment and until one menstrual cycle after stopping PAXLOVID.
Immunosuppressants	voclosporin	↑ voclosporin	Co-administration contraindicated due to potential for acute and/or chronic nephrotoxicity *[see Contraindications (4)]*.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Immunosuppressants	calcineurin inhibitors: cyclosporine, tacrolimus	↑ cyclosporine ↑ tacrolimus	Avoid concomitant use of calcineurin inhibitors with PAXLOVID when close monitoring of immunosuppressant concentrations is not feasible. If co-administered, dose adjustment of the immunosuppressant and close and regular monitoring for immunosuppressant concentrations and adverse reactions are recommended during and after treatment with PAXLOVID. Obtain expert consultation to appropriately manage the complexity of this co-administration *[see Warnings and Precautions (5.1)]*.
	mTOR inhibitors: everolimus, sirolimus	↑ everolimus ↑ sirolimus	Avoid concomitant use of everolimus and sirolimus and PAXLOVID. Refer to the individual immunosuppressant product label and latest guidelines for further information.
Janus kinase (JAK) inhibitors	tofacitinib, upadacitinib	↑ tofacitinib ↑ upadacitinib	Dosage adjustment of tofacitinib is recommended. Refer to the tofacitinib product label for more information. Dosing recommendations for co-administration of upadacitinib with PAXLOVID depends on the upadacitinib indication. Refer to the upadacitinib product label for more information.
Long-acting beta-adrenoceptor agonist	salmeterol	↑ salmeterol	Avoid concomitant use with PAXLOVID. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Microsomal triglyceride transfer protein (MTTP) inhibitor	lomitapide	↑ lomitapide	Co-administration contraindicated due to potential for hepatotoxicity and gastrointestinal adverse reactions *[see Contraindications (4)]*.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Migraine medications	eletriptan	↑ eletriptan	Co-administration of eletriptan within at least 72 hours of PAXLOVID is contraindicated due to potential for serious adverse reactions including cardiovascular and cerebrovascular events *[see Contraindications (4)]*.
	ubrogepant	↑ ubrogepant	Co-administration of ubrogepant with PAXLOVID is contraindicated due to potential for serious adverse reactions *[see Contraindications (4)]*.
Migraine medications	rimegepant	↑ rimegepant	Avoid concomitant use with PAXLOVID.
Mineralocorticoid receptor antagonists	finerenone	↑ finerenone	Co-administration contraindicated due to potential for serious adverse reactions including hyperkalemia, hypotension, and hyponatremia *[see Contraindications (4)]*.
Muscarinic receptor antagonists	darifenacin	↑ darifenacin	The darifenacin daily dose should not exceed 7.5 mg when co-administered with PAXLOVID. Refer to the darifenacin product label for more information.
Narcotic analgesics	fentanyl, hydrocodone, oxycodone, meperidine	↑ fentanyl ↑ hydrocodone ↑ oxycodone ↑ meperidine	Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl, hydrocodone, oxycodone, or meperidine is concomitantly administered with PAXLOVID. If concomitant use with PAXLOVID is necessary, consider a dosage reduction of the narcotic analgesic and monitor patients closely at frequent intervals. Refer to the individual product label for more information.
	methadone	↓ methadone	Monitor methadone-maintained patients closely for evidence of withdrawal effects and adjust the methadone dose accordingly.
Neuropsychiatric agents	suvorexant	↑ suvorexant	Avoid concomitant use of suvorexant with PAXLOVID.
	aripiprazole, brexpiprazole, cariprazine, iloperidone, lumateperone, pimavanserin	↑ aripiprazole ↑ brexpiprazole ↑ cariprazine ↑ iloperidone ↑ lumateperone ↑ pimavanserin	Dosage adjustment of aripiprazole, brexpiprazole, cariprazine, iloperidone, lumateperone, and pimavanserin is recommended. Refer to individual product label for more information.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Opioid antagonists	naloxegol	↑ naloxegol	Co-administration contraindicated due to the potential for opioid withdrawal symptoms *[see Contraindications (4)]*.
Pulmonary hypertension agents (PDE5 inhibitors)	sildenafil (Revatio®)	↑ sildenafil	Co-administration of sildenafil with PAXLOVID is contraindicated for use in pulmonary hypertension due to the potential for sildenafil associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope *[see Contraindications (4)]*.
Pulmonary hypertension agents (PDE5 inhibitors)	tadalafil (Adcirca®)	↑ tadalafil	Avoid concomitant use of tadalafil with PAXLOVID for pulmonary hypertension.
Pulmonary hypertension agents (sGC stimulators)	riociguat	↑ riociguat	Dosage adjustment is recommended for riociguat when used for pulmonary hypertension. Refer to the riociguat product label for more information.
Erectile dysfunction agents (PDE5 inhibitors)	avanafil	↑ avanafil	Do not use PAXLOVID with avanafil because a safe and effective avanafil dosage regimen has not been established.
	sildenafil, tadalafil, vardenafil	↑ sildenafil ↑ tadalafil ↑ vardenafil	Dosage adjustment is recommended for use of sildenafil, tadalafil or vardenafil with PAXLOVID when used for erectile dysfunction. Refer to individual product label for more information.
Sedative/hypnotics	triazolam, oral midazolam[a]	↑ triazolam ↑ midazolam	Co-administration contraindicated due to potential for extreme sedation and respiratory depression *[see Contraindications (4)]*.
Sedative/hypnotics	buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem	↑ sedative/hypnotic	A dose decrease may be needed for these drugs when co-administered with PAXLOVID and monitoring for adverse events.
	midazolam (administered parenterally)	↑ midazolam	Co-administration of midazolam (parenteral) should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered,

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
			especially if more than a single dose of midazolam is administered. Refer to the midazolam product label for further information.
Serotonin receptor 1A agonist/ serotonin receptor 2A antagonist	flibanserin	↑ flibanserin	Co-administration contraindicated due to potential for hypotension, syncope, and CNS depression *[see Contraindications (4)]*.
Vasopressin receptor antagonists	tolvaptan	↑ tolvaptan	Co-administration contraindicated due to potential for dehydration, hypovolemia and hyperkalemia *[see Contraindications (4)]*.

a. See Pharmacokinetics, Drug Interaction Studies Conducted with Nirmatrelvir and Ritonavir (12.3).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data on the use of nirmatrelvir during pregnancy are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Published observational studies on ritonavir use in pregnant women have not identified an increase in the risk of major birth defects. Published studies with ritonavir are insufficient to identify a drug-associated risk of miscarriage *(see Data)*. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy *(see Clinical Considerations)*.

In an embryo-fetal development study with nirmatrelvir, reduced fetal body weights following oral administration of nirmatrelvir to pregnant rabbits were observed at systemic exposures (AUC) approximately 11 times higher than clinical exposure at the authorized human dose of PAXLOVID. No other adverse developmental outcomes were observed in animal reproduction studies with nirmatrelvir at systemic exposures (AUC) greater than or equal to 3 times higher than clinical exposure at the authorized human dose of PAXLOVID *(see Data)*.

In embryo-fetal developmental studies with ritonavir, no evidence of adverse developmental outcomes was observed following oral administration of ritonavir to pregnant rats and rabbits at systemic exposures (AUC) 5 (rat) or 8 (rabbits) times higher than clinical exposure at the authorized human dose of PAXLOVID *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the authorized population is unknown. All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

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Clinical Considerations

Disease-associated Maternal and/or Embryo-fetal Risk
COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

Data

Human Data

Ritonavir
Based on prospective reports to the antiretroviral pregnancy registry of live births following exposure to ritonavir-containing regimens (including over 3,500 live births exposed in the first-trimester and over 3,500 live births exposed in the second and third trimesters), there was no difference in the rate of overall birth defects for ritonavir compared with the background birth defect rate of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The prevalence of birth defects in live births was 2.4% [95% confidence interval (CI): 1.9%-2.9%] following first-trimester exposure to ritonavir-containing regimens and 2.9% (95% CI: 2.4%-3.5%) following second and third trimester exposure to ritonavir-containing regimens. While placental transfer of ritonavir and fetal ritonavir concentrations are generally low, detectable levels have been observed in cord blood samples and neonate hair.

Animal Data

Nirmatrelvir
Embryo-fetal developmental (EFD) toxicity studies were conducted in pregnant rats and rabbits administered oral nirmatrelvir doses of up to 1,000 mg/kg/day during organogenesis [on Gestation Days (GD) 6 through 17 in rats and GD 7 through 19 in rabbits]. No biologically significant developmental effects were observed in the rat EFD study. At the highest dose of 1,000 mg/kg/day, the systemic nirmatrelvir exposure (AUC_{24}) in rats was approximately 9 times higher than clinical exposures at the authorized human dose of PAXLOVID. In the rabbit EFD study, lower fetal body weights (9% decrease) were observed at 1,000 mg/kg/day in the absence of significant maternal toxicity findings. At 1,000 mg/kg/day, the systemic exposure (AUC_{24}) in rabbits was approximately 11 times higher than clinical exposures at the authorized human dose of PAXLOVID. No other significant developmental toxicities (malformations and embryo-fetal lethality) were observed up to the highest dose tested, 1,000 mg/kg/day. No developmental effects were observed in rabbits at 300 mg/kg/day resulting in systemic exposure (AUC_{24}) approximately 3 times higher than clinical exposures at the authorized human dose of PAXLOVID. A pre- and postnatal developmental (PPND) study in pregnant rats administered oral nirmatrelvir doses of up to 1,000 mg/kg/day from GD 6 through Lactation Day (LD) 20 showed no adverse findings. Although no difference in body weight was noted at birth when comparing offspring born to nirmatrelvir treated versus control animals, a decrease in the body weight of offspring was observed on Postnatal Day (PND) 17 (8% decrease) and PND 21 (up to 7% decrease) in the absence of maternal toxicity. No significant differences in offspring body weight were observed from PND 28 to PND 56. The maternal systemic exposure (AUC_{24}) at 1,000 mg/kg/day was approximately 9 times higher than clinical exposures at the authorized human dose of PAXLOVID. No body weight changes in the offspring were noted at 300 mg/kg/day, where maternal systemic exposure (AUC_{24}) was approximately 6 times higher than clinical exposures at the authorized human dose of PAXLOVID.

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Ritonavir
Ritonavir was administered orally to pregnant rats (at 0, 15, 35, and 75 mg/kg/day) and rabbits (at 0, 25, 50, and 110 mg/kg/day) during organogenesis (on GD 6 through 17 in rats and GD 6 through 19 in rabbits). No evidence of teratogenicity due to ritonavir was observed in rats and rabbits at systemic exposures (AUC) 5 (rats) or 8 (rabbits) times higher than exposure at the authorized human dose of PAXLOVID. Increased incidences of early resorptions, ossification delays, and developmental variations, as well as decreased fetal body weights were observed in rats in the presence of maternal toxicity, at systemic exposures (AUC) approximately 10 times higher than exposure at the authorized human dose of PAXLOVID. In rabbits, resorptions, decreased litter size, and decreased fetal weights were observed at maternally toxic doses, at systemic exposures greater than 8 times higher than exposure at the authorized human dose of PAXLOVID. In a PPND study in rats, administration of 0, 15, 35, and 60 mg/kg/day ritonavir from GD 6 through PND 20 resulted in no developmental toxicity, at ritonavir systemic exposures greater than 10 times the exposure at the authorized human dose of PAXLOVID.

8.2 Lactation

Risk Summary

There are no available data on the presence of nirmatrelvir in human or animal milk, the effects on the breastfed infant, or the effects on milk production. A transient decrease in body weight was observed in the nursing offspring of rats administered nirmatrelvir *(see Data)*. Limited published data reports that ritonavir is present in human milk. There is no information on the effects of ritonavir on the breastfed infant or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PAXLOVID and any potential adverse effects on the breastfed infant from PAXLOVID or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

Data
In the PPND study, transiently lower body weight (up to 8%) was observed in the offspring of pregnant rats administered nirmatrelvir at maternal systemic exposure (AUC_{24}) approximately 9 times higher than clinical exposures at the authorized human dose of PAXLOVID. No body weight changes in the offspring were noted at maternal systemic exposure (AUC_{24}) approximately 6 times higher than clinical exposures at the authorized human dose of PAXLOVID.

8.3 Females and Males of Reproductive Potential

Contraception

Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Advise patients using combined hormonal contraceptives to use an effective alternative contraceptive method or an additional barrier method of contraception *[see Drug Interactions (7.3)]*.

8.4 Pediatric Use

PAXLOVID is not authorized for use in pediatric patients younger than 12 years of age or weighing less than 40 kg. The safety and effectiveness of PAXLOVID have not been established in pediatric patients. The authorized adult dosing regimen is expected to result in comparable serum exposures of nirmatrelvir and ritonavir in patients 12 years of age and older and weighing at least 40 kg as

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observed in adults, and adults with similar body weight were included in the trial EPIC-HR *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

8.5 Geriatric Use

Clinical studies of PAXLOVID include subjects 65 years of age and older and their data contributes to the overall assessment of safety and efficacy *[see Adverse Reactions (6.1) and Clinical Studies (14.1)]*. Of the total number of subjects in the integrated dataset consisting of EPIC-HR and EPIC-SR who were randomized to and received PAXLOVID (N=1,578), 165 (10%) were 65 years of age and older and 39 (2%) were 75 years of age and older. No overall differences in safety were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in safety between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

Renal impairment increases nirmatrelvir exposure, which may increase the risk of PAXLOVID adverse reactions. No dosage adjustment is recommended in patients with mild renal impairment (eGFR ≥60 to <90 mL/min). Reduce the PAXLOVID dosage in patients with moderate renal impairment (eGFR ≥30 to <60 mL/min). PAXLOVID is not recommended for use in patients with severe renal impairment (eGFR <30 mL/min) or patients with end stage renal disease (eGFR <15 mL/min) receiving dialysis until more data are available. The appropriate dosage for patients with severe renal impairment has not been determined *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*. *Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID.* Providers should counsel patients about renal dosing instructions *[see Patient Counseling Information (17)].*

8.7 Hepatic Impairment

No dosage adjustment of PAXLOVID is recommended for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic or safety data are available regarding the use of nirmatrelvir or ritonavir in subjects with severe (Child-Pugh Class C) hepatic impairment, therefore, PAXLOVID is not recommended for use in patients with severe (Child-Pugh Class C) hepatic impairment *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Treatment of overdose with PAXLOVID should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with PAXLOVID.

11 DESCRIPTION

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. Nirmatrelvir is a SARS-CoV-2 main protease (M^{pro}) inhibitor, and ritonavir is an HIV-1 protease inhibitor and CYP3A inhibitor.

Nirmatrelvir

The chemical name of active ingredient of nirmatrelvir is (1*R*,2*S*,5*S*)-*N*-((1*S*)-1-Cyano-2-((3*S*)-2-oxopyrrolidin-3-yl)ethyl)-3-((2*S*)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-3-

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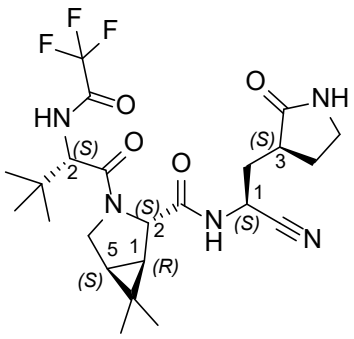
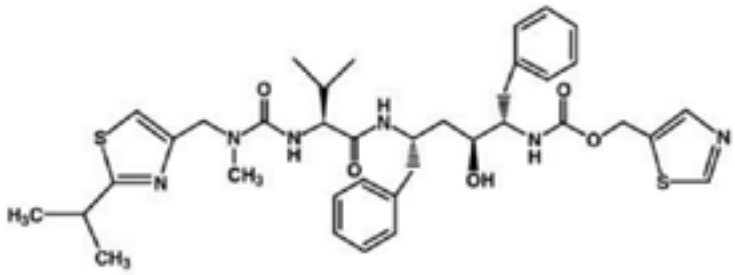
azabicyclo[3.1.0]hexane-2-carboxamide]. It has a molecular formula of $C_{23}H_{32}F_3N_5O_4$ and a molecular weight of 499.54. Nirmatrelvir has the following structural formula:



Nirmatrelvir is available as immediate-release, film-coated tablets. Each tablet contains 150 mg nirmatrelvir with the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, and sodium stearyl fumarate. The following are the ingredients in the film coating: hydroxy propyl methylcellulose, iron oxide red, polyethylene glycol, and titanium dioxide.

Ritonavir

Ritonavir is chemically designated as 10-Hydroxy-2-methyl-5-(1-methylethyl)-1- [2-(1 methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12- tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]. Its molecular formula is $C_{37}H_{48}N_6O_5S_2$, and its molecular weight is 720.95. Ritonavir has the following structural formula:



Ritonavir is available as film-coated tablets. Each tablet contains 100 mg ritonavir with the following inactive ingredients: anhydrous dibasic calcium phosphate, colloidal silicon dioxide, copovidone, sodium stearyl fumarate, and sorbitan monolaurate. The film coating may include the following ingredients: colloidal anhydrous silica, colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, polyethylene glycol, polysorbate 80, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nirmatrelvir is a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antiviral drug *[see Microbiology (12.4)].*

Ritonavir is an HIV-1 protease inhibitor but is not active against SARS-CoV-2 M^{pro}. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir.

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12.2 Pharmacodynamics

Cardiac Electrophysiology

At 3 times the steady state peak plasma concentration (C_{max}) at the recommended dose, nirmatrelvir does not prolong the QTc interval to any clinically relevant extent.

12.3 Pharmacokinetics

The pharmacokinetics of nirmatrelvir/ritonavir were similar in healthy subjects and in subjects with mild-to-moderate COVID-19.

Nirmatrelvir AUC increased in a less than dose proportional manner over a single dose range from 250 mg to 750 mg (0.83 to 2.5 times the authorized recommended dose) and multiple dose range from 75 mg to 500 mg (0.25 to 1.67 times the authorized recommended dose), when administered in combination with 100 mg ritonavir. Nirmatrelvir steady state was achieved on Day 2 following administration of the authorized recommended dosage and the mean accumulation ratio was approximately 2-fold.

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The pharmacokinetic properties of nirmatrelvir/ritonavir are displayed in Table 2.

Table 2: Pharmacokinetic Properties of Nirmatrelvir and Ritonavir in Healthy Subjects

	Nirmatrelvir (When Given With Ritonavir)	Ritonavir
Absorption		
T_{max} (hr), median	3.00[a]	3.98[a]
Food effect	Test/reference (fed/fasted) ratios of adjusted geometric means (90% CI) AUC_{inf} and C_{max} for nirmatrelvir were 119.67 (108.75, 131.68) and 161.01 (139.05, 186.44), respectively.[b]	
Distribution		
% bound to human plasma proteins	69%	98-99%
Blood-to-plasma ratio	0.60	0.14[d]
V_z/F (L), mean	104.7[c]	112.4[c]
Elimination		
Major route of elimination	Renal elimination[d]	Hepatic metabolism
Half-life ($T_{1/2}$) (hr), mean	6.05[a]	6.15[a]
Oral clearance (CL/F) (L/hr), mean	8.99[c]	13.92[c]
Metabolism		
Metabolic pathways	Nirmatrelvir is a CYP3A substrate but when dosed with ritonavir, metabolic clearance is minimal.	Major CYP3A, Minor CYP2D6
Excretion		
% drug-related material in feces	35.3%[e]	86.4%[f]
% of dose excreted as total (unchanged drug) in feces	27.5%[e]	33.8%[f]
% drug-related material in urine	49.6%[e]	11.3%[f]
% of dose excreted as total (unchanged drug) in urine	55.0%[e]	3.5%[f]

Abbreviations: CL/F=apparent clearance; hr=hour; L/hr=liters per hour; $T_{½}$=terminal elimination half-life; T_{max}=the time to reach C_{max}; V_z/F=apparent volume of distribution.

a. Represents data after a single dose of 300 mg nirmatrelvir (2 x 150 mg tablet formulation) administered together with 100 mg ritonavir tablet in healthy subjects.
b. Following a single oral dose of nirmatrelvir 300 mg boosted ritonavir 100 mg at -12 hours, 0 hours and 12 hours, administered under fed (high fat and high calorie meal) or fasted conditions.
c. 300 mg nirmatrelvir (oral suspension formulation) co-administered with 100 mg ritonavir (tablet formulation) twice daily for 3 days.
d. Red blood cell to plasma ratio.
e. Determined by ^{19}F-NMR analysis following 300 mg nirmatrelvir oral suspension administered at 0 hr enhanced with 100 mg ritonavir at -12 hours, 0 hours, 12 hours, and 24 hours.
f. Determined by ^{14}C analysis following 600 mg ^{14}C-ritonavir oral solution (6 times the authorized ritonavir dose).

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The predicted Day 5 nirmatrelvir exposure parameters in adult subjects with mild-to-moderate COVID-19 who were treated with PAXLOVID in EPIC-HR are presented in Table 3.

Table 3: Predicted Day 5 Nirmatrelvir Exposure Parameters Following Administration of Nirmatrelvir/Ritonavir 300 mg/100 mg Twice Daily in Subjects with Mild-to-Moderate COVID-19

Pharmacokinetic Parameter (units)[a]	Nirmatrelvir[b]
C_{max} (µg/mL)	3.43 (2.59, 4.52)
AUC_{tau} (µg*hr/mL)[c]	30.4 (22.9, 39.8)
C_{min} (µg/mL)	1.57 (1.16, 2.10)

Abbreviations: C_{max}=predicted maximal concentration; C_{min}=predicted minimal concentration (C_{trough}).

a. Data presented as geometric mean (10^{th} and 90^{th} percentile).
b. Based on 1,016 subjects with their post hoc PK parameters.
c. AUC_{tau}=predicted area under the plasma concentration-time profile from time 0 to 12 hours for twice-daily dosing.

Effect of Food

No clinically significant differences in the pharmacokinetics of nirmatrelvir were observed following administration of a high fat meal (800-1000 calories; 50% fat) to healthy subjects.

Specific Populations

There were no clinically significant differences in the pharmacokinetics of nirmatrelvir based on age (18 to 86 years), sex, or race/ethnicity.

Pediatric Patients

The pharmacokinetics of nirmatrelvir/ritonavir in patients less than 18 years of age have not been established.

Patients with Renal Impairment

The pharmacokinetics of nirmatrelvir in patients with renal impairment following administration of a single oral dose of nirmatrelvir 100 mg (0.33 times the authorized recommended dose) co-administered with ritonavir 100 mg are presented in Table 4. Compared to healthy controls with no renal impairment, the C_{max} and AUC of nirmatrelvir in patients with mild renal impairment was 30% and 24% higher, in patients with moderate renal impairment was 38% and 87% higher, and in patients with severe renal impairment was 48% and 204% higher, respectively.

Table 4: Impact of Renal Impairment on Nirmatrelvir/Ritonavir Pharmacokinetics

	Normal Renal Function (n=8)	Mild Renal Impairment (n=8)	Moderate Renal Impairment (n=8)	Severe Renal Impairment (n=8)
C_{max} (µg/mL)	1.60 (31)	2.08 (29)	2.21 (17)	2.37 (38)
AUC_{inf} (µg*hr/mL)	14.46 (20)	17.91 (30)	27.11 (27)	44.04 (33)
T_{max} (hr)	2.0 (1.0 - 4.0)	2.0 (1.0 – 3.0)	2.50 (1.0 – 6.0)	3.0 (1.0 - 6.1)
$T_{1/2}$ (hr)	7.73 ± 1.82	6.60 ± 1.53	9.95 ± 3.42	13.37 ± 3.32

Abbreviations: AUC_{inf}=area under the plasma concentration-time profile from time zero extrapolated to infinite time; C_{max}=the observed maximum concentration; CV=coefficient of variation; SD=standard deviation; $T_{½}$=terminal elimination half-life; T_{max}=the time to reach C_{max}.
Values are presented as geometric mean (geometric % CV) except median (range) for T_{max} and arithmetic mean ± SD for $T_{1/2}$.

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Patients with Hepatic Impairment
The pharmacokinetics of nirmatrelvir were similar in patients with moderate (Child-Pugh Class B) hepatic impairment compared to healthy subjects following administration of a single oral dose of nirmatrelvir 100 mg (0.33 times the authorized recommended dose) co-administered with ritonavir 100 mg. The impact of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of nirmatrelvir or ritonavir has not been studied.

Clinical Drug Interaction Studies

Table 5 describes the effect of other drugs on the C_{max} and AUC of nirmatrelvir.

Table 5: The Effect of Other Drugs on the Pharmacokinetic Parameters of Nirmatrelvir

Co-administered Drug	Dose (Schedule)		N	Percent Ratio (in combination with co-administered drug/alone) of Nirmatrelvir Pharmacokinetic Parameters (90% CI); No Effect=100	
	Co-administered Drug	Nirmatrelvir/ Ritonavir		C_{max}	AUC[a]
Carbamazepine[b]	300 mg twice daily (16 doses)	300 mg/100 mg once daily (2 doses)	10	56.82 (47.04, 68.62)	44.50 (33.77, 58.65)
Itraconazole	200 mg once daily (8 doses)	300 mg/100 mg twice daily (5 doses)	11	118.57 (112.50, 124.97)	138.82 (129.25, 149.11)

Abbreviations: AUC=area under the plasma concentration-time curve; AUC_{inf}=area under the plasma concentration-time profile from time zero extrapolated to infinite time; AUC_{tau}=area under the plasma concentration-time profile from time zero to time tau (τ), the dosing interval. CI=confidence interval; C_{max}=observed maximum plasma concentrations.
a. For carbamazepine, AUC=AUC_{inf}; for itraconazole, AUC=AUC_{tau}.
b. Carbamazepine titrated up to 300 mg twice daily on Day 8 through Day 15 (e.g., 100 mg twice daily on Day 1 through Day 3 and 200 mg twice daily on Day 4 through Day 7).

Table 6 describes the effect of nirmatrelvir/ritonavir on the C_{max} and AUC of other drugs.

Table 6: Effect of Nirmatrelvir/Ritonavir on Pharmacokinetics of Other Drugs

Co-administered Drug	Dose (Schedule)		N	Percent Ratio of Test/Reference of Geometric Means (90% CI); No Effect=100	
	Co-administered Drug	Nirmatrelvir/ Ritonavir		C_{max}	AUC[a]
Midazolam[b]	2 mg (1 dose)	300 mg/100 mg twice daily (9 doses)	10	368.33 (318.91, 425.41)	1430.02 (1204.54, 1697.71)
Dabigatran[b]	75 mg (1 dose)	300 mg/100 mg twice daily (4 doses)[b]	24	233.06 (172.14, 315.54)	194.47 (155.29, 243.55)

Abbreviations: AUC=area under the plasma concentration-time curve; CI=confidence interval; C_{max}=observed maximum plasma concentrations; P-gp=p-glycoprotein.
a. AUC=AUC_{inf} for both midazolam and dabigatran.
b. For midazolam, Test=nirmatrelvir/ritonavir plus midazolam, Reference=Midazolam. Midazolam is an index substrate for CYP3A. For dabigatran, Test=nirmatrelvir/ritonavir plus dabigatran, Reference=Dabigatran. Dabigatran is an index substrate for P-gp.

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In Vitro Studies
Cytochrome P450 (CYP) Enzymes:

- Nirmatrelvir is a reversible and time-dependent inhibitor of CYP3A, but not an inhibitor CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Nirmatrelvir is an inducer of CYP2B6, 2C8, 2C9, and 3A4, but there is minimal risk for pharmacokinetic interactions arising from induction of these CYP enzymes at the proposed therapeutic dose.
- Ritonavir is a substrate of CYP2D6 and CYP3A. Ritonavir is an inducer of CYP1A2, CYP2C9, CYP2C19, CYP2B6, and CYP3A.

Transporter Systems: Nirmatrelvir is an inhibitor of P-gp and OATP1B1. Nirmatrelvir is a substrate for P-gp, but not BCRP, MATE1, MATE2K, NTCP, OAT1, OAT2, OAT3, OCT1, OCT2, PEPT1, OATP1B1, OATP1B3, OATP2B1, or OATP4C1.

12.4 Microbiology

Mechanism of Action

Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (M^{pro}), also referred to as 3C-like protease ($3CL^{pro}$) or nonstructural protein 5 (nsp5) protease. Inhibition of SARS-CoV-2 M^{pro} renders it incapable of processing the viral polyproteins pp1a and pp1ab, preventing viral replication. Nirmatrelvir inhibited the activity of recombinant SARS-CoV-2 M^{pro} in a biochemical assay with a K_i value of 3.1 nM and an IC_{50} value of 19.2 nM. Nirmatrelvir was found to bind directly to the SARS-CoV-2 M^{pro} active site by X-ray crystallography.

Antiviral Activity

Cell Culture Antiviral Activity
Nirmatrelvir exhibited antiviral activity against SARS-CoV-2 (USA-WA1/2020 isolate) infection of differentiated normal human bronchial epithelial (dNHBE) cells with EC_{50} and EC_{90} values of 62 nM (31 ng/mL) and 181 nM (90 ng/mL), respectively, after 3 days of drug exposure.

The antiviral activity of nirmatrelvir against the Omicron sub-variants BA.2, BA.2.12.1, BA.4, BA.4.6, BA.5, BF.7, BQ.1, BQ.1.11, and XBB.1.5 was assessed in Vero E6-TMPRSS2 cells in the presence of a P-gp inhibitor. Nirmatrelvir had a median EC_{50} value of 83 nM (range: 39-146 nM) against the Omicron sub-variants, reflecting EC_{50} value fold-changes ≤1.5 relative to the USA-WA1/2020 isolate.

In addition, the antiviral activity of nirmatrelvir against the SARS-CoV-2 Alpha, Beta, Gamma, Delta, Lambda, Mu, and Omicron BA.1 variants was assessed in Vero E6 P-gp knockout cells. Nirmatrelvir had a median EC_{50} value of 25 nM (range: 16-141 nM). The Beta variant was the least susceptible variant tested, with an EC_{50} value fold-change of 3.7 relative to USA-WA1/2020. The other variants had EC_{50} value fold-changes ≤1.1 relative to USA-WA1/2020.

Clinical Antiviral Activity
In clinical trial EPIC-HR, which enrolled subjects who were primarily infected with the SARS-CoV-2 Delta variant, PAXLOVID treatment was associated with a 0.83 log_{10} copies/mL greater median decline in viral RNA shedding levels in nasopharyngeal samples through Day 5 (mITT1 analysis set, all treated subjects with onset of symptoms ≤5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment); similar results were observed in the mITT2 analysis set (all treated subjects with onset of symptoms ≤5 days). In the EPIC-SR trial, which included subjects who were infected with SARS-CoV-2 Delta (79%) or Omicron (19%) variants,

PAXLOVID treatment was associated with a 1.05 log_{10} copies/mL greater median decline in viral RNA shedding levels in nasopharyngeal samples through Day 5, with similar declines observed in subjects infected with Delta or Omicron variants. The degree of reduction in viral RNA levels relative to placebo following 5 days of PAXLOVID treatment was similar between unvaccinated high-risk subjects in EPIC-HR and vaccinated high-risk subjects in EPIC-SR.

Antiviral Resistance

In Cell Culture and Biochemical Assays
SARS-CoV-2 M^{pro} residues potentially associated with nirmatrelvir resistance have been identified using a variety of methods, including SARS-CoV-2 resistance selection, testing of recombinant SARS-CoV-2 viruses with M^{pro} substitutions, and biochemical assays with recombinant SARS-CoV-2 M^{pro} containing amino acid substitutions. Table 7 indicates M^{pro} substitutions and combinations of M^{pro} substitutions that have been observed in nirmatrelvir-selected SARS-CoV-2 in cell culture. Individual M^{pro} substitutions are listed regardless of whether they occurred alone or in combination with other M^{pro} substitutions. Note that the M^{pro} S301P and T304I substitutions overlap the P6 and P3 positions of the nsp5/nsp6 cleavage site located at the C-terminus of M^{pro}. Substitutions at other M^{pro} cleavage sites have not been associated with nirmatrelvir resistance in cell culture. The clinical significance of these substitutions is unknown.

Table 7: SARS-CoV-2 M^{pro} Amino Acid Substitutions Selected by Nirmatrelvir in Cell Culture

Single Substitutions (EC_{50} value fold-change)	T21I (1.1-4.6), L50F (1.5-4.2), P108S (ND), T135I (ND), F140L (4.1), S144A (2.2-5.3), C160F (ND), E166A (3.3), E166V (25-288), L167F (ND), T169I (ND), H172Y (ND), A173V (0.9-1.7), V186A (ND), R188G (ND), A191V (ND), A193P (ND), P252L (5.9), S301P (ND), and T304I (1.4-5.5).
≥2 Substitutions (EC_{50} value fold-change)	T21I+S144A (9.4), T21I+E166V (83), T21I+A173V (3.1), T21I+T304I (3.0-7.9), L50F+E166V (34-175), L50F+T304I (5.9), T135I+T304I (3.8), F140L+A173V (10.1), H172Y+P252L (ND), A173V+T304I (20.2), T21I+L50F+A193P+S301P (28.8), T21I+S144A+T304I (27.8), T21I+C160F+A173V+V186A+T304I (28.5), T21I+A173V+T304I (15), and L50F+F140L+L167F+T304I (54.7).

Abbreviation: ND=no data.

In a biochemical assay using recombinant SARS-CoV-2 M^{pro} containing amino acid substitutions, the following SARS-CoV-2 M^{pro} substitutions led to ≥3-fold reduced nirmatrelvir activity (fold-change based on K_i values): Y54A (25), F140A (21), F140L (7.6), F140S (260), G143S (3.6), S144A (46), S144E (480), S144T (170), H164N (6.7), E166A (35), E166G (6.2), E166V (7,700), H172Y (250), A173S (4.1), A173V (16), R188G (38), Q192L (29), Q192P (7.8), and V297A (3.0). In addition, the following combinations of M^{pro} substitutions led to ≥3-fold reduced nirmatrelvir activity: T21I+S144A (20), T21I+E166V (11,000), T21I+A173V (15), L50F+E166V (4,500), T135I+T304I (5.1), F140L+A173V (95), H172Y+P252L (180), A173V+T304I (28), T21I+S144A+T304I (51), T21I+A173V+T304I (55), L50F+E166A+L167F (210), T21I+L50F+A193P+S301P (7.3), L50F+F140L+L167F+T304I (190), and T21I+C160F+A173V+V186A+T304I (28). The following substitutions and substitution combinations emerged in cell culture but conferred <3-fold reduced nirmatrelvir activity in biochemical assays: T21I (1.6), L50F (0.2), P108S (2.9), T135I (2.2), C160F (0.6), L167F (0.9), T169I (1.4), V186A (0.8), A191V (0.8), A193P (0.9), P252L (0.9), S301P (0.2), T304I (1.0), T21I+T304I (1.8), and L50F+T304I (1.3). The clinical significance of these substitutions is unknown.

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In Clinical Trials

Treatment-emergent substitutions were evaluated among subjects in clinical trials EPIC-HR/SR with sequence data available at both baseline and a post-baseline visit (n=907 PAXLOVID-treated subjects, n=946 placebo-treated subjects). SARS-CoV-2 M^{pro} amino acid changes were classified as PAXLOVID treatment-emergent substitutions if they occurred at the same amino acid position in 3 or more PAXLOVID-treated subjects and were ≥2.5-fold more common in PAXLOVID-treated subjects than placebo-treated subjects. The following PAXLOVID treatment-emergent M^{pro} substitutions were observed: T98I/R/del(n=4), E166V (n=3), and W207L/R/del (n=4). Within the M^{pro} cleavage sites, the following PAXLOVID treatment-emergent substitutions were observed: A5328S/V(n=7) and S6799A/P/Y (n=4). These cleavage site substitutions were not associated with the co-occurrence of any specific M^{pro} substitutions.

None of the treatment-emergent substitutions listed above in M^{pro} or M^{pro} cleavage sites occurred in PAXLOVID-treated subjects who experienced hospitalization. Thus, the clinical significance of these substitutions is unknown.

Viral RNA Rebound (With and Without COVID-19 Symptoms) and Treatment-Emergent Substitutions

EPIC-HR and EPIC-SR were not designed to evaluate COVID-19 rebound; exploratory analyses were conducted to assess the relationship between PAXLOVID use and rebound in viral RNA shedding levels or self-reported COVID-19 symptoms.

Post-treatment increases in SARS-CoV-2 RNA shedding levels in nasopharyngeal samples were observed on Day 10 and/or Day 14 in a subset of PAXLOVID and placebo recipients in EPIC-HR and EPIC-SR, irrespective of COVID-19 symptoms. The frequency of detection of post-treatment viral RNA rebound varied according to analysis parameters, but was generally similar among PAXLOVID and placebo recipients. A similar or smaller percentage of placebo recipients compared to PAXLOVID recipients had nasopharyngeal viral RNA results <lower limit of quantitation (LLOQ) at all study timepoints in both the treatment and post-treatment periods.

In EPIC-HR, of 59 PAXLOVID-treated subjects identified with post-treatment viral RNA rebound and with available viral sequence data, treatment-emergent substitutions in M^{pro} potentially reducing nirmatrelvir activity were detected in 2 (3%) subjects, including E166V in 1 subject and T304I in 1 subject. Both subjects had viral RNA shedding levels <LLOQ by Day 14.

Post-treatment viral RNA rebound was not associated with the primary clinical outcome of COVID-19-related hospitalization or death from any cause through Day 28 following the single 5-day course of PAXLOVID treatment. The clinical relevance of post-treatment increases in viral RNA following PAXLOVID or placebo treatment is unknown.

The frequency of symptom rebound through Day 28, irrespective of viral RNA results, was similar among PAXLOVID and placebo recipients. The frequency of combined viral RNA rebound plus symptom rebound could not be fully assessed as most episodes of symptom rebound occurred after Day 14 (the last day SARS-CoV-2 RNA levels were routinely assessed).

Cross-Resistance

Cross-resistance is not expected between nirmatrelvir and remdesivir or any other anti-SARS-CoV-2 agents with different mechanisms of action (i.e., agents that are not M^{pro} inhibitors).

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13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Nirmatrelvir

Carcinogenicity studies have not been conducted with nirmatrelvir.

Nirmatrelvir was negative for mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the *in vitro* micronucleus assay using human lymphoblastoid TK6 cells, and the *in vivo* rat micronucleus assays.

In a fertility and early embryonic development study, nirmatrelvir was administered orally to male and female rats at doses of 60, 200, or 1,000 mg/kg/day once daily beginning 14 days prior to mating, throughout the mating phase, and continued through GD 6 for females and for a total of 32 doses for males. There were no effects on fertility, reproductive performance, or early embryonic development at doses up to 1,000 mg/kg/day, resulting in systemic exposure (AUC_{24}) approximately 5 times higher than exposure at the authorized human dose of PAXLOVID.

Ritonavir

Carcinogenicity studies in mice and rats have been conducted on ritonavir. In male mice, at levels of 50, 100, or 200 mg/kg/day, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 25 times higher than the exposure in humans at the authorized human dose of PAXLOVID. No carcinogenic effects were observed in females at up to the highest dose tested, resulting in systemic exposure (AUC_{24}) approximately 25 times higher than the exposure in humans at the authorized human dose of PAXLOVID. In rats dosed at levels of 7, 15, or 30 mg/kg/day, there were no carcinogenic effects. In this study, the exposure at the high dose was approximately 5 times higher than the exposure in humans at the authorized human dose of PAXLOVID.

Ritonavir was found to be negative for mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Ritonavir produced no effects on fertility in rats at drug exposures approximately 18 (male) and 27 (female) times higher than the exposure in humans at the authorized human dose of PAXLOVID.

14 CLINICAL STUDIES

14.1 Efficacy in Subjects at High Risk of Progression to Severe COVID-19 (EPIC-HR)

EPIC-HR (NCT04960202) was a Phase 2/3, randomized, double-blind, placebo-controlled trial in non-hospitalized symptomatic adult subjects with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Eligible subjects were 18 years of age and older with at least 1 of the following risk factors for progression to severe disease: diabetes, overweight (BMI >25), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease, hypertension, sickle cell disease,

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neurodevelopmental disorders, active cancer, medically-related technological dependence, or were 60 years of age and older regardless of comorbidities. Subjects with COVID-19 symptom onset of ≤5 days were included in the study. Subjects were randomized (1:1) to receive PAXLOVID (nirmatrelvir/ritonavir 300 mg/100 mg) or placebo orally every 12 hours for 5 days. The trial excluded individuals with a history of prior COVID-19 infection or vaccination and excluded individuals taking any medications with clinically significant drug interactions with PAXLOVID. The primary efficacy endpoint was the proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28. The analysis was conducted in the modified intent-to-treat (mITT) analysis set [all treated subjects with onset of symptoms ≤3 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic monoclonal antibody (mAb) treatment], the mITT1 analysis set (all treated subjects with onset of symptoms ≤5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment), and the mITT2 analysis set (all treated subjects with onset of symptoms ≤5 days).

A total of 2,113 subjects were randomized to receive either PAXLOVID or placebo. At baseline, mean age was 45 years; 51% were male; 71% were White, 15% were Asian, 9% were American Indian or Alaska Native, 4% were Black or African American, and 1% was missing or unknown; 41% were Hispanic or Latino; 67% of subjects had onset of symptoms ≤3 days before initiation of study treatment; 49% of subjects were serological negative at baseline; the mean (SD) baseline viral RNA in nasopharyngeal samples was 4.71 $\log_{10}$ copies/mL (2.89); 27% of subjects had a baseline viral RNA of ≥10^7 ($\log_{10}$ copies/mL); 6% of subjects either received or were expected to receive COVID-19 therapeutic monoclonal antibody treatment at the time of randomization and were excluded from the mITT and mITT1 analyses.

The baseline demographic and disease characteristics were balanced between the PAXLOVID and placebo groups.

The proportions of subjects who discontinued treatment due to an adverse event were 2.0% in the PAXLOVID group and 4.2% in the placebo group.

Table 8 provides results of the primary endpoint in mITT1 analysis population. For the primary endpoint, the relative risk reduction in the mITT1 analysis population for PAXLOVID compared to placebo was 86% (95% CI: 72%, 93%).

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Table 8: COVID-19 Related Hospitalization or Death from Any Cause Through Day 28 in Non-Hospitalized Adults with COVID-19 (mITT1 Analysis Set): EPIC-HR

	PAXLOVID (N=977)	**Placebo (N=989)**
COVID-19 Related Hospitalization or Death from Any Cause Through Day 28		
n (%) Reduction Relative to Placebo[a] (95% CI), %	9 (0.9%) -5.6 (-7.3, -4.0)	64 (6.5%)
COVID-19 Related Hospitalization Through Day 28, %	9 (0.9%)	63 (6.4%)
All-cause Mortality Through Day 28[b], %	0	12 (1.2%)

Abbreviations: CI=confidence interval; COVID-19=coronavirus disease 2019; mAb=monoclonal antibody; mITT1=modified intent-to-treat 1 (all treated subjects with onset of symptoms ≤5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment).

The determination of primary efficacy was based on a planned interim analysis of 754 subjects in mITT population. The estimated risk reduction was -6.5% with a 95% CI of (-9.3%, -3.7%) and 2-sided p-value <0.0001.

a. The estimated cumulative proportion of subjects hospitalized or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.

b. For the secondary endpoint of all-cause mortality through Week 24, there were 0 and 15 (1%) events in the PAXLOVID arm and placebo arm, respectively.

Consistent results were observed in the mITT and mITT2 analysis populations.

Similar trends have been observed across subgroups of subjects *(see Figure 1)*.

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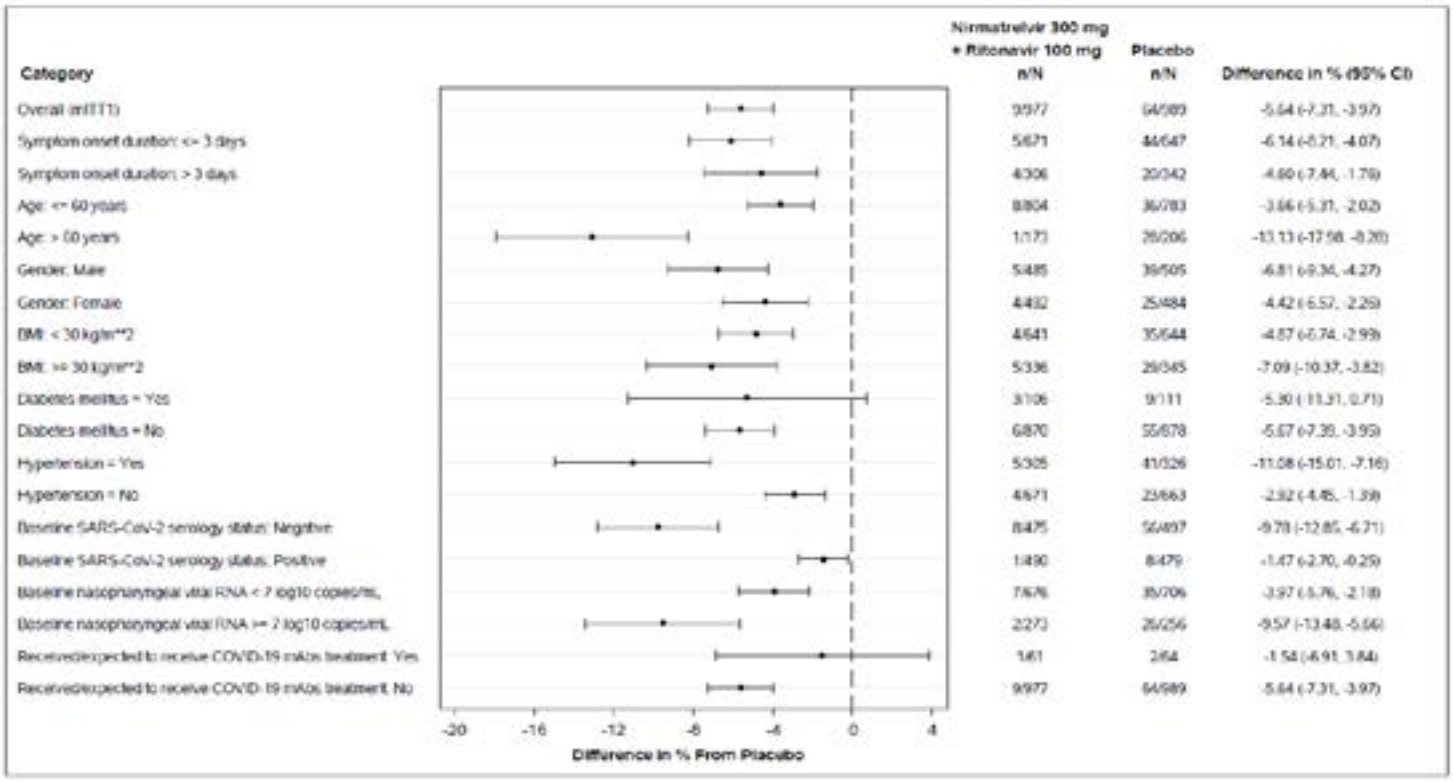
Figure 1: Subgroup Analysis of Adults with COVID-19 Dosed within 5 Days of Symptom Onset with COVID-19 Related Hospitalization or Death from Any Cause Through Day 28: EPIC-HR



Abbreviations: BMI=body mass index; COVID-19=coronavirus disease 2019; mAb=monoclonal antibody; mITT=modified intent-to-treat; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.
N=number of subjects in the category of the analysis set.
All categories are based on mITT1 population except for COVID-19 mAb treatment which is based on mITT2 population.
Seropositivity was defined if results were positive in either Elecsys anti-SARS-CoV-2 S or Elecsys anti-SARS-CoV-2 (N) assay.
The difference of the proportions in the 2 treatment groups and its 95% confidence interval based on normal approximation of the data are presented.

Among subjects who were SARS-CoV-2 seropositive at baseline, 1/490 (0.2%) PAXLOVID recipients versus 8/479 (1.7%) placebo recipients met the primary endpoint of COVID-19 related hospitalization or death from any cause through Day 28 [reduction relative to placebo -1.47% (-2.70%, -0.25%)].

14.2 Trial in Unvaccinated Subjects Without a Risk Factor for Progression to Severe COVID-19 or Subjects Fully Vaccinated Against COVID-19 With at Least One Factor for Progression to Severe COVID-19 (EPIC-SR)

PAXLOVID is not authorized for the treatment of COVID-19 in patients without a risk factor for progression to severe COVID-19.

EPIC-SR (NCT05011513) was a Phase 2/3, randomized, double-blind, placebo-controlled trial in non-hospitalized symptomatic adult subjects with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Eligible subjects were 18 years of age or older with COVID-19 symptom onset of ≤5 days who were at standard risk for progression to severe disease. The trial included previously unvaccinated subjects with no risk factors for progression to severe disease or subjects fully vaccinated against COVID-19 (i.e., completed a primary vaccination series) with at least 1 of the risk factors for progression to severe disease as defined in EPIC-HR. Through the December 19, 2021, data cutoff, a total of 1,075 subjects were randomized (1:1) to receive PAXLOVID or placebo orally every 12 hours for 5 days; of these, 59% were fully vaccinated high-risk subjects.

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The primary endpoint in this trial, the difference in time to sustained alleviation of all targeted COVID-19 signs and symptoms through Day 28 among PAXLOVID versus placebo recipients, was not met.

In an exploratory analysis of the subgroup of fully vaccinated subjects with at least 1 risk factor for progression to severe disease, a non-statistically significant numerical reduction relative to placebo for the secondary endpoint of COVID-19 related hospitalization or death from any cause through Day 28 was observed.

14.3 Post-Exposure Prophylaxis Trial

PAXLOVID is not authorized for the post-exposure prophylaxis of COVID-19.

In a double-blind, double-dummy, placebo-controlled trial, the efficacy of PAXLOVID when administered for 5 or 10 days as post-exposure prophylaxis of COVID-19 was evaluated. Eligible subjects were asymptomatic adults 18 years of age and older who were SARS-CoV-2 negative at baseline and who lived in the same household with symptomatic individuals with a recent diagnosis of SARS-CoV-2. A total of 2,736 subjects were randomized (1:1:1) to receive PAXLOVID orally every 12 hours for 5 days, PAXLOVID orally every 12 hours for 10 days, or placebo.

The primary endpoint for this trial was not met. The primary endpoint was the risk reduction between the 5-day and 10-day PAXLOVID regimens versus placebo in the proportion of subjects who developed RT-PCR or RAT-confirmed symptomatic SARS-CoV-2 infection through Day 14 who had a negative SARS-CoV-2 RT-PCR result at baseline. The proportion of subjects who had events through Day 14 was 2.6% for the 5-day PAXLOVID regimen, 2.4% for the 10-day PAXLOVID regimen, and 3.9% for placebo. There was not a statistically significant risk reduction versus placebo for either the 5-day or 10-day PAXLOVID regimen.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. It is supplied in two different Dose Packs.

Nirmatrelvir tablets and ritonavir tablets are supplied in separate blister cavities within the same child-resistant blister card.

<table>
<tr><th>Dose Pack</th><th>Content</th><th>NDC</th><th>Description</th></tr>
<tr><td rowspan="2">300 mg nirmatrelvir; 100 mg ritonavir</td><td rowspan="2">Each Carton Contains:

30 tablets divided in 5 daily-dose blister cards</td><td>0069-1085-30</td><td>Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side.

Ritonavir tablets: White film-coated ovaloid tablets debossed with the “a” logo and the code NK.</td></tr>
<tr><td colspan="2">Or</td></tr>
</table>

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		0069-0345-30	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Ritonavir tablets: White to off-white, capsule-shaped, film-coated tablets debossed with “H” on one side and “R9” on the other side.
	Each Blister Card[a] Contains: 4 nirmatrelvir tablets (150 mg each) and 2 ritonavir tablets (100 mg each)	0069-1085-06	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Ritonavir tablets: White film-coated ovaloid tablets debossed with the “a” logo and the code NK.
		Or	
		0069-0345-06	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Ritonavir tablets: White to off-white, capsule-shaped, film-coated tablets debossed with “H” on one side and “R9” on the other side.
150 mg nirmatrelvir; 100 mg ritonavir	**Each Carton Contains:** 20 tablets divided in 5 daily-dose blister cards	0069-1101-20	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Ritonavir tablets: White film-coated ovaloid tablets debossed with the “a” logo and the code NK.
	Each Blister Card[a] Contains: 2 nirmatrelvir tablets (150 mg each) and 2 ritonavir tablets (100 mg each)	0069-1101-04	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Ritonavir tablets: White film-coated ovaloid tablets debossed with the “a” logo and the code NK.

a. Indicates which tablets need to be taken in the morning and evening.

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Storage and Handling

Store at USP controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

17 PATIENT COUNSELING INFORMATION

As a healthcare practitioner, you must communicate to the patient and/or caregiver information consistent with the "FACT SHEET FOR PATIENTS, PARENTS, AND CAREGIVERS" and provide them with a copy of this Fact Sheet prior to administration of PAXLOVID.

Drug Interactions

Inform patients that PAXLOVID may interact with certain drugs and is contraindicated for use with certain drugs; therefore, advise patients to report to their healthcare provider the use of any prescription, non-prescription medication, or herbal products *[see Boxed Warning, Contraindications (4), Warnings and Precautions (5.1), and Drug Interactions (7)].*

Hypersensitivity Reactions

Inform patients that anaphylaxis, serious skin reactions, and other hypersensitivity reactions have been reported, even following a single dose of PAXLOVID. Advise them to immediately discontinue the drug and to inform their healthcare provider at the first sign of a skin rash, hives or other skin reactions, difficulty in swallowing or breathing, any swelling suggesting angioedema (for example, swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction *[see Warnings and Precautions (5.2)]*.

Dosage Modification in Patients with Moderate Renal Impairment

To ensure appropriate dosing in patients with moderate renal impairment, instruct such patients that they will be taking one 150 mg nirmatrelvir tablet with one 100 mg ritonavir tablet together twice daily for 5 days *[see Dosage and Administration (2.3)]*.

In the event that the PAXLOVID 150 mg;100 mg dose pack is unavailable: pharmacist should refer to the provided instructions entitled "IMPORTANT PAXLOVID™ EUA DISPENSING INFORMATION FOR PATIENTS WITH MODERATE RENAL IMPAIRMENT" for dispensing of PAXLOVID to patients with moderate renal impairment *[see Dosage and Administration (2.3)]* and patients should be informed that their daily blister card has been altered to ensure they receive the correct dose.

Administration Instructions

Inform patients to take PAXLOVID with or without food as instructed. Advise patients to swallow all tablets for PAXLOVID whole and not to chew, break, or crush the tablets. Alert the patient of the importance of completing the full 5-day treatment course and to continuing isolation in accordance with public health recommendations to maximize viral clearance and minimize transmission of SARS-CoV-2. If the patient misses a dose of PAXLOVID within 8 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 8 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose *[see Dosage and Administration (2.1)]*.

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18 MANUFACTURER INFORMATION

For general questions, visit the website or call the telephone number provided below.

Website	Telephone number
www.COVID19oralRx.com	1-877-219-7225 (1-877-C19-PACK)

For Medical Information about PAXLOVID, please visit www.pfizermedinfo.com or call 1-800-438-1985.

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