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

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Package 3A

USAID FROM THE AMERICAN PEOPLE

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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

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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 3A. Tier A Document information (click each entry to link to document)

#	DOCUMENT TITLE	SOURCE
3A.1	Therapeutics and COVID-19: Living Guideline (January 13, 2023) – 6.9 Molnupiravir, pages 70-77	WHO
3A.2	NIH Guidance for Molnupiravir	NIH
3A.3	EMA Withdrawal Assessment Report, Lagevrio (February 23, 2023)	EMA
3A.4	EMA Assessment Report of Lagevrio (January 27, 2022)	EMA
3A.5	EMA Conditions of Use, Conditions for Distribution and Patients Targeted and Conditions for Safety Monitoring Addressed to Member States for Unauthorized Product Lagevrio (molnupiravir) Available for Use	EMA
3A.6	U.S. FDA Emergency Use Authorization (EUA) for Molnupiravir 200 mg Capsules Center for Drug Evaluation and Research (CDER) Review (December 23, 2021)	U.S. FDA
3A.7	U.S. FDA Emergency Use Authorization (EUA) for Molnupiravir 200 mg Capsules Center for Drug Evaluation and Research (CDER) Review Memorandum (February 17, 2023)	U.S. FDA
3A.8	U.S. FDA Fact Sheet for Patients and Caregivers Emergency Use Authorization (EUA) of Lagevrio (molnupiravir) capsules for Coronavirus Disease 2019 (COVID-19)	U.S. FDA
3A.9	U.S. FDA Fact Sheet for Healthcare Providers: Emergency Use Authorization for Lagevrio (molnupiravir) Capsules	U.S. FDA

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Therapeutics and COVID-19: Living Guideline (January 13, 2023) – 6.9 Molnupiravir, pages 70-77

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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5. **Imprecision: very serious.**
6. **Risk of Bias: serious. Imprecision: serious.**

6.8.1 Mechanism of action

Colchicine is an anti-inflammatory drug used to treat gout, recurrent pericarditis, familial Mediterranean fever, and other inflammatory indications. There are several proposed mechanisms of action that are theorized to obviate inflammation-associated pathology seen in COVID-19 *(84)(85)*, which include a reduction in chemotaxis of neutrophils, inhibition of inflammasome signalling, and decreased production of cytokines such as interleukin-1b (IL-1b). There are no published data at the time of publication from animal models of SARS-CoV-2 infection to support or refute pre-clinical efficacy or harm of colchicine in associated disease pathology. The mechanism of action is postulated to be similar to that for the indications for which colchicine is already approved, but plausibility of effect in COVID-19 requires assumptions around similarities between COVID-19 and other diseases to be accepted. There are marked differences between trials in terms of the doses and schedules that have been investigated in COVID-19. Within the studies included in the NMA, doses ranged between 0.5 and 2 mg per day, course durations ranged between 6 and 30 days, some studies used once daily dosing, some used twice daily dosing, and others used three times daily dosing. In addition, some studies used dosing schedules which changed throughout the course, starting with one dose or schedule and then changing to a different dose or schedule after a predetermined interval. The pharmacokinetics of colchicine are dose linear between 0.5 mg and 1.5 mg *(86)(87)* but the substantive variation between studies included in the NMA precludes a robust interpretation of differences in outcome associated with dose and schedule.

6.9 Molnupiravir (published 3 March 2022)

Info Box

Recommendations concerning molnupiravir for patients with non-severe COVID-19 were published on 3 March 2022 as the ninth version of the WHO living guideline and in the BMJ as Rapid Recommendations. It followed the availability of six RCTs, as per the LNMA on drug therapies *(1)*. No changes were made to the molnupiravir recommendation in this 13th version of the guideline.

For patients with non-severe COVID-19 at highest risk of hospitalization (excluding pregnant and breastfeeding women, and children)

Conditional recommendation for

We suggest treatment with molnupiravir *(conditional recommendation for)*.

- *See Section 6.1 for help to identify patients at highest risk for hospitalization.*
- *Several therapeutic options are available: see decision support tool that displays benefits and harms of nirmatrelvir-ritonavir, molnupiravir and remdesivir.*
- *The longer-term harms of molnupiravir remain unknown in the absence of clinical evidence, both for individual patients and at the population level. These include genotoxicity, emergence of resistance, and emergence of new variants (see Mechanism of action).*
- *The conditional recommendation reflects the concern for widespread treatment with molnupiravir before more safety data become available.*
- *Use of molnupiravir should be accompanied by mitigation strategies such as avoiding the drug in younger adults, active pharmacovigilance programmes, and monitoring viral polymerase and spike sequences (see Justification).*

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Practical Info

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

- The recommended dose for molnupiravir is 800 mg tablet every 12 hours daily for 5 days, as per the regimen evaluated in large trials informing the recommendation.
- Administration should be as early as possible in the time course of the disease. In the included studies, molnupiravir was administered within 5 days of disease onset.

Evidence To Decision

Benefits and harms

In patients with non-severe COVID-19, molnupiravir probably reduces admission to hospital and time to symptom resolution, and may reduce mortality. The effect of molnupiravir on mechanical ventilation is very uncertain. Treatment does not increase the likelihood of adverse effects leading to drug discontinuation.

However, potential long-term harms of molnupiravir remain uncertain and a matter of concern, in the absence of clinical data. Potential harms include emergence of resistance, and the potential harm coming from the risk of molnupiravir-induced mutagenesis. These deliberations (see Justification section) were based on molnupiravir's mechanism of action and available pre-clinical data (see Mechanism of action section).

The balance between benefits and potential harms was close, but favoured treatment in the highest risk group, if implemented with other mitigation strategies to avoid harm at individual and population level (see Mitigation strategies section). There is a risk that monotherapy with molnupiravir (as for other antiviral monotherapies) may be associated with emergence of drug resistance, as has been seen with other antivirals (see Mechanism of action section).

The absolute benefits of molnupiravir on hospital admission depend on the prognosis. The GDG defined a threshold of a 6% absolute reduction in hospital admission to represent what most patients would value as an important benefit. Molnupiravir would exert such a benefit in patients at highest risk of hospitalization (above 10% baseline risk), such as those that lack COVID-19 vaccination, older people, or those with immunodeficiencies and/or chronic diseases. The conditional recommendation for the use of molnupiravir in those at highest risk reflects this threshold: 60 fewer hospitalizations per 1000 patients, and a greater anticipated absolute survival benefit, although this was not possible to quantify in the absence of data.

The planned subgroup analyses could not be performed in the absence of subgroup data reported publicly or provided by investigators.

Certainty of the Evidence

The evidence summary was informed by six trials with 4796 participants included in the LNMA, including the MOVe-OUT study *(88)*.

Certainty of evidence was rated as: moderate for decreased hospitalization (rated down due to serious imprecision); low for mortality (rated down due to serious imprecision and indirectness); moderate for time to symptom resolution (rated down due to serious risk of bias); very low for mechanical ventilation (rated down due to extremely serious imprecision and serious risk of bias); and high for adverse effects leading to drug discontinuation.

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)*. In addition, the GDG felt that there was some indirectness because of the possible emergence of variants (including Omicron) for which the effectiveness of currently available monoclonal antibodies may be reduced.

The GDG decided against rating certainty down for imprecision for outcomes where low event rates reflected very low baseline risks (e.g. mortality).

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Values and preferences

Applying the agreed values and preferences (see Section 7), the GDG inferred that almost all well-informed patients with a low risk of hospitalization would decline molnupiravir, and only those at highest risk (e.g. unvaccinated, older, or immunosuppressed) would choose to receive treatment.

In the absence of research evidence, in a previous survey (see recommendation for casirivimab-imdevimab), the GDG expressed the view that most patients with a risk of hospitalization above 10%, and thus an absolute risk reduction of approximately 6%, would choose to receive treatment, whereas most of those below that risk level would decline treatment. A similar survey was completed by the GDG for this recommendation; the GDG expressed the view that most patients would consider a reduction in the absolute risk of death of 3 per 1000 (increase in survivors from 995 to 998 per 1000 patients) to be important.

Resources and other considerations

Acceptability and feasibility

Molnupiravir is unlikely to be available for all individuals who, given the option, would choose to receive the treatment. This reinforces that molnupiravir should be reserved for those at highest risk.

Obstacles to access in LMICs due to cost and availability are of concern *(30)*. Challenges in shared decision-making and in communicating the harms versus benefits of molnupiravir may also be increased in LMICs. For example, 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 highest 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. UN partners procure these products and are making them available to low- and middle-income countries. 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 according.

Access to SARS-CoV-2 diagnostics: Since this recommendation emphasizes the need to administer treatment with molnupiravir within 5 days of symptom onset; increasing access and ensuring appropriate use of diagnostic tests is essential. Thus, availability and use of reliable and timely COVID-19 diagnostic tests (including the use of NAAT and Ag-RDTs) is needed to improve access to drugs, especially those targeting the early phase of disease. The appropriate use of Ag-RDTs by individuals and trained professionals can improve early diagnosis and earlier access to clinical care, particularly in the community and in primary health care settings. National programs should optimize their testing systems to reflect local epidemiology, response objectives, available resources and needs of their populations.

Justification

A combination of the evidence, safety concerns based on preclinical data, values and preferences, and feasibility contributed to the conditional recommendation for the use of molnupiravir only in patients with non-severe COVID-19 at highest risk of hospitalization. Typical characteristics of people at highest risk include those who are unvaccinated, older people, or those with immunodeficiencies and/or chronic diseases (e.g. diabetes).

Only a minority of patients who are at highest risk are likely to achieve sufficient benefit to compensate for the risks, and other limitations and disadvantages of therapy. These include a lack of reliable tools to identify high-risk patients, limited availability of the drug, and the safety concerns summarized below.

- The GDG had concerns about the risk of emergent resistance with a new antiviral deployed as monotherapy (see Mechanism of action section). Significant uncertainty exists regarding how quickly resistance will emerge; in the absence of sufficient clinical data, the GDG concluded large uncertainties remain.
- Concerning the risk of the drug promoting the emergence of new variants, the GDG noted that there was a low likelihood that the drug would result in a selective pressure for a new variant; large uncertainty remains in the absence of sufficient clinical data.

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- Molnupiravir is mutagenic in mammalian cells in vitro, but there is no evidence of mutagenicity in animal models or humans. The GDG therefore acknowledged uncertainty regarding longer term genetic toxicity and potential for malignancy associated with molnupiravir.
- Given evidence from rat pups of an impact on growth plate thickness, molnupiravir should not be used in children. Similarly, since molnupiravir elicited embryo-fetal lethality and teratogenicity in offspring when given to pregnant animals, it should not be used in pregnant or breastfeeding women.
- The GDG acknowledged that spermatogenesis may also be especially prone to the mutagenic effects of molnupiravir, but that there was uncertainty regarding the consequences to children conceived by fathers receiving or having recently received molnupiravir.

Applicability

The applicability of this recommendation to children, breastfeeding and pregnant women, is currently uncertain, as the included RCTs enrolled only non-pregnant adults. However, the GDG concluded that molnupiravir should not be offered to children, breastfeeding or pregnant women with COVID-19. In addition, men planning to conceive should be oriented on the potential for temporary genotoxic effect on sperm cell production (see Mitigation strategies section). The unknown long-term risk of genotoxicity is likely to be higher in younger patients as compared with older patients, thus its use in younger adults not a high risk should be avoided.

The GDG also had concerns about whether the drug would retain efficacy against emerging variants of concern such as Omicron. While there is no molecular basis for a loss of efficacy, the GDG noted that the higher viral loads and associated disease severity may impact the effectiveness of molnupiravir. This represents another area of uncertainty, given currently available data did not include patients with newer variants, including Omicron (see Section 9).

Clinical Question/ PICO

Population:	Patients with non-severe COVID-19
Intervention:	Molnupiravir
Comparator:	Standard care

Summary

Evidence summary

The LNMA for molnupiravir was informed by six RCTs which enrolled 4827 patients with non-severe illness in outpatient settings; the LNMA team had access to data for 4796 patients. All RCTs were registered; none were published in peer-reviewed journals. None of the included studies enrolled children or pregnant women. The appendix summarizes study characteristics and risk of bias ratings, effect estimates by outcome and associated forest plots for molnupiravir versus standard care.

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

Subgroup analysis

Five pre-specified subgroup analyses were requested by the GDG:

1. Age: children (≤ 19 years) versus adults (20–60 years) versus older adults (≥ 60 years).
2. Severity of illness at time of treatment initiation: non-severe versus severe versus critical.
3. Time from symptom onset.
4. Serological status (seropositive versus seronegative).
5. Vaccination status (unvaccinated versus vaccinated).

Studies did not enrol children, nor patients with severe or critical illness. All studies enrolled unvaccinated individuals with time from symptom onset < 5 days. Data regarding serological status were not reported.

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Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Molnupiravir	**Certainty of the Evidence** (Quality of evidence)
		6 per 1000 Difference:	0 per 1000 **6 fewer per 1000** (CI 95% 6 f ewer — 4 f ewer)	
		8 per 1000 Difference:	8 per 1000 **0 fewer per 1000** (CI 95% 8 f ewer — 317 more)	
		35 per 1000 Difference:	19 per 1000 **16 fewer per 1000** (CI 95% 24 f ewer — 4 f ewer)	
		60 per 1000 Difference:	33 per 1000 **27 fewer per 1000** (CI 95% 41 f ewer — 6 f ewer)	
		100 per 1000 Difference:	57 per 1000 **43 fewer per 1000** (CI 95% 68 f ewer — 10 f ewer)	
		0 per 1000 Difference:	0 per 1000 **0 fewer per 1000** (CI 95% 0 f ewer — 2 more)	
		9 (Median) Difference:	5.6 (Mean) **MD 3.4 f ewer** (CI 95% 4.8 fewer — 1.7 fewer)	

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Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Molnupiravir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Malignancy		In vitro and animal studies sugg est the possibility of carcinogenesis		Very low No human da ta with long-term follow-up	The effect of molnupiravir on cancer is uncertain

1. **Indirectness: serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, who are not easily identifiable. For these patients, molnupiravir may have an important impact on mortality. **Imprecision: serious.** There were only 11 events total (10 in the control arms and 1 in the molnupiravir arms).
2. **Risk of Bias: serious.** The single trial reporting mechanical ventilation was not blinded. **Imprecision: extremely serious.** Very few events, resulted in very large credible intervals that include important and unimportant effects.
3. **Imprecision: serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
4. **Imprecision: serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
5. **Imprecision: serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
6. **Risk of Bias: serious.** All three trials were at high risk of bias for deviations from intended intervention (lack of blinding). One trial was at high risk of bias for possible inadequate randomization concealment.

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Mitigation strategies to address safety concerns

Info Box

With the safety concerns related to molnupiravir (see Mechanism of action section), the WHO recognizes the need to mitigate risks, both for individual patients and at the population level.

The conditional recommendation takes into account one such strategy: limiting the intervention to patients that are at higher risk of hospitalization or death. Typical characteristics with older age, immunodeficiencies and/or chronic diseases (e.g. diabetes) and lack of COVID-19 vaccination. See WHO recommendations for further information on COVID-19 vaccination Strategic Advisory Group of Experts on Immunization for more details.

Other mitigation strategies include:

- Decisions around treatment with molnupiravir must be done using a shared decision-making model, ensuring the clinician is well educated on the potential benefits and harms of therapy and able to explain these to the patient in order to make well-informed decisions. See Practical information section.
    - Molnupiravir should not be given to pregnant or breastfeeding women or to children. In case of doubt about pregnancy, a pregnancy test should be performed prior to treatment initiation. If a woman of child bearing age is considered for treatment, counselling regarding birth control during treatment and for 4 days after the last dose of molnupiravir should be facilitated.
    - Men planning to conceive should be oriented on the potential for temporary genotoxic effect on sperm cell production, and those who are sexually active with females should be counselled to use birth control during treatment and for at least 3 months after the last dose of molnupiravir *(89)*.
    - The unknown long-term risk of genotoxicity is likely to be higher in younger patients as compared with older patients; thus use in younger adults who are not at high risk should be limited.
- Active sequence monitoring of SARS-CoV-2 detected in clinical respiratory samples (i.e. may include polymerase and spike) should be arranged for patients receiving therapy, including higher risk individuals (immunocompromised).
- Pharmacovigilance: use of molnupiravir should be accompanied by a robust, active pharmacovigilance programme.

6.9.1 Mechanism of action

Molnupiravir an orally available antiviral, which was originally designed as an influenza treatment, although not approved. The drug inhibits replication of SARS-CoV-2 with an in vitro potency broadly, similar to remdesivir, and was re-purposed early in development as an antiviral for SARS-CoV-2 *(90)(91)*.

Molnupiravir is an orally available prodrug of ß-D-N4-hydroxycytidine (NHC). It is a nucleoside drug, but the mechanism of action involves lethal mutagensis of the virus. This contrasts with chain-termination seen with other antiviral nucleoside analogues (e.g. remdesivir and those used in HIV or HCV) *(92)*. NHC is incorporated by the SARS-CoV-2 RdRp, instead of either C or U nucleosides, in to the genomic or subgenomic RNA during copying of the RNA template genome. The resultant NHC-containing RNAs are then themselves used as a template for production of subsequent RNAs which are predicted to be mutated and therefore not believed to form functional viruses *(92)(93)*.

Molnupiravir is given orally twice daily unlike remdesivir, which is given by intravenous infusion once daily. In healthy volunteers, molnupiravir (800mg) achieves maximum plasma concentrations of its active metabolite at 3600 ng/mL *(94)*. This is higher than that of remdesivir (2200 ng/mL) *(95)*. However, the intracellular half-life of molnupiravir active metabolite is shorter in human cell lines (3h) compared with that of remdesivir's active metabolite (35h) *(94)*.

High doses of molnupiravir (250 mg/kg twice daily) have been shown to be effective in SARS-CoV-2-infected Syrian golden hamsters; however, the animal plasma pharmacokinetics were not reported to benchmark against those seen in humans *(96)*. Evidence of antiviral activity is also available from a study in SARS-CoV-2-infected ferrets at lower doses *(97)*. When molnupiravir was combined with favipiravir in infected Syrian golden hamsters, the efficacy was greater than when either drug was given alone *(98)*.

Molnupiravir retains activity against Alpha and Beta variants in vivo *(99)*, and the Delta and Omicron variants in vitro *(100)(101)*. No data are currently available demonstrating activity against the Delta or Omicron variants in vivo, and while there appears to be no molecular basis for a loss of activity, there is residual uncertainty around whether a higher replication or transmission rate may impact efficacy of the drug.

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Emergence of resistance: The emergence of resistance to drugs used for other viruses is varied; with some resistance emerges readily, and with others emerging more slowly. The barrier to resistance for a given drug with a given virus is generally considered to increase with the number of mutations that are required to emerge. Insufficient data are currently available to ascertain how high the barrier of resistance is with SARS-CoV-2 for molnupiravir. Based on experiences with other nucleoside antiviral drugs (some have a high barrier to resistance and some have a low barrier to resistance), molnupiravir will place a selective pressure for viral resistance mutations within an individual, with the potential to spread at a population level. Non-clinical and/or clinical data are therefore needed, but are not currently available for molnupiravir.

Resistance occurs through inherent variability in viral sequences that happen spontaneously as the virus replicates. Chance variations become selected, known as selective pressure, when they confer a survival advantage in the presence of the drug. Sometimes, there is a fitness cost to the virus and secondary mutations can subsequently be selected to restore fitness. The major uncertainty relates to how quickly resistance will emerge rather than whether it will emerge. There may be a higher risk of resistance in immunocompromised patients because of a longer tail of replication in this group. There may also be a higher risk of resistance in patients with poor adherence where the virus is exposed to suboptimal drug concentrations. The rate at which resistance emerges will be slower if drugs are given in combination because more mutations will be required to confer resistance to multiple drugs than will be required for one drug. Of note, animal studies have also demonstrated drug combinations to be more effective. The risk of resistance to individual patients is drug failure due to compromised efficacy. If resistance is transmitted, there is a risk of efficacy failure at a population level and subsequent attempts to combine the drug may be futile because of "functional monotherapy" with the partner agent. The genetic barrier to resistance cannot be estimated without data.

Emergence of new variants: It has been proposed that random mutagenesis arising from the molnupiravir mechanism of action might increase diversity in the viral sequences that may result in more rapid emergence of new variants *(102)*. Unlike in the considerations for resistance, there is no conceptual basis for molnupiravir placing a selective pressure on emergence of new variants. Sequence variation is lower given molnupiravir is only incorporated in place of two of the four nucleotide bases in the genome than it would be if incorporated in place of any nucleotide. There is no direct evidence to support or refute the variants hypothesis and as such the risk is currently unquantifiable.

The rate of resistance emergence and the risk of additional diversity in the viral genome leading to new variants, were acknowledged to be higher with a higher number of patients receiving the intervention.

Non-clinical safety: The GDG reviewed the publically available data on non-clinical safety of molnupiravir from the FDA meeting documents for molnupiravir Emergence Use Authorization (30 November 2021) *(103)*. The following safety concerns were highlighted:

- Genetic toxicology data demonstrated that molnupiravir is mutagenic in vitro, but there was no evidence of mutagenicity in animal models. The GDG acknowledged uncertainties in the available data and concluded that based upon the available information molnupiravir may or may not be carcinogenic in humans.
- An increase in thickness of growth plate associated with decreased bone formation was observed in rapidly growing rats but not in mice, rats or dogs. The GDG determined that molnupiravir should not therefore be administered to paediatric patients.
- Importantly, low concentrations of NHC (0.09% maternal exposures) were detectable in 10-day old rat pups suggesting that NHC is present in breast milk. The GDG determined molnupiravir should not be administered to breastfeeding women.
- In developmental and reproductive toxicology assessments, reduced foetal body weights were observed in rats and rabbits, with higher exposures also being associated with embryo-foetal lethality and teratogenicity in rats. Accordingly, molnupiravir should not be administered during pregnancy.
- There was an absence of available data relating to spermatogenesis, which may be particularly prone to the effect of a mutagen in adult males. No data are available to quantify the consequences of this for embryo/foetus conceived by fathers who were receiving or had recently received molnupiravir.

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Document 3A.2

NIH Guidance for Molnupiravir

Document URL

https://files.covid19treatmentguidelines.nih.gov/guidelines/section/section_170.pdf

Reference website URL

https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/molnupiravir/?utm_source=site&utm_medium=home&utm_campaign=highlights

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Molnupiravir

Last Updated: April 20, 2023

Molnupiravir is the oral prodrug of beta-D-N4-hydroxycytidine (NHC), a ribonucleoside that has shown antiviral activity against SARS-CoV-2 in vitro and in some clinical trials.[1,2] NHC uptake by viral RNA-dependent RNA-polymerases results in viral mutations and lethal mutagenesis.[3,4] On December 23, 2021, the Food and Drug Administration (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.[5,6] Molnupiravir is expected to be active against the Omicron variant and its subvariants.[6]

As a mutagenic ribonucleoside antiviral agent, there is a theoretical risk that molnupiravir will be metabolized by the human host cell and incorporated into the host DNA, leading to mutations. Molnupiravir has been evaluated in 2 in vivo rodent mutagenicity assays. One study produced equivocal results. In the other study, there was no evidence for mutagenicity.[6] The FDA concluded that, based on the available genotoxicity data and the 5-day duration of treatment, molnupiravir has a low risk for genotoxicity. In addition, there have been concerns about the potential effects of molnupiravir on SARS-CoV-2 mutation rates; the FDA has required that the manufacturer monitor genomic databases for the emergence of SARS-CoV-2 variants.

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using **molnupiravir 800 mg** orally (PO) twice daily for 5 days as an alternative therapy in nonhospitalized patients aged ≥18 years with mild to moderate COVID-19 who are at high risk of disease progression when ritonavir-boosted nirmatrelvir (Paxlovid) and remdesivir are not available, feasible to use, or clinically appropriate; treatment should be initiated as soon as possible and within 5 days of symptom onset **(CIIa)**.
- The Panel **recommends against** the use of **molnupiravir** for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated **(AIII)**. For more details, see Considerations in Pregnancy below.
- People who engage in sexual activity that may result in conception should use effective contraception during and following treatment with molnupiravir. For more details, see Considerations in Sexually Active Individuals below.

Molnupiravir may be used in patients who are hospitalized for a diagnosis other than COVID-19, provided they have mild to moderate COVID-19 and are at high risk of progressing to severe disease. 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.

Rationale

The MOVe-OUT trial enrolled high-risk, unvaccinated, nonhospitalized adults and reported that molnupiravir reduced the rate of hospitalization or death among these patients by 31% compared to placebo.[7] This trial was conducted in 2021 before the emergence of the Omicron variant and its subvariants. A secondary analysis of the patients who required hospitalization during the trial found a reduced need for respiratory interventions among those who received molnupiravir compared to those

who received placebo.[8] Molnupiravir has shown activity against the Omicron subvariants in vitro and in animal studies.[2,9-11]

The PANORAMIC trial enrolled participants during a period when the Omicron variant was circulating.[12] The participants were nonhospitalized adults with COVID-19 who were at high risk of progressing to severe disease, and 94% had received at least 3 doses of a COVID-19 vaccine. The study found that the use of molnupiravir plus usual care did not reduce the primary composite outcome of hospitalization or death compared to usual care alone. The rates of this composite outcome were low (1%) in both arms. Molnupiravir plus usual care was superior to usual care alone for several secondary clinical endpoints. For example, patients who received molnupiravir plus usual care reported recovering from COVID-19 an estimated 4 days earlier than those who received usual care alone. However, because the PANORAMIC trial was an open-label study and the patients knew whether they were receiving molnupiravir or not, this may have affected their reported symptoms. As a result, these findings are less reliable than those from a placebo-controlled trial.

Although the different COVID-19 treatment options have not been directly compared in clinical trials, the Panel recommends using **molnupiravir** only when ritonavir-boosted nirmatrelvir and remdesivir are not available, feasible to use, or clinically appropriate **(CIIa)**. Molnupiravir appears to have lower clinical efficacy than these other treatment options.

Some observational studies have evaluated the use of molnupiravir in nonhospitalized or hospitalized adults who are at high risk of progressing to severe disease, including some patients who received COVID-19 vaccines, but these studies have limitations.[13-15] For treatment considerations for vaccinated individuals, see Therapeutic Management of Nonhospitalized Adults With COVID-19.

Additional Considerations

- Patients should complete the 5-day treatment course of molnupiravir. It is unknown whether a shorter course is less effective or associated with the emergence of molnupiravir-resistant mutations.
- If a patient requires hospitalization after starting treatment, the full treatment course of molnupiravir can be completed at the health care provider's discretion.
- The FDA EUA for molnupiravir provides instructions for preparing and administering capsule contents through orogastric or nasogastric tubes.[6]
- There are no data on using combination antiviral therapies for the treatment of nonhospitalized patients with COVID-19. Clinical trials are needed to determine whether combination therapy has a role in the treatment of SARS-CoV-2 infection.
- Patients who are severely immunocompromised can experience prolonged periods of SARS-CoV-2 replication, which may lead to rapid viral evolution. There are theoretical concerns that using a single antiviral agent in these patients may produce antiviral-resistant viruses. Additional studies are needed to assess this risk. The role of combination antiviral therapy in treating patients who are severely immunocompromised is not yet known. See Special Considerations in People Who Are Immunocompromised for more information.
- There are limited data on the frequency of SARS-CoV-2 rebound in patients who have completed treatment with molnupiravir. During the MOVe-OUT trial, rates of symptomatic SARS-CoV-2 rebound were low (approximately 1%) in both those who received molnupiravir and those who received placebo.[6]

Monitoring, Adverse Effects, and Drug-Drug Interactions

The most common adverse effects of molnupiravir are diarrhea, nausea, and dizziness. Based on in vitro studies, neither molnupiravir nor its active metabolite NHC are inhibitors or inducers of major drug-metabolizing enzymes or inhibitors of major drug transporters.

According to the FDA EUA, no drug-drug interactions have been identified for molnupiravir.

Considerations in Sexually Active Individuals

For individuals of childbearing potential, clinicians should assess the patient's pregnancy status before initiating molnupiravir.

Patients of childbearing potential should be counseled about abstaining from sex or using reliable contraception for the duration of therapy and for up to 4 days after taking molnupiravir. Reproductive toxicity has been reported in animal studies of molnupiravir, and molnupiravir may be mutagenic during pregnancy.

The FDA EUA states that men of reproductive potential who are sexually active with individuals of childbearing potential should be counseled to abstain from sex or use a reliable method of contraception for the duration of treatment **and for at least 3 months after the last dose of molnupiravir**.

Considerations in Pregnancy

The Panel **recommends against** the use of **molnupiravir** for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated **(AIII)**. See Pregnancy, Lactation, and COVID-19 Therapeutics for more information.

Considerations in Lactating People

Because the risk of adverse effects in infants is currently unknown, the FDA EUA fact sheet **recommends against** feeding an infant breast milk from a patient who is taking molnupiravir for the duration of the treatment course and for 4 days after the final dose. See Pregnancy, Lactation, and COVID-19 Therapeutics for more information.

Considerations in Children

The MOVe-OUT and PANORAMIC trials excluded participants aged <18 years. There are no data available on the use of molnupiravir in children aged <18 years. Molnupiravir is not authorized for use in those aged <18 years due to potential effects on bone and cartilage growth.

Clinical Data

MOVe-OUT

MOVe-OUT was a multinational, Phase 3 trial that evaluated the use of molnupiravir in unvaccinated, nonhospitalized adults with mild to moderate COVID-19 who were at high risk of progressing to severe COVID-19 and enrolled within 5 days of symptom onset.[7] The trial was conducted in 2021 before the emergence of the Omicron variant and its subvariants. Pregnant people, lactating people, and children were excluded from the study. Patients were randomized to receive molnupiravir 800 mg PO every 12 hours for 5 days or placebo.

The primary composite endpoint was all-cause hospitalization (defined as a hospital stay >24 hours) or death by Day 29.

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Results

- The final analysis included 1,433 patients:
  - The median age was 43 years (with 17% aged >60 years); 49% of patients were men, 57% were White, 50% were Hispanic/Latinx, and 5% were Black or African American.
  - Four percent had a body mass index ≥30, and 16% had diabetes.
- The time from the onset of COVID-19 symptoms to randomization was ≤3 days in 48% of patients.
- By Day 29, the use of molnupiravir reduced the risk of hospitalization or death by 31%.
  - Forty-eight of 709 patients (6.8%) in the molnupiravir arm and 68 of 699 patients (9.7%) in the placebo arm experienced hospitalization or death (adjusted difference -3.0%; 95% CI, -5.9% to -0.1%).
  - One death occurred in the molnupiravir arm and 9 deaths occurred in the placebo arm.
- There were no significant differences between the arms in the proportion of patients who experienced adverse events or serious adverse events.
- A secondary analysis of data from the patients who were hospitalized during the trial revealed that the use of molnupiravir reduced the risk of requiring respiratory interventions (conventional or high-flow oxygen delivery, noninvasive ventilation, or mechanical ventilation) by 21%.[8]

Limitations and Interpretation

- When compared with placebo, the use of molnupiravir had a modest benefit in reducing the risk of hospitalization or death in unvaccinated, nonpregnant, high-risk adults with mild to moderate COVID-19. Molnupiravir also reduced the risk of pulmonary complications in these patients. However, this study was conducted before the emergence of the Omicron variant and its subvariants.

PANORAMIC

PANORAMIC was a large, multicenter, open-label, adaptive platform trial that was conducted in the United Kingdom.[12] The study evaluated the use of molnupiravir in nonhospitalized adults who were at high risk of progressing to severe COVID-19. The participants were aged ≥50 years or ≥18 years with comorbid conditions, and they had either a positive SARS-CoV-2 reverse transcription polymerase chain reaction result or rapid antigen test result at baseline. Patients were enrolled within 5 days of symptom onset. Pregnant people, lactating people, children, and those of childbearing potential who were unwilling to use effective contraception were excluded from the study. Patients were randomized to receive molnupiravir 800 mg PO twice daily for 5 days plus usual care or usual care alone.

The primary endpoint was a composite of all-cause hospitalization (defined as ≥1 overnight hospital stay, ≥1 night at home with care and monitoring by hospital clinicians, or an overnight stay in an emergency room) or death within 28 days of randomization. The trial was conducted from December 8, 2021, to April 27, 2022, when the Omicron variant was the dominant variant in the United Kingdom.

Results

- The final analysis included 25,708 patients. The mean age was 56.6 years (with 26.5% aged ≥65 years), 94% of patients were White, and 59% were women.
- Ninety-four percent of the patients had received ≥3 doses of a COVID-19 vaccine.
- Overall, 69% of patients had comorbidities, including 25% with lung disease, 15% with obesity, 12% with diabetes, 8% with heart disease, and 8.5% were immunocompromised.

- Twenty-four percent of patients were taking inhaled corticosteroids.
- The mean time from symptom onset to starting molnupiravir was 3 days (range 3–5 days). Among the patients who provided information on their molnupiravir use, 95% reported completing the 5-day treatment course.
- Data on the primary outcome was available for 25,054 patients (97%).
  - In both arms, approximately 1% of patients were hospitalized or died. There were 103 hospitalizations and 3 deaths in the molnupiravir arm compared with 96 hospitalizations and 5 deaths in the usual care alone arm (aOR 1.06; 95% CrI, 0.81–1.41; probability of superiority 0.33).
  - Subgroup analyses revealed no evidence for treatment interaction.
- Molnupiravir plus usual care was superior to usual care alone for several secondary clinical endpoints.
  - The time from randomization to self-reported first recovery was significantly shorter among those who received molnupiravir (median of 9 days; IQR 5–23) than those who received usual care alone (median of 15 days; IQR 7–not reached).
  - After adjusting for age and baseline comorbidities, molnupiravir significantly reduced the estimated median time to first recovery. The median time to first recovery was 10.4 days (95% CrI, 10.1–10.6) in the molnupiravir arm and 14.6 days (95% CrI, 14.2–15) in the usual care alone arm (HR 1.36; 95% BCI, 1.32–1.40; probability of superiority >0.99).
  - The use of molnupiravir also significantly reduced the time to early sustained recovery (defined as recovery by Day 14 that was sustained until Day 28), the time to sustained recovery, the time to alleviation of all symptoms, the time to sustained alleviation of all symptoms, and the time to initial reduction of symptom severity.
- Serious adverse events occurred in 0.4% of patients in the molnupiravir arm and 0.3% of patients in the usual care alone arm. No serious adverse events related to molnupiravir were reported; 145 patients (1.1%) withdrew because of adverse effects attributed to molnupiravir.

Limitations and Interpretation

- The use of molnupiravir did not reduce the rate of progression to hospitalization or death among vaccinated, nonpregnant, high-risk adults, but it did reduce the time to improvement of symptoms. However, because the PANORAMIC trial was an open-label study and the patients knew whether they were receiving molnupiravir or not, this may have affected their reported symptoms. As a result, these findings are less reliable than those from a placebo-controlled trial.

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Document 3A.3

EMA Withdrawal Assessment Report, Lagevrio (February 23, 2023)

Document URL

https://www.ema.europa.eu/en/documents/withdrawal-report/withdrawal-assessment-report-lagevrio_en.pdf

Reference website URL

https://www.ema.europa.eu/en/medicines/human/withdrawn-applications/lagevrio#

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27 January 2022
EMA/719664/2021 Rev. 1[1]
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure under Article 5(3) of Regulation (EC) No 726/2004

Use of molnupiravir for the treatment of COVID-19

INN: molnupiravir

Procedure number: EMEA/H/A-5(3)/1512

Note:

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

[1] Statement on BCS classification was updated

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List of abbreviations

Abbreviation	Definition
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase
APaT	all participants as treated
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-12}	area under the concentration-time curve from time 0 to 12 hours
$AUC_{0-\tau}$	area under the concentration-time curve from time 0 to end of dosing interval
AUC_{0-inf}	area under the concentration-time curve from time 0 to time infinity
AUC_{0-last}	area under the concentration-time curve from time 0 to the time of the last measured concentration
BID	twice a day
BLOQ	below the limit of quantitation
BMI	body mass index
CHMP	Committee for Medicinal Products for Human Use
C_{max}	maximum concentration
COVID-19	coronavirus disease 2019
CSR	clinical study report
CYP	cytochrome P450
DDI	drug-drug interaction
DFC	dry filled capsule
DILI	drug-induced liver injury
ECG	electrocardiogram
ECI	event of clinical interest
eDMC	external Data Monitoring Committee
eGFR	estimated glomerular filtration rate

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Abbreviation	Definition
EIDD	Emory Institute for Drug Development
EMA	European Medicines Agency
EOT	end of treatment
ER	exposure-response
ESRD	end-stage renal disease
EUA	emergency use authorization
FaSSIF	fasted state simulated intestinal fluid
FDA	Food and Drug Administration
IA	interim analysis
IAV	Influenza A virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	investigational new drug
IRT	intervention randomization system
IV	intravenous
LLOQ	lower limit of quantitation
MAA	marketing authorisation application
mAbs	monoclonal antibodies
MAD	multiple-ascending dose
MERS-CoV	Middle East respiratory syndrome coronavirus
MHV	mouse hepatitis virus
MITT	modified intent-to-treat
MOV	molnupiravir (MK-4482)
N/A	not applicable
NEWS	National Early Warning Score
NGS	next generation sequencing
NHC	N-hydroxycytidine
NHC-TP	N-hydroxycytidine-5´-triphosphate
NP	nasopharyngeal

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Abbreviation	Definition
OP	oropharyngeal
PCR	polymerase chain reaction
PIB	powder in bottle
PK	pharmacokinetic(s)
PO	oral administration
PopPK	population PK
Q12H	every 12 hours
RdRP	RNA-dependent RNA polymerase
RNA	ribonucleic acid
RT-PCR	reverse-transcriptase polymerase chain reaction
SAD	single-ascending dose
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-2	SARS-associated coronavirus-2
SD	standard deviation
SGF	simulated gastric fluid
$t_{1/2}$	apparent terminal half-life
T_{max}	time of maximum concentration
ULN	upper limit of normal
ULOQ	upper limit of quantitation
US	United States
USA	United States of America
US FDA	United States Food and Drug Administration
VEEV	Venezuelan equine encephalitis virus
WHO	World Health Organization
WOCBP	women of childbearing potential

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Merck Sharp & Dohme B.V. submitted on 22 October 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Lagevrio, 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 12 October 2020.

The applicant applied for the following indication: Lagevrio is indicated for treatment of coronavirus disease 2019 (COVID-19) in adults.

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 test(s) 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) P0345/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P0345/2021 was not 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.

1.4.2. Derogation(s) from market exclusivity

N/A

1.5. Applicant's request for consideration

1.5.1. New active substance status

The applicant requested the active substance molnupiravir 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. PRIME

N/A

1.7. 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
21 August 2020	EMEA/H/SA/4650/1/2020/II	Ingrid Schellens, Rune Kjeken
18 September 2020	EMEA/H/SA/4650/2/2020/I	Paolo Foggi, Ewa Balkowiec-Iskra

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

- Sufficiency of the completed and planned nonclinical safety studies to support a MAA.
- Proposal of an adaptive placebo-controlled design with multiple MK-4482 dose levels to be assessed in Part 1 (Phase 2), and a single dose selected for evaluation in Part 2 (Phase 3) in study P001 in hospitalised patients, and study P002 in non-hospitalised patients. Timing and definition of primary and secondary efficacy endpoints, including the use of a patient diary. The proposed dose range to be evaluated in Part 1, and the duration of treatment (5 days). The plan to allow participants who become unable to swallow during treatment to receive capsule contents via a nasogastric or orogastric tube. Criteria for patient inclusion. Stratification factors and Type I error control.
- **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 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.

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1.8. Steps taken for the assessment of the product

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

Rapporteur: Jayne Crowe Co-Rapporteur: Maria Concepcion Prieto Yerro

Lagevrio 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.

The CHMP confirmed eligibility to the centralised procedure on	12 October 2020
The ETF recommended to start the rolling review procedure on	12 October 2021
The application was received by EMA on	22 October 2021
Submission of the first package via eCTD	22 October 2021
The procedure (Rolling Review 1) started on	23 October 2021
ETF discussion on the Rapporteurs' recommendation to ETF for closing the RR and considering the data submitted already in the context of a formal MAA	18 November 2021
Extraordinary CHMP to endorse the Rapporteurs' position	19 November 2021
The procedure started on	23 November 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	23 November 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	23 November 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	25 November 2021
ETF discussion on Rolling Review procedure	30 November 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	02 December 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	16 December 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	23 December 2021
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	31 January 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 February 2022
ETF discussions on the consolidated List of Questions	14 February 2022

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The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	24 February 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	29 March 2022
ETF discussions on the consolidated List of Outstanding Issues	12 April 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	13 April 2022
The CHMP agreed on second list of outstanding issues in writing to be sent to the applicant on	22 April 2022
The applicant submitted the responses to the second CHMP List of Outstanding Issues on	17 October 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the second List of Outstanding Issues to all CHMP and PRAC members on	21 November 2022
ETF discussions on the consolidated third List of Outstanding Issues	02 December 2022
The CHMP agreed on clock-stop to address agreed third list of outstanding issues in writing to be sent to the applicant on	15 December 2022
The applicant submitted responses to the third CHMP List of Outstanding Issues on	24 January 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the third List of Outstanding Issues to all CHMP and PRAC members on	08 February 2022
ETF discussions on the consolidated third List of Outstanding Issues	14 February 2023
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	21 February 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Lagevrio on	23 February 2023
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) on	23 February 2023

In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.

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2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

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 can reduce the number of patients that progress to more severe disease and require hospitalisation or admittance to ICU.

2.1.2. Epidemiology

Since the initial description of the novel SARS-CoV-2 causing human disease, more than 756,411,740 of cumulative caseshave been diagnosed globally resulting in more than 6 million deaths (https://covid19.who.int/;last time accessed February 2023). Unprecedented scientific effort has led to advances in understanding the biology of the virus, pathogenesis of disease, modes of transmission, and treatment approaches. Despite this, the morbidity and mortality from infection remains unacceptably high, and more recently a greater emphasis on disease prevention afforded by a variety of vaccines is proving effective in reducing incidence of disease.

Currently, the world is experiencing a switch from a predominant delta variant pandemic to an omicron variant pandemic. In some countries, the peak of the omicron wave has already passed. It is not yet known if omicron will become the "endemic phase" strain.

2.1.3. Aetiology and pathogenesis

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, positive-sense, single-stranded ribonucleic acid (RNA) beta coronavirus causing coronavirus disease-2019 (COVID-19). It was first identified following reports of a cluster of acute respiratory illness cases in Wuhan, Hubei Province, China in December 2019. Genomic sequencing was performed on bronchoalveolar lavage fluid samples collected from patients with viral pneumonia admitted to hospitals in Wuhan, which identified a novel RNA virus from the family Coronaviridae. Phylogenetic analysis of the complete viral genome revealed that the virus, SARS-CoV-2, is part of the subgenus Sarbecovirus of the genus Betacoronavirus and is most closely related (approximately 88% identity) to a group of SARS-CoV-like coronaviruses previously sampled from bats in China.

2.1.4. Clinical presentation, diagnosis

Infection with SARS-CoV-2 may be asymptomatic in ~one third of subjects, depending on age and other factors. Symptomatic infection may range in severity from very mild ranging to fatal. Several factors have been shown or are hypothesised to contribute to the severity of the clinical disease and its outcome.

2.1.5. Management

Once infection is clinically apparent, two antiviral agents are available (approved or under art 5(3)) for treatment in the EU. Some, but not all, of the monoclonal antibodies directed at the spike protein retain activity against the omicron variant.

2.2. About the product

Molnupiravir is a pro-drug that is rapidly converted to N-hydroxycytidine (NHC) after oral administration. NHC then requires phosphorylation to NHC-TP in host cells to form the active moiety, which interferes with viral replication.

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as hard capsules containing 200 mg of molnupiravir as active substance.

Other ingredients are:

- Capsule content: croscarmellose sodium (E468), hydroxypropyl cellulose (E463), magnesium stearate (E470b), and microcrystalline cellulose (E460).
- Capsule: hypromellose (E464), titanium dioxide (E171) and red iron oxide (E172)
- Printing ink: potassium hydroxide, shellac and titanium dioxide (E171)

The product is available in HDPE bottles with a polypropylene closure.

2.3.2. Active Substance

General information

The chemical name of the active substance is {(2R,3S,4R,5R)-3,4-dihydroxy-5-[(4Z)-4-(hydroxyimino)-2-oxo-3,4-dihydropyrimidin-1(2H)-yl]oxolan-2-yl}methyl 2-methylpropanoate corresponding to the molecular formula $C_{13}H_{19}N_3O_7$. It has a relative molecular mass of 329.31 g/mol and the following structure:

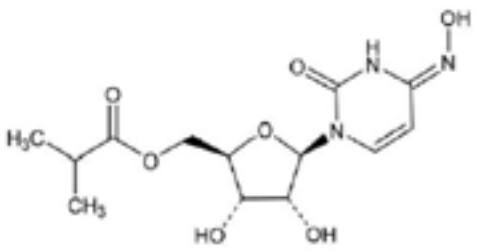

Figure 1: Active substance structure

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The chemical structure of the active substance was elucidated by a combination of UV spectroscopy, ATR FTIR spectroscopy, ^{1}H-NMR, ^{13}C-NMR, and MS.

The active substance is a non-hygroscopic white to off-white powder freely soluble in methanol and soluble in water.

Molnupiravir has four chiral centres. The specific rotation of molnupiravir was measured and has an optical rotation value of -8.4^{o}. The chiral purity is determined by the starting material and is routinely controlled in the specifications of the same.

Molnupiravir manufactured by the process described in this application is crystalline (predominantly Form 1) as determined by XRPD.

Manufacture, characterisation and process controls

There are several manufacturing sites proposed for the active substance.

Data has been provided for all active substance sites, consistently meeting the specifications.

The manufacturing process is provided and incorporates one starting material (SM) and several chemical transformations. The active substance is synthesised in 5 main steps.

A detailed justification of the staring material (SM) designation is provided and can be accepted, as steps before the SM do not affect the active substance impurity profile. Details of suppliers and synthetic routes of the SM have been provided and considered satisfactory. The staring materials specifications are acceptable and include control of chiral impurities.

A series of PARs are proposed for each step of the process. The applicant has justified that the ranges have been investigated and no detrimental trends for quality have been observed. This is considered satisfactory.

The overall process is unchanged from earlier stages of development, with only minor changes in reagents and additions. A significant number of batches using the commercial process across a range of batch sizes have been produced, which assures that the process is well-understood and under control. Similarly, the discussion provided on CQAs and the risk assessment is logical and acceptable. The applicant has laid out the parameters investigated during PAR studies.

Packaging comply with the EC 10/2011 as amended. The specifications are acceptable.

Specification

The active substance specification includes tests for appearance (visual), identification (IR, HPLC), assay (HPLC), impurities (HPLC), residual solvents (GC), and water content (KF).

Specifications were established based on ICH guidelines, batch analysis data, safety assessment, development studies, and stability studies. Graphical representations of batch data are provided. The applicant has provided a justification of the proposed limits.

The analytical methods are suitably described and validated.

The provided batch data demonstrates that the active substance is being manufactured to a consistent quality at each site (and using earlier processes). The data support the process being under control.

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Stability

Stability data from a number of commercial scale batches of active substance from the proposed manufacturers stored in the intended commercial package for up to 12 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* appearance, water content, assay, impurities, identity, chiral purity, x-ray powder diffraction, and particle size distribution. The analytical methods used were the same as for release and were stability indicating.

No out-of-specification (OOS) results or trends have been observed under long term and accelerate conditions.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable.

2.3.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is supplied as a reddish brown (Swedish Orange) opaque capsule with corporate logo and "82" printed with white ink. Each capsule has overall closed length of approximately 21.70 mm and maximum external diameter of approximately 7.64 mm.

The primary strategy of the molnupiravir development program was to rapidly develop a physically and chemically stable solid oral dosage form with the intended biopharmaceutical properties consistent with the quality target product profile (QTPP). The safety and efficacy were used to inform the dosage form design, primary packaging design, and critical quality attributes (CQAs) selection.

The safety and efficacy considerations defined the QTPP, were used to guide decisions on the dosage form selection and formulation performance.

Selected QTTP categories were translated into product CQAs. These CQAs were used to aid in risk assessments made during development.

Prior knowledge is mentioned in different aspects during the pharmaceutical development.

Active substance physicochemical and biopharmaceutical properties were evaluated. Relevant physicochemical and biopharmaceutical properties of the active substance have been identified and are adequately controlled. Active substance attributes that may affect the finished product critical quality attributes have been evaluated.

Excipients were selected to provide a chemically and physically stable formulation with the intended biopharmaceutical properties as well as appropriate process robustness. All excipients are of compendial grade with the exception of printing ink, which is comprised of compendial ingredients. Molnupiravir has been shown to be compatible with the excipients/capsule shell in the proposed commercial formulation. Standard excipients are used in quantities and functions typically seen for oral solid dose products, taking into account the pharmaceutical form and method of manufacture. There are no novel excipients used in the finished product formulation.

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The impact of compositional changes on in process granule attributes and finished product quality attributes was evaluated, and outputs used to define the final composition. No overages are used.

Dissolution method development was presented, and the final dissolution method has been adequately justified. Nevertheless, the proposed method is acceptable.

The objective of the manufacturing process development program was to develop a process to produce a finished product that reproducibly meets predetermined acceptance criteria as developed by the Quality Target Product Profile and the products critical quality attributes as provided. This objective was accomplished through experimentation to identify linkages between process variables (raw material attributes, process parameters, in-process material attributes) and process outputs (finished product quality attributes) as well as through scale-up and stability studies. The knowledge gained for the identified linkages was used to develop an effective control strategy which is comprised of controls for in-process materials, process parameters, and environmental conditions along with finished product specifications to ensure the product meets all critical quality attributes.

A robust finished product manufacturing process has been developed through a systematic risk based development program. The manufacturing process has been demonstrated through various development scales, including the intended commercial scale at the intended commercial manufacturing site(s). The manufacturing process has been deemed robust and is suitable for the manufacturing of the intended commercial finished product.

Principles consistent with ICH Q8, Q9, and Q10 were used during development, including a target product profile to guide development and the use of quality risk management. Manufacturing process development is split into several sections, each one representing a unit operation in in the manufacturing process. Experimentation to identify linkages between process variables and process outputs, as well as scale-up and stability studies was performed. Impact on CQAs assay, dissolution and degradation were studied using DOEs. From this, provisional Proven Acceptable Ranges (PARs) were defined.

Although all unit operations have been studied, for which extensive information is presented. Based on outcomes from the manufacturing process development (typically) performed at lab, pilot and commercial scales, control strategies for each unit operation have been derived. Of note, are the large number of PARs proposed, a number of which have been derived at pilot scale.

The control strategy proposed for the development of the finished product includes proven acceptable ranges (PARs) for the control of process parameters, and in process controls. Some elements of ICH Q8-Q11 were utilised. The control strategy was developed to achieve a manufacturing process that consistently provides a final product meeting product CQAs and includes process parameter controls per the established proven acceptable ranges and the in-process controls. Overall, the manufacturing process development program has confirmed that the proposed unit operations have been shown to be appropriate for the product in question.

The primary packaging is HDPE bottles with a polypropylene closure. The material complies with Ph. Eur. and EC requirements. The container closure system has been adequately justified, as have the microbiological attributes. Compatibility is not relevant for oral solid dose products.

Manufacture of the product and process controls

The finished product is manufactured by a number of manufacturing sites. The manufacturers and their activities are defined, and it is confirmed that the manufacturers operate to GMPs.

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The manufacturing process consists of 7 main steps.

Initial PPQ batches have been manufactured, and all process validation acceptance criteria are stated to have been met. A formal validation of the complete finished product manufacturing process will take place prior to the release of the finished product to the market from that production facility. Critical process parameters have been defined. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual), identity (UV, HPLC), assay (HPLC), degradations products (HPLC), uniformity of dosage unit (Ph. Eur.), dissolution (HPLC) and microbiological quality (Ph. Eur.).

The proposed specification is generally acceptable. The proposed tests and acceptance criteria in the specification for molnupiravir capsules have been established based on current manufacturing experience, release and stability batch data, and the applicable guidelines.

A specification for water content is not included in the release specification of molnupiravir capsules. The water content level has no impact to any of the other critical quality attributes. Therefore, the product is expected to maintain stability throughout the proposed shelf life.

A satisfactory discussion regarding impurities was provided, covering organic impurities and inorganic impurities. Generally, acceptable justifications for the proposed specification has been provided, referencing ICH and EMA guidance and batch/stability data as appropriate.

The total maximum contribution from all potential sources of elemental impurities in molnupiravir capsules was calculated using the ICH Q3D approach to provide a worst case daily exposure level for each elemental impurity based on a maximum daily dose of 8 x 200 mg of molnupiravir capsules (1600 mg total). as the risk of elemental impurities being present at levels above their PDEs has been established to be negligible via the risk assessment process and supporting analytical data. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed 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). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

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Stability of the product

Stability data from commercial and pilot scale batches of finished product stored under long term conditions (25°C/ 60% RH and 30°C/ 75% RH) are collected in the 30-count 60 cc HDPE bottles and up to 6 months of data are collected in the in the 30-count 60 cc HDPE bottles and up to 12 months of data are collected in the 40-count 60 cc HDPE bottles and 6 months at the accelerated condition of 40°C/ 75% RH according to the ICH guidelines were provided.

Furthermore, 24 months of stability data are collected in the 30-count 60 cc HDPE bottles from the clinical stability study including long term storage condition of 25°C/ 60% RH and 12 months at an intermediate condition of 30°C/ 65% RH, and 6 months at the accelerated condition of 40°C/ 75% RH according to the ICH guidelines were provided.

The batches of the medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for assay, degradation products, description, dissolution, moisture, water activity and microbiological quality tests. The analytical procedures used are stability indicating.

No significant changes in any of the critical quality attributes were observed at any storage condition.

A bulk hold time stability study was performed. No significant changes were observed.

Based on available stability data, the proposed shelf-life of 30 months without any special storage conditions are acceptable.

Post approval change management protocol(s)

A process validation scheme has been submitted and is generally acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

The applicant has applied QbD principles in the development of the active substance and/or finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

The CHMP identified issues which have not been fully addressed by the applicant during the assessment These issues are not considered to have an impact on the benefit risk balance but should be considered in case of any future development.

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2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way and there are no unresolved quality issues which might have negative impact on the benefit/risk balance.

2.3.6. Recommendation(s) for future quality development

Not applicable.

2.4. Non-clinical aspects

2.4.1. Introduction

2.4.2. Pharmacology

Molnupiravir (MOV), which is also referred to as MK-4482 and EIDD-2801 throughout the non-clinical dossier, is the 5′-isobutyrate prodrug of a broadly active, antiviral ribonucleoside analogue, N-hydroxycytidine (NHC; also referred to as EIDD-1931), developed for the oral treatment of adult patients with COVID-19. MOV is hydrolysed by esterases either during or after absorption to deliver NHC into systemic circulation. Once distributed inside cells, NHC is phosphorylated to its corresponding triphosphate anabolite (NHC-TP; also referred to as EIDD-2061) and acts as a competitive alternative substrate for virally encoded RNA-dependent RNA polymerase (RdRp). Owing to the ability of the N4-hydroxycytosine base of NHC to tautomerise, NHC-TP can pair with either guanosine or adenosine, and consequently can substitute for either Cytidine Triphosphate (CTP) or Uridine Triphosphate (UTP), respectively. This results in an accumulation of mutations in the viral genome with each cycle of viral replication, referred to as an error catastrophe mechanism of action, which inhibits viral replication by increasing the viral mutation rate beyond a threshold where the virus can replicate, leading to viral extinction.

2.4.2.1. Primary pharmacodynamic studies

NHC was shown to dose-dependently reduce viral titres of murine hepatitis virus (MHV, EC_{50} =0.17 μM) and Middle East respiratory syndrome CoV (MERS-CoV, EC_{50} = 0.56 μM) infected cells, via specific antiviral activity that was not a result of cytotoxicity in Vero cells (selectivity index >1000 and >20 respectively). NHC inhibited MHV replication in the early stages of the viral replication cycle (≤6h post-infection) with a 10-fold reduction in RNA, and a 5000-fold reduction in viral titre at the highest concentration tested, consistent with a mutagenic mechanism of antiviral activity. In addition, full-genome next-generation sequencing on viral populations revealed a dose-dependent accumulation of transition mutations (Agostini et al, 2019).

Similarly, in-vitro data from Venezuelan equine encephalitis virus (VEEV) infected Vero cells also demonstrate that NHC is a potent antiviral agent (EC_{50} < 1μM) independent of cytotoxicity (CC_{50} > 200μM). NHC caused a significant reduction in infectious virus titres, although the antiviral effect was strongly time-dependent, being most effective when applied early in the viral replication cycle (≤4h post-infection). The primary antiviral effect of NHC was again demonstrated to be based on potent RNA-mutagenic activity, with 2 μM NHC

inducing at least a 10-fold increase in accumulation of mutations in VEEV G RNA within a single passage. In addition, in the presence of NHC, VEEV-infected cells produced 10- to 20-fold fewer G RNA-containing viral particles and the mutated virions released were mostly incapable of replication (Urakova et al, 2018). This error catastrophe mechanism of action is also demonstrated *in vitro* in influenza A virus (IAV) infected cells, with deep sequencing used to demonstrate a lethal viral mutagenesis as the underlying mechanism of activity (Toots et al, 2019).

Importantly, the antiviral activity of NHC against SARS-CoV-2 was also reported in multiple cell types (including Vero E6, HuH-7, Calu-3 lung epithelial cells and A549-ACE2 cells), with EC_{50}s in the sub- to low-µM range. These literature data again support specific antiviral activity of NHC against SARS-CoV-2, with CC_{50} values all above the IC_{50} values and selectivity index values between 1.24 and >130 depending on the cell line used.

Regarding the potential development of resistance to NHC*,* while other mutagenic nucleoside analogue antivirals have been ineffective at potently inhibiting CoVs due to the proofreading capabilities of viral 3'-5' exoribonuclease (ExoN), NHC was shown to decrease the titres of both WT and ExoN(-) MHV in a dose-dependent manner. There was a minimal difference in sensitivity, suggesting that NHC potency is only marginally affected by ExoN proofreading activity. In addition, to further assess the potential development of resistance to NHC, MHV and MERS were passaged 30 times in the presence of NHC, revealing only low-level acquired resistance (~2-fold increase in EC_{90}), suggesting a high genetic barrier to resistance (Agostini et al, 2019). Furthermore, only low levels of resistance to NHC developed in VEEV-infected Vero cells, with a more efficient cytopathic effect developing only after 15 passages in the presence of NHC. The authors suggest an NHC drug-resistance phenotype requiring acquisition and cooperative function of multiple mutations (Urakova et al, 2018).

In vitro data from the literature also demonstrate the antiviral activity of NHC against remdesivir-resistant coronavirus. An approximately 6-fold resistance to remdesivir was conferred by two mutations in the CoV RdRp, F476L and V553L (Agostini et al, 2018). RdRp sequences are highly conserved amongst CoV, including SARS-CoV-2, but these two remdesivir-resistant mutations did not confer cross-resistance to NHC. Instead, an increased sensitivity to inhibition by NHC was demonstrated in an in-vitro replication assay (Sheahan et al, 2020). Indeed, the authors suggest that NHC and remdesivir may select for exclusive and mutually sensitising resistance pathways. In agreement with this study, while the remdesivir IC_{50} was increased 2- to 2.5-fold against remdesivir-resistant mutant Rem2.5p13.5, the MOV IC_{50} was very similar to its IC_{50} against SARS-CoV-2Engl2 (Szemiel et al, 2021). Equally, in a non-infectious SARS-CoV-2 reporter replicon assay, NHC was similarly active (EC_{50} values <1.6-fold) against remdesivir resistance-associated variants in the NSP12 (polymerase) protein (NSP12-F480L, NSP12-D484Y, NSP12-V557L, NSP12-E802A, NSP12-E802D) (He et al, 2021).

Importantly, the antiviral activity of NHC against SARS-CoV-2 variants of concern, B.1.1.7 (Alpha), B.1351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta) was evaluated in Vero E6 cells using a cytopathic effect (CPE) assay and compared to WA1 (USA-WA1/2020) isolate (PD010). NHC was similarly efficacious against all variants tested with IC_{50} values of 1.59 µM, 1.77 µM, 1.32 µM and 1.68µM reported for Alpha, Beta, Gamma and Delta variants respectively, compared with 1.41 µM for WA1. In addition, in a study to evaluate the antiviral activity of NHC on MOV treatment-emergent NSP12 and NSP14 (exonuclease) variants, observed in NP swab samples from 3 or more participants who had received MOV in Phase 2 studies, NHC was found to be similarly active against all replicons tested (NSP12-T739I, NSP14-A220S, NSP14-A220T, NSP14-A220V, NSP14-S503L, and NSP14-S503; EC_{50} values <1.6-fold) (PD011).

Additional data was subsequently provided by the applicant regarding the *in vitro* antiviral activity of NHC against SARS-CoV-2 Omicron variants BA.2, BA.4 and BA.5 in the CPE assay and compared to WA1 (Study reports PD017, PD018 and PD020 respectively). NHC was shown to have similar antiviral activity against BA.2, BA.4 and BA.5 isolates compared to the original WA-1 isolate. The applicant also provided additional data reporting similar *in vitro* NHC activity in a SARS-CoV-2 reporter replicon assay against SARS-CoV-2 replicons with amino acid substitutions in nsp12 (polymerase), nsp13, and nsp14 (exonuclease), (EC50 fold change ≤1.4 compared to the Wuhan sequence replicon; Study report PD019).

NHC exhibited low cytotoxicity (CC_{50}) in a range of mammalian cell lines, with values in the range of 7.5μM to >100μM reported from the literature, demonstrating good selectivity index for antiviral effects (EC_{50} = 0.32 μM to 2.66 μM). CC_{50} values are also reported from a sponsor-conducted study, with some overlapping cell lines evaluated in both. While the reported cytotoxicity of NHC in Huh7 cells is in good agreement between both literature and sponsor conducted data (CC_{50} =165.5 μM vs >100 μM), there is a discrepancy between cytotoxicity reported for CEM cells (7.5 μM vs >100 μM) from the literature data vs the sponsor conducted study (PD009). The reason for this discrepancy is unknown but may be due to potential differences in CEM cell lineage or passage number, source of NHC and concentration ranges used. Overall, the cytotoxic effect of NHC and MOV in the cellular models assayed was low with good selectivity index against SARS-CoV. In addition, NHC demonstrated poor efficiency at incorporating into mitochondrial RNA, suggesting that it does not result in toxicity or dysfunction of mitochondria *in vitro*. MOV inhibited erythroid and myeloid progenitor proliferation with MOV IC_{50} values of 24.9 and 7.7 μM respectively, but no hematologic effects indicative of bone marrow toxicity were noted in clinical trials.

In vivo, MOV 500 mg/kg was shown to significantly reduce infectious SARS-CoV-2 levels in lung tissue from infected Lung only Mice (LoM) when treatment was initiated 12hr pre-infection and 24 or 48 hrs post-infection, although antiviral activity was decreased when treatment initiation was delayed to the 48hour post-infection time point (Wahl et al, 2021).

The ability of MOV to mitigate SARS-CoV-2 infection and block transmission was examined in an *in vivo* ferret model of intranasal infection with 1×10^5 pfu of SARS-CoV-2 (Cox et al, 2020). Treatment of infected ferrets with MOV twice daily via oral gavage (either 5 or 15 mg/kg BID starting 12 hours post-infection, or 15 mg/kg BID starting 36 hours post-infection) significantly reduced the SARS-CoV-2 viral load in the upper respiratory tract within 12h of treatment initiation, although viral RNA was still detectable. When treatment was initiated at 12hr post-infection, infectious particles were undetectable within 24hrs of starting treatment. When treatment was initiated at the peak of virus replication (36 hr post-infection), complete suppression of the release of infectious particles took longer, i.e., 36 hrs, while vehicle control animals continued to shed infectious particles until study end.

In a second study to examine the impact of MOV treatment on viral transmission, ferrets were infected and treated with 5 mg/kg MOV twice daily or vehicle starting 12 h post-infection. After 30 h, each ferret was co-housed with 2 uninfected ferrets. The contact ferrets of vehicle-treated animals began to shed SARS-CoV-2 within 24 h of co-housing, but no infectious particles or RNA were detected in the contacts of ferrets that had been treated with MOV (Cox et al, 2020).

In a study investigating the effect of oral MOV on SARS-CoV-2 replication in a Syrian hamster model of SARS-CoV-2 infection and disease, the applicant reports that MOV prophylactic (12 or 2 hr pre-infection) or therapeutic (12 h post-infection) treatment showed decreased viral RNA titres and infectious virus from lungs several days post-infection (Rosenke et al, 2021). However, while both prophylactic and therapeutic treatment with MOV decreased the infectious titre ($TCID_{50}$) in lung tissue, the reported decreased viral RNA titre is statistically significant only in lung tissue from the prophylactic treatment group. In addition, viral

shedding as measured by RT-PCR or $TCID_{50}$ from oral swabs decreased from days 2 to 4 post-infection as a function of time, a result of the transient nature of SARS-CoV-2 infection in this model. MOV treatment had no effect on viral shedding by these measures. In contrast, MOV treatment (200 mg/kg BID) in Syrian hamsters infected with 1×10^5 $TCID_{50}$ units of the B.1-G (Wuhan strain), B.1.1.7 (Alpha) or B.1.351 (Beta) variants of SARS-CoV-2, induced statistically significant reductions in viral RNA copies per mg of lung tissue and in infectious virus lung titres regardless of variant (Abdelnabi et al, 2021).

In summary, the *in vivo* proof of concept studies consistently support the antiviral activity of molnupiravir, as demonstrated by reduced infectious lung titres in multiple SARS-CoV-2 infection models (LoM, ferret, hamster). In addition, data from the ferret coronavirus infection model support the ability of molnupiravir to suppress viral transmission in a relevant non-clinical model.

2.4.2.2. Secondary pharmacodynamic studies

Both MOV and NHC were tested for potential secondary pharmacodynamics activity *in vitro* against a panel of 108 enzymes, receptors and ion channels, up to a maximum concentration of 10μM, with ≥50% inhibitory activity considered significant and reported at only one target, human COX-2. For MOV, a follow-up dose-response assay reported an IC_{50} of 6.33μM against COX-2, which is not considered clinically relevant given an anticipated clinical MOV C_{max} of 0.26μM at the 800 mg BID dose. However, there is a very small margin (~1.4-fold) from the reported NHC IC_{50} against COX-2 (15.1μM) to anticipated clinical C_{max} (10.8μM), suggesting the potential for COX-2 inhibition at clinically relevant concentrations, although there are no findings suggestive of potential secondary effect of COX-2 inhibition in the safety pharmacology and repeat-dose toxicity studies conducted in rats at dogs at NHC C_{max} values 16-fold and 5-fold the clinical C_{max} respectively.

2.4.2.3. Safety pharmacology programme

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. *In vitro* hERG assays were conducted with both MOV and NHC applied to HEK cells stably expressing the hERG channel. Greater than 50% inhibition of the hERG current was not achieved in either study at the concentrations of test-article applied. The molnupiravir IC_{50} was estimated at > 30 μM, and the NHC IC_{50} at > 300μM, 1000-fold and 28-fold greater than the respective clinical C_{max} at the 800mg BID dose, supporting a low potential for inhibition of IKr and QT prolongation associated with both molnupiravir and NHC at clinically relevant concentrations.

For the *in vivo* safety pharmacology studies, no TK parameters were included but NHC C_{max} values were extrapolated from 28-day TK studies in rats and dogs. Exposure margins are expressed based on population pharmacokinetics analysis in adult patients with COVID-19 from P001 and P002 clinical trials (Part 1), where a 800 mg BID molnupiravir dose resulted in an NHC C_{max} of 10.8 μM.

The CNS and respiratory safety pharmacology studies were conducted in male Sprague Dawley rats and no test-article related findings are reported. A single dose no observed effect level (NOEL) of 500 mg/kg for neuropharmacological, body temperature and respiratory changes in male rats is reported, associated with NHC exposures 16-fold higher than the anticipated clinical C_{max}. Two CVS safety pharmacology studies were conducted in conscious telemetered beagle dogs and no test-article related findings are reported. A NOEL at

the highest dose tested of 17 mg/kg is reported from the first study, associated with a 1.4-fold margin to the anticipated clinical C_{max}, providing minimal reassurance of safety. However, the second CVS safety pharmacology study also reported no test article-related effects on any BP parameters, HR, ECG parameters, QT-related parameters or body temperature following single oral dosing at 50mg/kg. This dose level was reportedly chosen based on previous PK and TK studies in dogs and on expected exposure margin to clinical C_{max}. Extrapolation from the same available TK data gives a 5-fold margin from the dog NOEL to the anticipated clinical C_{max}.

2.4.2.4. Pharmacodynamic drug interactions

The antiviral activity of NHC against SARS-CoV-2 was evaluated *in vitro* by measuring the reduction of the SARS-CoV-2 cytopathic effect on infected Vero E6 cells. The antiviral activity of lamivudine (3TC), abacavir, emtricitabine (FTC), hydroxychloroquine, nelfinavir, remdesivir, ribavirin, sofosbuvir and tenofovir against SARS-Cov-2 was also determined for each compound alone and in combination with NHC across a range of concentrations. NHC, nelfinavir and remdesivir when tested alone demonstrated antiviral activity against SARS-CoV-2 with EC_{50} values of 1 µM, 0.7 µM and 1.7 µM, respectively. Cytotoxicity in Vero E6 cells was also measured in parallel, in uninfected cells, to quantify compound toxicity. No cytotoxicity was reported for any compound tested (CC_{50} >20 µM) with the exception of nelfinavir, which was cytotoxic at high concentrations (CC_{50} = 11 µM). Neither synergy nor antagonism was observed for anti-viral activity *in vitro* against SARS-COV-2 between NHC and the other agents tested, supporting a lack of relevant pharmacodynamics drug interactions between NHC and any of the other anti-viral compounds tested.

2.4.3. Pharmacokinetics

A nonclinical pharmacokinetic program was carried out to evaluate the ADME properties of MOV and the nucleoside NHC. Pharmacokinetic studies were conducted in mice, rats, dogs, monkeys and ferrets, as well as the distribution and exposure of NHC-TP in tissues. Interspecies comparison of metabolism, excretion and plasma protein binding was also conducted. In addition, MOV and NHC were evaluated as a substrate, inhibitor, or inducer of various metabolizing enzymes and transporters.

For toxicokinetic studies in mouse, rat, rabbit, dog, and monkey, the MOV and NHC concentrations in plasma and tissue samples were determined using protein precipitation followed by LC-MS/MS methods. The LLOQ of MOV GLP plasma assays ranged from 1.0 to 10 ng/mL and the ULOQ ranged from 100 to 10,000 ng/mL. The LLOQ of NHC GLP plasma assays ranged from 5.0 to 20 ng/mL and the ULOQ ranged from 5000 to 20,000 ng/mL. Inter-run accuracy of QC samples ranged from 6.4% to 9.0%, and precision ranged from 1.7% to 13.7%.

For metabolite profiling, the total radioactivity in plasma, urine, and faeces samples was determined by liquid scintillation counting (LSC). Bioanalytical methods were developed to analyse levels of MOV, NHC, NHC-MP and NHC-TP in a variety of tissues and cells. Samples are prepared via extraction with 70% acetonitrile and their metabolite concentrations are determined via LCMS-MS.

Absorption

MOV is a 5′-isobutyrate ester prodrug cleaved by esterases present in the intestine and liver during absorption/hepatic first pass, delivering the nucleoside metabolite NHC into systemic circulation, as a result only very low levels of MOV was detected in plasma. MOV is efficiently absorbed in mice after oral feeding and converted to NHC generating high levels of NHC in animal plasma. The oral bioavailability of NHC in mice

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is 37-45%. MOV when orally administered in rats and dogs was well absorbed and resulted in high bioavailability of NHC, and significantly improved the oral exposure to NHC in monkeys when compared to oral administration of NHC itself. The bioavailability of NHC after an oral dose of MOV in rats and dogs was 52% and ≥77%, respectively. MOV generally provided dose-proportional exposures of NHC in all preclinical species after oral dosing.

Distribution

MOV, NHC, and NHC-TP were quantified in major tissues (lung, spleen, kidney, liver, heart and brain) from mice, rats, dogs, monkeys and ferrets following single or multiple oral doses of MOV (exposures in bone marrow were also assessed in rats). In general, MOV was either not detected or was near the detection limit in any tissue. NHC and NHC-TP were observed in all tissues and their exposures were generally dose dependent. In most species, NHC-TP typically had the highest exposures in lung and spleen, and the lowest levels in brain. In most studies brain, spleen, lung, kidney, liver and heart only were examined. Monkey study report PK013, and dog study report PK068, have tissue collection tables listing other tissues not reported on by the applicant, such as, and not limited to, bone marrow, intestine, testes, skeletal muscle and trachea (PK068). The applicant clarified that the distribution study was performed prior to the toxicology study, and no retrospective analysis of other tissues collected was performed. The applicant considers that the tissues selected for bioanalysis were the major organs pertinent for viral indications at the time of the distribution study.

Whole body autoradiography distribution studies were not performed as the applicant considers a QWBA of a little interpretative value based on the metabolism and distribution of MOV.

The diverse tissues where NHC and NHC-TP have been measured do not suggest very significant differences in NHC metabolite exposure. Along with the expectation that pyrimidine uptake and metabolism is ubiquitous among cell types, these data suggest large differences in exposure in tissues where NHC and NHC-TP were not measured is unlikely.

However different patterns of distribution in tissues have been reported, including accumulation in the liver at 2000 mg/kg/day in the repeat dose studies, but distribution has not been investigated in all tissues. Given the concerns in terms of potential toxicity, the absence of this analysis at extended time points in relevant organs (i.e. bone marrow and testes) is not justified.

The applicant has advised that a tissue pharmacokinetic study to measure NHC and NHC-TP levels in testis has been initiated with a final report due by 31st March 2022.

The applicant submitted the study; TT#22-1003: Exploratory 14-Day Oral Tissue Distribution and Toxicokinetic Study in Fischer 344 Rats.

Male rats were dosed daily with 500 and 750 mg/kg NHC for 14 days. A justification was provided for the dose levels, 500 mg/kg/day, as it was the highest dose used in the previous in vivo mutation assay at the cII Locus in Big Blue® transgenic F344 rats. The high dose, 750 mg/kg/day, was included per Health Authority's recommendation. Male rats were dosed daily for 14 days. Both NHC and NHC-TP were detected in the testes of rats in all MK-4482-treated groups at 3 and 24 hours after MK-4482 dosing on Study Day 14. Mean plasma NHC AUC0-24hr and C_{max} values on Study Day 14 were approximately dose proportional in male F344/NHsd rats. NHC and NHC-TP were detected in the testes of rats in all MK-4482-treated groups at 3 and 24 hours after MK-4482 dosing on Study Day 14, with concentrations that increased in a dose-related manner.

The protein binding of NHC in CD-1 mouse, SD rat, beagle dog, cynomolgus monkey, and human plasma, and in human alpha1-acid glycoprotein and human serum albumin was measured. The unbound fraction of

NHC was approximately 1 in all matrices and at all concentrations tested. The plasma binding of MOV was not assessed since it is not stable in plasma.

Metabolism

The *in vivo* metabolism of MOV was studied in male BDC Wistar Han rats and male intact beagle dogs following oral administration of [^{14}C]MOV. In BDC rats, the uridine metabolites uracil and 3-ureidopropionic acid were the major metabolites in urine, along with small amounts of cytidine, NHC, a glucuronidation metabolite of NHC, and a methylation metabolite of NHC. Uracil was also the major metabolite detected in rat faeces, with a small amount of 3-ureidopropionic acid. Cytidine, uridine and 3-ureidopropionic acid were the major drug-related components in rat plasma (53, 21 and 14% of the radioactivity), with small amounts of uracil and NHC (each <10% of radioactivity). In intact dogs, the hydrolysis metabolite of MK-4482, NHC, was the major metabolite in urine. Similarly, NHC was the major circulating component in dog plasma at 2 h post dose (96% of the radioactivity) with a small amount of cytidine and a trace amount of MK-4482 detected. The majority of the radioactive dose was retained in the body, with 54% recovered from the animal carcasses. The low recovery in faeces (6.8%) indicates MOV-related radioactivity was well absorbed in rats, likely >90%. Some release of [^{14}C]-labelled CO_2 is also anticipated to have occurred in these studies because of metabolism of [^{14}C]MK-4482 to uracil and/or 3-ureidopropionic acid which are known to be further metabolised to release CO_2.

In humans administered 100 mg or 800 mg BID, N-Hydroxycytidine (NHC), cytidine, uridine, and NHC-glucuronide were all detected in urine from both dose groups with exposures that increased in an approximate dose-dependent manner. Overall, these data are consistent with the expectation that the majority of the MOV-related dose in animals and humans is converted to NHC, NHC-TP, and (or ultimately to) uridine and/or cytidine which then mix with the endogenous nucleoside pool.

MOV was relatively unstable in mouse, rat, and monkey plasma (all t½ ≤0.4 hr), while more stable in human and dog plasma (t½ 1.05 and 3.2 hr, respectively). MOV was relatively unstable in mouse, rat, dog, and monkey liver microsomes (t½ 0.02 - 0.08 hr) while more stable in human liver microsomes (t½ 1.2 hr). MOV was stable in simulated gastric and intestinal fluids (t½ >24 hr).

NHC was stable when incubated with plasma, whole blood, liver microsomes, and liver S9 extracts and intestinal microsomes from mouse, rat, dog, monkey, and human (t½ all ≥3 hr).

Like other nucleotide analogues, NHC is subjected to phosphorylation to form bioactive triphosphate, which is substrate-competitive with ATP for incorporation by viral RdRp and induction of point mutations with subsequent viral catastrophe.

The conversion of MOV and NHC to NHC-TP was demonstrated in a variety of cell lines and primary cells.

The applicant discussed anabolic pathways where MOV and/or NHC are taken up by all tissue culture cells tested and converted to the pharmacologically active NHC-TP. Different cell types when treated with 10-20 µM NHC (concentrations similar to the clinical C_{max} observed of 10.8 µM) convert NHC to NHC-TP at different rates with large differences in C_{max} and T_{max} achieved. For example, A549 cells C_{max} = 1866.5 pmol/10^6 cells, T_{max} = 24 h, CEM cells C_{max} = 158.4 pmol/10^6 cells, T_{max} = 1 h. In primary cells, concentrations of NHC-TP in primary lung cells were significantly higher than in primary hepatocytes. The intracellular stability (t½) of NHC-TP was 4-5 hr in human astrocytes and hBTEC, and it was significantly less (0.4-1.1 hr) in primary hepatocytes. Of note, poor conversion of NHC/1931 to NHC-TP/2061 occurred in primary mouse hepatocytes. Studies PK047 (2017) and PK048 (2018) are very similar, both report protocols state that they used Primary Bronchial/Tracheal Epithelial Cells treated with 20 µM of EIDD-1931. However, in PK047 there appears to be

incomplete conversion of 1931 to 2061, with more of 2871, the mono-phosphate (MP), being produced (Figure 1 in the study report), whereas in PK048 there is very little of the MP generated with almost all 1931 converted to 2061 (Figure 1 in the study report). The applicant has clarified that the results obtained in PK047 are generally inconsistent with the conversion of NHC to NHC-TP observed in other assays, and that the results of PK048 are more in line with expectations. PK048 was performed after PK047, and the data from this study is to be considered to supersede the data in PK047. This can be accepted.

In addition, from a nonclinical point of view, the conversion rate of NHC to NHC-TP is not described. The applicant was asked to provide a more thorough description of the NHC to NHC-TP conversion mechanism. In response the applicant has provided the conversion rate for NHC to NHC-TP in three species: rat, dog and human (report PD012MK4482). In this new report, the conversion rate is described to be dose-dependent and conversion activity has been shown even at 24 hours (it should be noted that Nonclinical Study Report PD012 was not found in the documentation initially provided by the applicant). Dog and human data showed a more similar profile than that of rats, in which NHC-TP levels were much higher than for human and dog species. This difference could have explained the different ratio of NHC/NHC-TP observed in rats and dogs. However, the data provided by the applicant related to NHC conversion to NHC-TP are not in line with the data showed in the PK section of the initial submission (4.2.2 7-day repeat dose, tissue distribution of NHC and NHC-TP in rats or dogs after repeat dose of MOV). In the PK studies (tables 2.6.4; 10 and 12), rat samples analysis showed higher levels of NHC than NHC-TP, whereas dog samples exhibited higher concentration of NHC-TP than NHC.

The applicant clarified that the tissue concentrations of NHC and NHC-TP are determined by a number of factors, including uptake rates of NHC from plasma via nucleoside transporters, metabolism by cellular enzymes to uridine and/or cytidine (elimination), anabolism to the mono-, di-, and triphosphates, as well as catabolism of the triphosphate back to NHC. As such, any differences in these rates would affect the metabolite levels and/or ratios, it is not unanticipated that in vitro metabolism data do not completely reflect in vivo metabolism. In addition, larger species tending to have longer intracellular NHC-TP half-life.

Table 2.6.2:9 in the Pharmacology written summary references Sticher et al [Ref 05JF0B, Table 1 and Supplemental Table 1] who report cytotoxicity CC_{50} values of NHC for A549 cells of 46 µM, CEM cells of 7.5 µM, HepG2 cells of 42.3 µM, Huh-7 cells of 165.5 µM, PC3 cells of 267.1 µM and Vero cells of 53 µM. NHC was used at 100 µM, in A549 cells, CEM cells and Vero cells, the applicant was asked to discuss the reliability of these *in vitro* results considering the CC_{50} values reported for NHC in these cell lines. The applicant considers that even though the potential for cytotoxicity to occur at the highest concentration tested in CEM, A549 and Vero cells, both NHC and NHC-TP increase in a generally dose-proportional manner relative to NHC and NHC-TP formed at lower non-cytotoxic concentrations. Other cell lines tested below the CC_{50} also demonstrate that generation of intracellular NHC-TP levels are generally concentration dependent. Because of this, the applicant's argument can be accepted. No cytotoxicity data was provided for NHC in all the primary cell lines tested, namely astrocytes, BTECs and hepatocytes. None of the studies included an assessment of NHC or MOV cytotoxicity (CC_{50}). However, the concentrations used in the primary cell metabolism assays were lower than those used in the cell lines, namely 10-20 µM. In general, in most of the cell lines where data is available, CC_{50} values tend to be mostly > 40 µM. Cytotoxicity does not appear to be a concern in primary cells at the concentrations used.

In primary hepatocytes from male SD rat, male Beagle dog, male Cynomolgus monkey, and mixed gender humans treated with 10 µM [^{14}C]MK-4482, hydrolysis to NHC was the major route of metabolism, and NHC accounted for 56, 73, 86, and 71% of the radioactivity in rat, dog, monkey, and human hepatocytes,

respectively. All metabolites observed in human hepatocytes were also detected in hepatocytes from nonclinical species.

In cycling cells during S-phase, for DNA replication, in all cells the major supply of dNTPs comes from the *de novo* reduction of ribonucleoside diphosphates to deoxyribonucleoside diphosphates by the enzyme ribonucleotide reductase (RNR). Ribonucleotide reduction is a cytosolic process and the potential for reduction of NHC to 2'-deoxy-NHC has not been discussed by the applicant. The potential for this to occur has implications for incorporation of 2'-deoxy-NHC into DNA and the creation of point mutations as discussed by Zhou *et al.* (2021). The applicant was asked to discuss the potential for generation of 2'-dNHC in proliferating cells, if there are any species differences in the generation of this metabolite, and to report if they looked for the generation of this metabolite in any of the pharmacokinetic studies. In response the applicant claimed they specifically looked for the formation of 2'deoxy-NHC when [^{14}C]MOV was incubated with hepatocytes from rats, dogs, monkeys and humans. However, study report PK082, In Vitro Metabolism of MK-4482 in Hepatocytes from Rat, Dog, Monkey, and Human, only details those metabolites present and detected. The investigation as to whether 2'-deoxy-NHC was generated as a result of metabolism of NCH is not noted in either the study report or the PK written or tabulated summaries. An unknown metabolite was detected in dog at 7 minutes in small amounts (1.3%). Study report PK082 (2021) broadly agrees with previously published literature (Hernandez-Santiago et al., (2004), 05JF07) where it was demonstrated that when treated with 10 µM NHC, it is metabolised in the cytoplasm of the liver cells (Huh-7, HepG2 and primary hepatocytes) to NHC-MP, NHC-DP, and NHC-TP; in addition, the different metabolites of cytidine and uridine MP, DP, and TP were also detected. Representative chromatographs in PK082 indicate the presence of NHC, uridine, cytidine, and their monophosphates. There is no indication of any other major metabolites, however there is no discussion in the PK written summary, PK082 study report or in Hernandez-Santiago et al., (2004) of the theoretical generation of 2'-deoxy-NHC or of any investigation into its existence.

The applicant clarified that under the conditions used in PK082 or in Hernandez-Santiago et al., (2004), 2'-deoxy-NHC would be expected to elute in the same region of the chromatogram that NHC and cytidine elute and would be readily detectable by LC-MS/MS. From the radio-chromatograms in study report PK082, and knowing that if present, 2'-deoxy-NHC would be expected to elute in the same region of the chromatogram that NHC and cytidine elute, it is clear that there is no other peak in this region (Figure 2 PK082) and this absence of a peak clearly suggests that 2'-deoxy-NHC was not detected in vivo.

Excretion

The recovery of [^{14}C]MOV-related radioactivity in excreta from BDC rats and intact dogs was low (<13%) indicating that the majority of the dose was retained in the body. The low recovery in rats and dog excreta was anticipated given a major route of metabolism of [^{14}C]MOV *in vitro* was the ultimate formation of uridine and/or cytidine, which *in vivo* would mix with the endogenous nucleoside pools and remain in the body.

Drug-drug Interactions

MOV is hydrolysed to NHC by the high capacity esterases CES1 and CES2. Following the uptake of circulating NHC into cells, host kinases and phosphatases involved in the endogenous pyrimidine nucleoside pathways then anabolise/catabolise NHC to/from NHC-TP. Preclinical *in vitro* and *in vivo* metabolism studies suggest the ultimate route of elimination of MOV/NHC-related material is metabolism to endogenous pyrimidine nucleosides (uridine and/or cytidine). The mitochondrial amidoxime reducing components (mARC1 and mARC2) have been reported to convert NHC to cytidine, and cytidine deaminase readily converts NHC to uridine. *In vitro*, NHC was found to be a substrate of the human nucleoside transporters CNT1, CNT2, CNT3, and ENT2 while MOV was a comparatively weak substrate of CNT1, and neither MOV nor NHC were

substrates of human MDR1 P-gp or BCRP. Based on these data, other drugs are not anticipated to affect the tissue levels of NHC-TP resulting from an oral dose of MOV.

In vitro studies demonstrated that neither MOV nor NHC are inhibitors of major human CYPs (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4). The maximum concentration tested for both MOV and NHC was 100 µM, which is approximately 10-fold the clinical NHC C_{max} (10.8 548µM). Given the lack of plasma protein binding, the concentration range tested was not in accordance with EMA guidance (CPMP/EWP/560/95/Rev. 1 Corr. 2**), which states that for hepatic and renal exposure "*the concentration range should allow determination of a Ki which is ≤ 50-fold the mean unbound C_{max} obtained during treatment with the highest dose.*" This applies to both the parent drug and major metabolites. In addition, if the drug is orally administered and the enzyme studied has pronounced intestinal expression (e.g. CYP3A4), the concentration range should be sufficient for determining a Ki ≤0.1-fold the maximum expected dose taken at one occasion /250 ml, which for an MOV dose of 800mg is calculated as 972µM. Two new study reports [PK088 and PK089], both dated November 2021, were submitted to address CYP inhibition by MOV and NHC. The design of these studies was similar to the previously submitted study PK080, but used an expanded concentration range (7 concentrations between 1.29 µM and 1000 µM). For both MOV and NHC, the IC_{50s} for all CYPs tested were >1000 µM. The concentration ranges used in these follow up studies are in accordance with EMA guidance (CPMP/EWP/560/95/Rev. 1 Corr. 2**), and no potential for inhibition has been identified for any of the 8 CYPs investigated. Therefore, it can be concluded that the potential for CYP inhibition in humans is low and the risk of drug-drug interactions (DDIs) associated with MOV and NHC due to inhibition of CYPs is minimal.

Similarly, studies *in vitro* did not demonstrate inhibition of major human drug transporters (OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2K, MRP2, MDR1 P-gp and BCRP) at MOV or NHC concentrations up to 100 µM. Depending on the transporter studied, in-vivo inhibition of a transporter at a certain site can be excluded if Ki ≥ to 0.1*dose/250 ml, 25*[I]u,inlet,max, or 50* unbound C_{max} (CPMP/EWP/560/95/Rev. 1 Corr. 2**). Therefore, based on the information provided, MOV does not inhibit pre-systemic OAT and OCT transporters (OATP1B1, OATP1B3, OCT1) or P-pg and BCRP. On the other hand, for NHC, it has not been demonstrated that the Ki is greater than or equal to the relevant cut off, except in the case of P-gp and BCRP (see Table 2.6.5.31, Study PK064). The applicant had claimed that concentrations higher than 100 µM were not tested in cellular assays due to the potential for cytotoxicity, and further information on cytotoxicity in relevant cell lines was requested. No additional information was provided; however, the literature reference (Sticher et al., [Ref. 4.3: 05JF0B]) reports a CC_{50} value of 299.8 for MDCK cells, which were used in some of the transporter inhibition studies. Thus, it can be accepted that higher concentrations of NHC (e.g., 300 and 1000 µM) would likely result in cytotoxicity in cellular assays. The applicant has also noted the structural similarity of NHC to endogenous cytidine, and it can be agreed that this minimises the potential for NHC to inhibit human drug transporters. While the observed Ki value (> 100 µM) could be less than the concentrations given for 25*[I]u,inlet,max (600 µM), or 50* unbound C_{maxu}, (540 µM), it is accepted that the potential for NHC to inhibit major human transporters is low, and additional studies are not required.

In vitro studies demonstrated that neither MOV nor NHC are inducers of major human CYPs (1A2, 2B6, and 3A4) [Studies PK065, PK071 and PK072]. The applicant has acknowledged that the range of concentrations used in CYP induction studies is not in accordance with relevant EMA guidance. They cite increased concern in relation to cytotoxicity given that the test article is replenished daily for 3 days and the associated potential for nucleotides to accumulate. As noted above, the structural similarity to endogenous cytidine is acknowledged, and it can be accepted that the potential for CYP induction in humans is low.

2.4.4. Toxicology

As a new chemical entity, the nonclinical toxicology package for molnupiravir has been designed in line with the requirements of ICH M3 (R2) and taking into consideration the proposed treatment period of 5 days duration. The species used for the GLP-compliant pivotal studies included rats, dogs and rabbits. These species are considered appropriate based on their similar PK profiles compared to humans. Furthermore, the pharmacological target of molnupiravir is an exogenous entity and therefore there are no uncertainties related to potential differences in pharmacological activity between species. For some studies, the toxicokinetics of molnupiravir and NHC were measured. Considering the rapid conversion of molnupiravir to NHC and the low levels of molnupiravir measured, exposure margins in the majority of instances have been calculated relative to the NHC levels measured.

2.4.4.1. Single dose toxicity

Single dose toxicities studies were incorporated into preliminary non-GLP exploratory studies in mice, rats and dogs with a top dose utilised in each study of 2000 mg/kg. No mortality was seen in any of the studies. For the study in mice, the animals were dosed directly with NHC and not molnupiravir. In mice, there was evidence of doses of NHC ≥1500 mg/kg not being tolerated, with decreases in food consumption and body weight gain seen in the days after treatment. Similar signs of weight loss and decreased food consumption were seen in rats at the top dose of 2000 mg/kg. In contrast, GI effects were seen at all dose levels in dogs (from 300 mg/kg). Although the studies are not GLP compliant, they provide some limited information in relation to the potential effects associated with overdosing.

2.4.4.2. Repeat dose toxicity

Exploratory 7-day studies, which were non-GLP compliant, were conducted in mice, rats and dogs as Phase B of the studies for which Part A encompassed the single dose studies as discussed above. Mice were administered NHC directly, which was well tolerated up to the top dose of 1000 mg/kg with no test article related effects after 7 days of dosing. In rats the top dose of 2000 mg/kg resulted in decreased body weight, food consumption as well as modulation of haematology counts (RETs, WBC total lymphocytes), clinical chemistry parameters (ALT, AST, ALT, glucose and calcium) and organ weight (spleen, brain, lung, adrenal glands, testes and epididymis). In general, the effects were more pronounced in males than females, which correlated with higher exposure levels in this sex. At 2000 mg/kg, there was a margin of exposure for NHC levels of 91 in males and 61 in females based on AUC and a clinical dose of 800 mg Q12H. In dogs, doses of ≥300 mg/kg/day were not tolerated with decreased activity, emesis, diarrhoea, progressive weight loss and deteriorating physical condition. Decreased absolute lymphocyte counts were seen and dose-responsive changes in the clinical chemistry parameters. Macroscopic observations were observed in the GI tract. The TK measured at 300 mg/kg suggested a margin of exposure of 19-fold. In the 100 mg/kg group, the findings were mostly limited to decreased body weight and food consumption. The margin of exposure for NHC at this dose level was 8.4-fold based on AUC and a clinical dose of 800 mg Q12H.

The pivotal nonclinical repeat dose toxicity studies include 28-day studies in rats and dogs as well as a 13-week study in rats. All of the studies involved daily oral dosing and the 28-day studies included recovery periods of 14 days in rats and 28-days in dogs. However, for the study in dogs the recovery period was more limited for the top dose group because of the toxicity observed, which necessitated the early termination of this group. In addition, a 28-day study with once daily dosing has been completed in mice. As outlined in ICH M3 (R2), for a therapeutic indicated for up to 2-weeks duration, a 1-month study is expected in both rodent

and non-rodent species and therefore the duration of the studies provided is in-line with the expectations for the proposed posology of 5 days treatment. The choice of species used for the studies is considered acceptable taking into account that the pharmacological target is a foreign entity and not exogenously expressed.

In mice, molnupiravir was not associated with mortality or any clinical observations at doses up to 2000 mg/kg/day. The only test-article related effects were decreased body weight gain in males in all dose groups, and at ≥ 700 mg/kg/day in females. The toxicokinetic measurements of NHC for this study were not considered GLP compliant due to bioanalytical assay issues and this fact is covered under the GLP compliance statement of the study. Based on an extrapolation to an additional 7-day study in the same mouse strain, the margin of exposure at the NOAEL of 300 mg/kg is 1-fold. Of note, in the 7-day study no effects were seen on body weight gain.

In the 28-day study in rats, the test article was generally well-tolerated and findings were limited to slightly lower body weights and food consumption for males at the top dose of 500 mg/kg in the initial weeks of treatment. The only other finding of note was increased liver weight at 500 mg/kg, which was not associated with any microscopic findings or changes in any clinical chemistry parameters. In addition, this finding was not seen in the subsequent 13-week study. However, it is noted that increased transaminases have been observed in the clinic. The exposure at this dose level represents a margin of exposure of 7.8 and 4.2 fold respectively for males and females compared to the expected clinical exposure based on AUC at 800 mg Q12H.

The subsequent 13-week study in rats utilised 1000 mg/kg as the top dose group, presumably because of the absence of significant toxicities noted and without including a recovery group. Based on the previous findings, the absence of such recovery groups appears appropriate and in line with the 3Rs. The lowest dose differed between the sexes with 150 mg/kg used in males and 200 mg/kg in females because of expected differences in exposure, which did not materialise. In this study with the extended dosing period much more pronounced effects were seen on body weight, particularly in males at all dose levels and in a dose-dependent manner. The effect was less pronounced in females and only seen at the mid and high-dose groups. The decreases in body weight gain correlated with slight decreases in mean food consumption. Upon necropsy, there were significant alterations in the weight of multiple organs in males at the 1000 mg/kg dose. This was considered secondary to the decreased body weight gain, which can be agreed as the likely cause, and did not correlate with microscopic findings. The most notable findings from the study were effects on cartilage and bone seen at doses ≥ 500 mg/kg. This included increased thickness of the growth cartilage of the epiphysis of long bones and patella. In the femur and tibia at 1000 mg/kg in males, the increased thickness was associated with decreased osteogenesis and decreased trabecular bone in the metaphysis. In addition to these findings in the long bones, alterations of chrondrocyte distribution within the matrix of the cartilage of the trachea were seen in males at doses ≥ 500 mg/kg. Because of the lack of recovery groups, there is no information on the potential reversibility of these findings. Such effects were not seen in the previous 28-day study and therefore the effects may only occur with longer duration of treatment. In addition, the rats used were 5 weeks old at the time of initiation of the 13-week study compared to the 8–9-week-old animals used in the 28-day study, which may also have affected the observations seen. Long-bone growth would be more active in younger rats than in older rats (Zoetis et al, 2003). Furthermore, considering that the proposed indication is for adults only, where the bone growth plates are closed, the findings are likely of limited relevance. The effects seen on the trachea were minimal in nature and did not have any functional consequence. Based on the bone/cartilage findings the NOAEL was considered 150 mg/kg in males (margin of exposure of 0.7-fold) and 500 mg/kg in females (3.3-fold margin of exposure).

Significant toxicities were seen in the 28-day study in Beagle dogs, which necessitated an interruption of dosing in the mid- and top-dose groups of 17 and 50 mg/kg on Days 12/14 and Days 21/22 respectively, due to marked weight loss, inappetence and critical haematology findings. Upon necropsy, the major finding in these groups was discolouration in the GI tract, which was judged secondary to haemorrhaging due to thrombocytopenia. The severity of the macroscopic and microscopic findings appeared to be dose-related. The haematology findings suggested bone marrow changes affecting all haematopoietic cell lines and causing subsequent haematological abnormalities (including total WBC count, lymphocytes, neutrophils, reticulocytes, RBCs and platelets) at doses ≥ 17 mg/kg. The effects on haematopoietic cells worsened with increased duration of treatment, with the most severe effects seen between 14 and 21 days of treatment depending on the dose involved. At the mid dose of 17 mg/kg there was some evidence of reversibility of the bone marrow effects upon treatment cessation. Of note, no effects were seen on bone or cartilage in dogs.

Much more significant toxicity was seen with molnupiravir administration in dogs compared to rats, despite the higher dosing and longer durations of treatment in rats. The basis for such differential sensitivity between species is unclear, however, the applicant suggests that it is unlikely related to differences in exposure or distribution in this species. There are limitations in the secondary pharmacology screen as the maximum concentration use was 10 µM but the anticipated clinical C_{max} is 10.8 µM. The pronounced effects on bone marrow seen in dogs have to date not been seen clinically (see clinical AR) and were not observed in mice, rats, rabbits or monkeys at exposures in excess of that seen clinically and for durations of at least 7-days up to 3-months.

In rats and dogs, the measured molnupiravir levels were typically low and only detectable for a short period of time following oral dosing suggesting its conversion to NHC. Therefore, the focus of the toxicokinetic measurements has been on NHC levels, which can be measured from the plasma and serve as a surrogate for the active NHC-TP that is produced upon intracellular uptake.

In rats, some sex differences in NHC exposure were seen with males having higher C_{max} and AUC levels than females in the 28-day study and in the 13-week study. No sex differences in NHC exposure were seen in dogs. Exposures in both species increased in a dose proportional or slightly greater than dose proportional manner for C_{max} and AUC. Of note, there was no evidence of accumulation following repeated administration in either rats or dogs. Because of analytical issues, NHC levels could not be measured in the 28-day study in mice and instead were extrapolated from a subsequent 7-day repeat dose study at the same dose levels.

2.4.4.3. Genotoxicity

A non-GLP compliant Ames study was performed with NHC and a GLP compliant study with molnupiravir. With NHC in the *E. coli WP2 uvrA* strain all plates ≥5 µg with and without metabolic activation were positive for revertants. With molnupiravir, mutagenic potential was again seen in the WP2 uvrA strain, as well as in the TA102 strain, which was not tested in the study with NHC. In contrast to that seen with NHC, metabolic activation of molnupiravir reduced the dose level at which mutagenicity was seen. The applicant has argued that the positive bacterial mutagenicity result is likely to be a result of incorporation into the bacterial DNA of the NHC-TP. NHC-TP is a ribo- and not a deoxy-nucleotide, and thus the ribonucleotide itself is not expected to be significantly incorporated into eukaryotic cell DNA *in vivo*.

The *in vitro* micronucleus test was performed in TK6 cells using levels up to 330 µg/mL, which is equivalent to the maximum concentration of 1 mM in the OECD 487 guideline. Under the conditions of the study there was no increased percent of micronucleated cells noted for the test article, with the positive controls functioning as expected.

The *in vivo* micronucleus test was performed in rats after 2 consecutive days of dosing up to 2000 mg/kg. No increase in micronuclei was seen up to the top dose of 2000 mg/kg. The study did not include a measurement of toxicokinetics, although effects were seen on body weight gain and food consumption in both males and females. However, no evidence of bone marrow toxicity was seen up to the top dose. Bone marrow is a well perfused tissue and exposure levels in the blood plasma are generally similar to those observed in the bone marrow. Additional exposure calculations provided by the applicant demonstrated that the measured peak bone marrow concentrations of NHC are similar to that seen in the plasma.

To better understand if the mutation effects observed in bacteria are relevant in a whole animal mammalian system the mutagenicity of molnupiravir was assessed using the phosphatidyl inositol glycan class A gene (Pig-a) mutation assay on circulating blood erythrocytes in rats after daily dosing at 50, 150 or 500 mg/kg for 28 days. No substantial reduction in the %RETs was observed for any of the molnupiravir-treated groups when compared to the concurrent negative control value. Therefore, molnupiravir did not cause cytotoxicity following daily oral administration up to 500 mg/kg/day for 28 consecutive days to male rats. Statistically significant differences from control animals were seen at all dose levels for mutant RBCs and at the top dose of 500 mg/kg for mutant RETs. However, based on a lack of a dose-related trend and the fact that the values measured fell within the historical control range, the study was deemed equivocal in-line with the predetermined criteria for positive results.

Because of the equivocal findings in the Pig-a mutation assay, an additional *in vivo* mutation assay was performed at the cII Locus in Big Blue® Transgenic F344 Rats. Doses of 0 (vehicle control), 50, 150 and 500 mg/kg/day were administered daily for 28 days with sampling on Day 31. The results of the assay met all validity criteria and no significant increase in mutant frequencies were seen in either the liver or the bone marrow indicating a lack of mutagenic effect in these tissues. No exposure was measured, however, there were some clinical observations noted in the top dose group as well as effects on body weight. Exposure in this strain of rats was measured in an exploratory 7-day study in F344 rats (Study TT #20-9027). The AUC and C_{max} values measured at the 500 mg/kg dose are 3.1 and 8.5-fold the clinically measured levels. In general, the exposure in F344 rats appears lower than in SD rats. Normalised NHC-TP tissue levels suggest that the NHC-TP levels are highest in the bone marrow and liver compared to the other tissues examined, including the lung, kidney and spleen. Furthermore, the applicant submitted another *in vivo* mutation assay at the cII Locus in Big Blue® Transgenic F344 Rats dosed daily for 28-days at doses up to 500 mg/kg of molnupiravir and in which the testis, liver and bone marrow were collected for mutant analysis at Day 56. However, the study was deemed surplus to requirements since negative results in somatic cells from liver and bone marrow were seen in the other study in Big Blue® transgenic F344 rats (TT #20-9025).

A study in the literature has suggested that NHC is mutagenic in an animal cell culture assay using a modified hypoxanthine phosphoribosyltransferase (HPRT) gene mutation assay (Zhou et al. J Infect Dis. 2021. doi: 10.1093/infdis/jiab247). The non-standard protocol of the literature reference is acknowledged, as is the fact that the cells were subjected to NHC treatment for 32 days with the media being replaced every time the cells reached confluence. Whilst cytotoxicity was not directly measured the study does include a measurement of cell number which did not appear to be modulated at ≤ 3 μM with effects only seen at 10 μM, however, cell growth was only quantified up to 5 days. The materials and methods section of the paper is very sparse and there is no reference even to the source of NHC or information in relation to its purity. These issues, and notwithstanding the lack of GLP considerations, restrict the utility of the literature study for risk assessment. Nevertheless, the study does raise an issue that NHC-TP could be metabolised by ribonucleotide reductase to the 2′ -deoxyribonucleotide form, which then could be incorporated into DNA. The applicant has indicated that the formation of 2′ -deoxy- NHC has not been detected when radiolabelled molnupiravir was incubated with hepatocytes of rat, dog, monkey or human origin and that the *in vivo* mutation assay at the

cII Locus in Big Blue® Transgenic F344 Rats is sufficient to address the concern in line with the relevant guideline ICH S2R1.

2.4.4.4. Carcinogenicity

A six-month carcinogenicity study was completed in CByB6F1/Tg rasH2 hemizygous mice with daily administration via oral gavage of molnupiravir at doses of 30, 100 and 300 mg/kg. The design of the study included two control groups dosed with the vehicle (1% Methylcellulose), as well as an additional water control group. No molnupiravir related effects were seen on mortality, clinical observations or body weights for the duration of the study.

An analysis of tumour incidence revealed no increased incidence of neoplastic events in males. For females, a statistically significant increase in haemangiosarcomas in the spleen was observed at the top dose of 300 mg/kg. A step-down analysis revealed no significant increasing trend in the mid dose group of 100 mg/kg. The statistically significant findings have been attributed to the unusually low concurrent control rate in which no haemangiosarcomas in the spleen were observed. The incidence of 3/25 (12%) in the top dose group of 300 mg/kg was within the historical control range of the facility and that of other similar facilities performing such studies in these transgenic mice (range 0-20% in females). From a review of the provided historical control data from the study site and published literature it is apparent that splenic haemangiosarcomas are routinely found as common spontaneous neoplasms in these transgenic mice. Therefore, the finding is unlikely to be related to molnupiravir treatment.

There were no other pre-neoplastic changes associated with molnupiravir treatment and the positive control, N-Nitrosomethylurea (NMU), resulted in tumour findings consistent with that expected for this transgenic mouse model.

A limited bioanalytical analysis was performed with samples collected 1 hour post dose on Day 182. Plasma levels of 7.37, 18.7 and 60.1 μM were measured for the 30, 100 and 300 mg/kg groups respectively. For both the 100 and 300 mg/kg dose groups the levels measured are in excess of the C_{max} of 10.8 μM of the clinical dose.

2.4.4.5. Reproductive, developmental toxicity and toxicokinetic data

Separate male and female fertility studies were performed in rats with molnupiravir oral doses up to 500 mg/kg/day. In both studies, no effects were seen on fertility parameters or early fetal development. The male fertility study did not include an examination of sperm parameters. Toxicokinetics were measured in both sexes and suggested that the males achieved exposures approximately 3-fold higher than females at the top dose of 500 mg/kg. Non-adverse clinical effects on weight and food consumption were seen at the top dose in males only. At the NOAEL of 500 mg/kg in the male fertility study, there is a margin of exposure of 6.1. At the NOAEL of 500 mg/kg in females, there is a margin of exposure of 2.1 compared to the predicted clinical exposure at 800 mg Q12H.

In a preliminary study in rats, significant maternal toxicity was noted at the top dose of 1000 mg/kg with body weight losses resulting in the early termination of 2 females at GD10. At this dose level, an increase in post-implantation loss was seen (22.0%, versus 6.3% in controls), as well as reduced fetal body weights (26.4% for males and 23.5% for females). In addition, malformations were seen including abnormal and/or small eye/eye socket, absent kidney, rib malformations, thoracic and lumbar vertebra malformations. Rib malformations (mostly detached) had the highest incidence with 13 noted out of 75 fetuses, malformations of

the eye in 3 fetuses and absent kidney in 2 fetuses. There was also an increased incidence of skeletal variations, particularly observations of cervical ribs, in all dose groups compared to the control group. At the lower dose of 500 mg/kg, decreased fetal body weight was seen in the absence of effects on post-implantation loss or molnupiravir related malformations.

Because of the maternal toxicity seen in the DRF, the definitive study utilised 500 mg/kg as the top dose. No molnupiravir-related malformations were seen at any dose level and the only developmental toxicity noted was decreased fetal weights at the top dose (13% and 11% for males and females respectively). In particular, there was no skeletal malformations seen in the study and the variations in all dose groups were comparable to that of the control group suggesting that the increased incidence seen in the pEFD study was incidental. Maternal toxicity was seen at the top dose of 500 mg/kg as evidenced by effects on maternal body weight and food consumption.

Toxicokinetics were measured as part of both studies in rats; however, toxicokinetics were not calculable in the definitive study at the top dose of 500 mg/kg in rats due to a sample volume error. The exposures measured at 100 and 250 mg/kg in the definitive study are largely comparable to that seen in the DRF study. The NOAEL for maternal and developmental toxicity was 250 mg/kg, which represents a margin of exposure of 0.8-fold the NHC exposure measured at the RHD of 800 mg Q12H. The effects on fetal weight were seen at a margin of exposure of 2.9-fold and the post-implantation loss and malformations at 7.5 fold (both based on TK from the preliminary study).

In rabbits, the preliminary EFD study identified maternal toxicity at the top dose of 1000 mg/kg with effects on body weight and food consumption similar to that seen in rats. In addition, decreased faecal output was seen at this dose level. No test-article developmental toxicity was reported at any dose level. For the definitive study, the top dose used was 750 mg/kg based on the maternal toxicity noted at 1000 mg/kg in the preliminary study. At ≥ 400 mg/kg maternal toxicity was noted (effects on body weight, food consumption and faecal output during the dosing period) and based on these findings the applicant has concluded that the NOAEL for maternal toxicity is 125 mg/kg. Developmental toxicity effects seen in the definitive study in rabbits and attributed to molnupiravir were limited to decreased live fetal weights (10% and 8.5% for males and females respectively) at the top dose of 750 mg/kg. In the study report provided (Study TT #21-7010) there is an increased number of visceral malformations with molnupiravir treatment in 6 foetuses from 6 different litters in the 750 mg/kg group, compared to 2 in the control group. However, the applicant has provided historical control data for the test facility in which the rabbit EFD studies were performed. These data indicate that the malformations seen, which included effects on the kidney and gallbladder, were within the range of the findings seen in the historical control data for the facility. At the NOAEL for maternal toxicity of 125 mg/kg, there is a margin of exposure of 1.5 fold and at the applicant's NOAEL for developmental toxicity of 400 mg/kg a margin of exposure of 6.5 fold. At the 750 mg/kg dose level there is a margin of exposure of 18-fold.

A GLP compliant PPND study was performed in which the animals were dosed from GD6 through to LD 20 at 100, 250 or 500 mg/kg/day. Transient decreases in body weight gain were seen at ≥ 250 mg/kg that were fully recovered in the lactation phase. The duration of gestation was found to be statistically significantly increased at 500 mg/kg by 0.5 day; however, this was still within the bounds of historical control data for the study site. No effect was seen on the values for the number of dams delivering litters, implantation sites per delivered litter, the gestation index, females with liveborn, live birth index, number of live newborn pups and the percentage of live male pups per litter at birth. For the F1 generation in the pre-weaning period no effects were seen on survival, body weight, measures of reflex and physical development. In the post-weaning period no effects were seen on mortality, weight, clinical observations or sexual maturation parameters

investigated for the F1 generation. In addition, motor activity assessed on Day 60 postpartum, acoustic startle habituation assessed on Day 65 postpartum and learning and memory (Morris Water Maze) as assessed between Day 70-90 did not indicate any molnupiravir related effects in the F1 generation. A mating and fertility assessment was also performed on a subset of the F1 generation. The number of days in cohabitation, rats with confirmed mating dates during the first, second, or third week of cohabitation, and the Mating Index were comparable across groups. The Fertility Index and Pregnancy Index were reduced in a dose dependent manner in the 250 and 500 mg/kg groups compared to controls, however, this change was not statistically significant, and the values were within the historical control range.

The developmental NOEL for viability and growth in the F1 offspring were each considered to be 500 mg/kg/day. The NHC exposure measured at this dose level was 122 µM*hr which is approximately 1.6-fold the exposure at the RHD, lower than the 8-fold NHC exposures achieved in the EFD study in rats. Exposure levels of NHC in the pups was assessed on PND 10 with low levels of up to 0.09% of mean plasma concentrations achieved in maternal rats at respective times, suggesting that NHC is present in breast milk.

2.4.4.6. Local Tolerance

Local tolerance was assessed as part of the repeat dose toxicity studies in mice, rats and dogs as is appropriate for an orally administered drug. The significant GI tract issues seen in the dog studies were considered secondary to the thrombocytopenia seen in this species. Additional ocular and dermal irritation studies were performed which concluded that molnupiravir was a mild irritant in both settings, however, given the oral route of administration the significance of these findings is limited.

2.4.4.7. Other toxicity studies

Phototoxicity

Both molnupiravir and NHC absorb light between 290 and 700 nm with a MEC > 1000 M-1 cm-1. A photoreactivity test using a ROS generation assay was conducted. Neither molnupiravir nor NHC generated ROS at an aqueous concentration of 200 µM and, in line with ICH S10, they were not considered photoreactive.

Impurities

Proposed limits for NHC are justified based on it being a major metabolite in all species. In addition, EIDD-2960, the penultimate intermediate in the drug substance synthesis, is qualified up to levels of 0.22% based on the 800 mg Q12H dosing regimen and the levels seen in the batches used in the nonclinical toxicity studies. However, the applicant was requested to tighten the impurity limit and a specification limit of 0.15% was agreed.

Immunotoxicity

Based on the guidance in ICH S8, immunotoxicity studies were not considered necessary by the applicant since they suggest there is no significant evidence from the repeat dose toxicity studies to suggest autoimmune or inflammatory adverse effects. However, the 28-day repeat-dose toxicity study in dogs has shown adverse bone marrow toxicity that affected all hematopoietic cell lines at dosages of 17 and 50 mg/kg/day. Furthermore, individual thymic and splenic weights were considered to be lower than expected both at end of dosing and recovery necropsies at 50 mg/kg/day in both sexes, but especially in females, and at end of dosing in both sexes at 17 mg/kg/day (0.4 and 1.6-fold the clinical exposure). In addition,

microscopically, thymic changes included minimal to marked decreased lymphocytes and minimal to mild increased apoptosis as well as decreased lymphocytes were diagnosed in spleen of a few animals. At the NOAEL established of 6 mg/kg/day, there was no safety margin in dogs (0.13 times the NHC exposure at the 800 mg Q12H human dose). Although these effects were not observed in rats, it is noted that exposure levels for NHC and NHC-TP in bone marrow were quantified after a more prolonged exposition to MOV and, by contrast, these levels are not shown after repeated dose of MOV in dogs. Therefore, an immunotoxic potential in humans cannot be completely ruled out (mainly on the basis that there was no margin of safety at any of the doses tested in dogs). However, the applicant has indicated that there were no haematologic changes indicative of bone marrow toxicity or immunosuppression in clinical trials.

A local lymph node assay in mice was performed with 25% molnupiravir formulated in Dimethylformamide (DMF) to support the occupational safety program. No erythema or increases in ear thickness were noted, however, a sensitivity index of 3.2 was measured which was greater than the predefined value of 3, denoting that a substance is a sensitiser. Therefore, molnupiravir was considered a sensitiser in the LLNA.

2.4.5. Ecotoxicity/environmental risk assessment

Summary of main study results

Substance (INN/Invented Name): Molnupiravir			
CAS-number (if available): 2492423-29-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	pH 5 = -0.630 pH 7 = -0.534 pH 9 = -2.07	Potential PBT (**N**)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Toxicity	CMR	Reproductive toxicity	T
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	8	µg/L	> 0.01 threshold (**Y**)
Other concerns (e.g. chemical class)			(**N**)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	Sludge (n=2): K_{oc} = 0.063 – 0.118 mL/g Soil (n=4): K_{oc} = 4.42 – 28.3 mL/g	
Ready Biodegradability Test	OECD 301		Not conducted
Biodegradability in Activated Sludge	OECD 314B	Primary degradation (biotic): DT_{50} = 0.08 days DT_{75} = 0.17 days DT_{90} = 0.28 days k_e = 8.2534 day^{-1}	Determined during linear degradation between d 0 and d 0.25
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	20°C: DT50, water = 5.91 d (T), 3.50 d (W) DT50, sediment = not determined	T - Taunton River W - Weweantic River

		DT50, whole system = 6.56 d (T), 5.51 d (W) 12°C: DT50, whole system = 14.0 d (T), 11.76 d (W) % shifting to sediment = 27 % CO2 = 77.5 (T), 80.3 (W) % NER = 14.6 (T), 9.2 (W) transformation products (TP1 and TP2) >10% identified TP1: DT50 = 16.6 to 20.7 days DT90 = 55.2 to 68.9 days TP2: DT50 = 59.1 to 136 days DT90 = 196 to 450 days			At d 16 (parent + NER) At d 101 At d 101 TP2 seems to be persistent
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Raphidocelis subcapitata*	OECD 201	EC10 Yield Growth rate	 43 89	mg/L	
Daphnia sp. Reproduction Test	OECD 211	EC10	>8.8	mg/L	
Fish, Early Life Stage Toxicity *Pimephales promelas*	OECD 210	EC10	5.8	mg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	EC10 NOEC	143.1 90	mg/L	Total respiration
Phase IIb Studies					
Sediment dwelling organism, *Chironomus riparius*	OECD 218	NOEC NOEC	810 3375	mg/kg	2.4% organic carbon (o.c.) content Normalised to 10% o.c.

Molnupiravir is not a PBT substance. Considering the above data, molnupiravir is not expected to pose a risk to the environment.

2.4.6. Discussion on non-clinical aspects

Pharmacology

In-vitro data from the literature have shown that NHC has antiviral activity against several RNA viruses, including SARS-CoV-2, in multiple cell types (including Vero E6, HuH-7, Calu-3 lung epithelial cells and A549-ACE2 cells), with EC_{50}s in the sub- to low- µM range. The antiviral activity of NHC was specific and not due to cellular toxicity since CC_{50} values were above the IC_{50} with selectivity index values between 1.24 and >130 depending on the cell line used.

The antiviral activity of NHC against SARS-CoV-2 variants of concern B.1.1.7 (Alpha), B.1351 (Beta), P.1 (Gamma) and B.1.617.2 (Delta) was demonstrated using a cytopathic effect protection assay in Vero E6

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cells, with reported IC_{50} values of 1.59 µM, 1.77 µM, 1.32 µM and 1.68 µM respectively, compared with 1.41 µM for WA1 (USA-WA1/2020). The corresponding IC_{50} values for remdesivir were 0.91 µM, 0.96 µM, 0.59 µM and 1.08 µM, for Alpha, Beta, Gamma and Delta variants respectively, and 1.07 µM for WA1.

A non-infectious SARS-CoV-2 reporter replicon assay was used to assess the activity of NHC against replicons encoding specific NSP12 (polymerase) and NSP14 (exonuclease) substitutions. Remdesivir resistance-associated variants in the NSP12 protein (NSP12-F480L, NSP12-D484Y, NSP12-V557L, NSP12-E802A, NSP12-E802D) identified in tissue culture passaging experiments were tested. NHC was similarly active (EC_{50} values <1.6-fold) against all remdesivir resistance-associated replicons tested. Moreover, MOV-treatment-emergent NSP12 and NSP14 variants, NSP12-T739I, NSP14-A220S, NSP14-A220T, NSP14-A220V, NSP14-S503L and NSP14-S503 were evaluated. These variants were observed in NP swab samples from 3 or more participants who had received molnupiravir in Phase 2 studies. NHC was similarly active (EC_{50} values <1.6-fold) against all treatment-emergent NSP12 and NSP14 variants in the replicon assay.

NHC was evaluated in resistance selection assays against WT mouse hepatitis virus (MHV) and WT MERS-CoV by passage in cell culture and the NHC sensitivity of passage 30 populations was tested. After 30 passages there was a modest change in NHC susceptibility (~2-fold increase in EC90) for MHV and MERS-CoV, suggesting a low likelihood of resistance development to NHC.

In addition, two remdesivir-resistance mutations (F476L and V553L) did not confer cross-resistance to NHC in an *in vitro* virus replication assay. The activity of molnupiravir was evaluated in Vero E6-ACE2 cells against SARS-CoV-2Engl2 after serial passage in media supplemented with or without remdesivir. Remdesivir, showed 2- to 2.5-fold increase in IC_{50} against the Rem2.5p13.5 strain. Molnupiravir showed a minimal change in IC_{50} against Rem2.5p13.5 (IC_{50} 9.14 µM) compared with SARS-CoV-2Engl2 (IC_{50} 8.92 µM).

NHC exhibited low cytotoxicity in a range of mammalian cell lines, demonstrating good selectivity index for antiviral effects. NHC demonstrated poor efficiency at incorporating into mitochondrial RNA, suggesting that it does not result in toxicity or dysfunction of mitochondria *in vitro*. MOV inhibited erythroid and myeloid progenitor proliferation with IC_{50} values of 24.9 and 7.7 µM respectively, but no hematologic effects indicative of bone marrow toxicity were noted in clinical trials.

The *in vivo* proof of concept studies consistently support the antiviral activity of molnupiravir, as demonstrated by reduced infectious lung titres in multiple SARS-CoV-2 infection models (LoM, ferret, hamster). In addition, data from the ferret coronavirus infection model supports the ability of molnupiravir to suppress viral transmission in a relevant non-clinical model. However, antiviral activity was decreased in LoM when treatment initiation was delayed to the 48-hour post-infection time point.

Secondary Pharmacodynamics

Both MOV and NHC were tested for potential secondary pharmacodynamics activity *in vitro* against a panel of 108 enzymes, receptors and ion channels, with ≥50% inhibitory activity considered significant and reported at only one target, human COX-2. There is a very small margin (~1.4-fold) from the reported NHC IC_{50} against COX-2 (15.1 µM) to anticipated clinical C_{max} (10.8 µM), suggesting the potential for COX-2 inhibition at clinically relevant concentrations. However, the safety pharmacology and repeat-dose toxicity studies conducted in rats and dogs achieved NHC C_{max} values 16-fold and 5-fold the clinical C_{max} respectively, without reporting any findings suggestive of potential secondary effect of COX-2 inhibition.

Safety Pharmacology

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, and no findings of concern are reported which is acceptable.

Pharmacokinetics

A nonclinical pharmacokinetic program was carried out to evaluate the ADME properties of MOV and the nucleoside NHC.

MOV is a 5´-isobutyrate ester prodrug cleaved by esterases present in the intestine and liver during absorption/hepatic first pass, delivering the nucleoside metabolite NHC into systemic circulation, as a result only very low levels of MOV was detected in plasma. Pharmacokinetic studies were conducted in mice, rats, dogs, monkeys and ferrets.

The distribution of MOV, NHC and NHC-TP was quantified in a limited number of tissues (lung, spleen, kidney, liver, heart and brain). NHC and NHC-TP were observed in all tissues and their exposures were generally dose dependent. In most species, NHC-TP typically had the highest exposures in liver, heart, spleen, and lung and the lowest levels in brain. Monkey study report PK013, and dog study report PK068, have tissue collection tables listing other tissues not reported on by the applicant, such as, and not limited to, bone marrow, intestine, testes, skeletal muscle and trachea (PK068). The applicant clarified that the distribution study was performed prior to the toxicology study, and no retrospective analysis of other tissues collected was performed. The applicant considers that the tissues selected for bioanalysis were the major organs pertinent for viral indications at the time of the distribution study. Whole body autoradiography distribution studies were not performed as the applicant considers a QWBA of a little interpretative value based on the metabolism and distribution of MOV, the tissues where NHC and NHC-TP have been measured do not suggest very significant differences in NHC metabolite exposure.

A separate study on distribution to the bone marrow in rats following a single 500 mg/kg dose, demonstrated similar exposure in the bone marrow to that achieved in rat plasma following 320 mg/kg.

A new study to determine distribution and concentration of NHC and NHC-TP in the testes was submitted. NHC and NHC-TP were detected in the testes of rats in all MK-4482-treated groups at 3 and 24 hours after MK-4482 dosing on Study Day 14, with concentrations that increased in a dose-related manner.

The binding of NHC to plasma proteins was evaluated, and it was determined that NHC does not bind to plasma proteins.

The metabolism of MOV and NHC was determined both *in vivo* and *in vitro*. Near complete hydrolysis of MOV to NHC occurs during absorption/first pass, with the high capacity esterases CES1 and CES2 involved. Following the uptake of circulating NHC into cells, host kinases and phosphatases involved in the endogenous pyrimidine nucleoside pathways then anabolise/catabolise NHC to/from NHC-TP. Preclinical *in vitro* and *in vivo* metabolism studies suggest the ultimate route of elimination of MOV/NHC-related material is primarily metabolism to endogenous pyrimidine nucleosides (uridine and/or cytidine).

The conversion of NHC to NHC-TP was evaluated in a variety of cell lines and primary cells. Two of the studies, PK047 and PK048, were in primary bronchial/tracheal epithelial cells treated with 20 µM of EIDD-1931. There was complete conversion of NHC to NHC-TP in one study (PK048) and incomplete conversion in the other (PK047). The applicant has clarified that the results obtained in PK047 are generally inconsistent with the conversion of NHC to NHC-TP observed in other assays, and that the results of PK048 are more in line with expectations. PK048 was performed after PK047, and the data from this study is to be considered to supersede the data in PK047. This can be accepted.

In response to a request to provide more detail regarding the conversion rate of NHC to NHC-TP, more data was provided, the applicant further clarified that the tissue concentrations of NHC and NHC-TP are determined by a number of factors, including uptake rates of NHC from plasma via nucleoside transporters, metabolism by cellular enzymes to uridine and/or cytidine (elimination), anabolism to the mono-, di-, and triphosphates, as well as catabolism of the triphosphate back to NHC.

In cell lines, concentrations of up to 100 µM were tested on cells, CC_{50} values for some of the cell lines tested are below 100 µM. Even though the potential for cytotoxicity to occur at the highest concentration tested in CEM, A549 and Vero cells, both NHC and NHC-TP increase in a generally dose-proportional manner relative to NHC and NHC-TP formed at lower non-cytotoxic concentrations. Other cell lines tested below the CC50 also demonstrate that generation of intracellular NHC-TP levels are generally concentration dependent. Cytotoxicity does not appear to be a concern regarding the reliability of the results in these studies.

In cycling cells during S-phase, for DNA replication, in all cells the major supply of dNTPs comes from the *de novo* reduction of ribonucleoside diphosphates to deoxyribonucleoside diphosphates by the enzyme ribonucleotide reductase (RNR). Ribonucleotide reduction is a cytosolic process and the potential for reduction of NHC to 2'-deoxy-NHC has not been discussed by the applicant. The potential for this to occur has implications for incorporation of 2'-deoxy-NHC into DNA and the creation of point mutations as discussed by Zhou *et al.* (2021). The applicant was asked to discuss the potential for generation of 2'-dNHC in proliferating cells, and to report if they looked for the generation of this metabolite in studies. In response, the applicant stated they did, the applicant further clarified that 2'-deoxy-NHC would be expected to elute in the same region of the chromatogram that NHC and cytidine elute and would be readily detectable by LC-MS/MS. From the radio-chromatograms, if present, 2'-deoxy-NHC would be expected to elute in the same region of the chromatogram that NHC and cytidine elute, it is clear that there is no other peak in this region suggesting that 2'-deoxy-NHC was not detected *in vivo*.

Based on *in vitro* data, MOV and NHC are not likely to be either perpetrators or victims of human CYP or transporter DDIs.

Toxicology

Repeat dose toxicity studies

Toxicity noted in the repeat dose toxicity studies in rats include increased liver weight in the 28-day study, which was deemed non-adverse and was recoverable upon treatment cessation, as well as effects on bone and cartilage in the 3-month study. In contrast, in dogs, significant bone marrow toxicity was noted in a dose and time-dependent manner, and which limited the duration of treatment that was tolerated in this species. Some of the margins of exposure at the identified NOAELs are less than 1. This is particularly the case for dogs in which there is a margin of exposure of 0.1-fold at the NOAEL of 6 mg/kg. However, it is important to note that the reported toxicity (depletion of all lineages in the bone marrow) has not be seen to date in the clinical studies and were not observed in studies in mice, rats, rabbits or monkeys at exposures in excess of that seen clinically and for durations of at least 7-days up to 3-months. Some effects on RET, WBCs and lymphocyte levels were seen in the 7-day exploratory study in rats at a margin of exposure of 91-fold. For rats in the 28-day study, the margin of exposure at the NOAEL, which was the top dose, used was 4.2 for females and 7.8 for males. In the 3-month study this was 0.7-fold at the 150 mg/kg NOAEL for males and 3.3 fold at the 500 mg/kg NOAEL for females, however, as previously discussed there is limited relevance of the findings in relation to bone and cartilage in an adult indication.

The reasoning for the increased sensitivity of dogs to the effects of molnupiravir are unclear. As discussed in the pharmacology section, the concentration of molnupiravir for the secondary pharmacology screen may not

have been sufficient to detect potential off-targets. Furthermore, there is no information provided on potential differences in bone marrow exposure in dogs compared to other species. The applicant was asked to discuss the basis for the differential sensitivity for bone marrow toxicity in dogs. The provided discussion suggested the effects were unlikely related to differences in exposure or distribution in this species, however, no potential hypothesis or explanation was provided.

These findings of the repeat dose toxicity studies which were not seen clinically i.e., bone marrow toxicity and effects on bone and cartilage will be included in Section 5.3.

Genotoxicity

Positive bacterial mutagenicity results were seen with both molnupiravir and NHC. In both the *in vitro* and *in vivo* micronucleus studies, negative results were seen. In the case of the in-vivo study, no exposure was measured. Bone marrow is a well perfused tissue and exposure levels in the blood plasma are generally similar to those observed in the bone marrow. Additional exposure calculations provided by the applicant demonstrated that the measured peak bone marrow concentrations of NHC are similar to that seen in the plasma. Therefore, it is reasonable to assume that exposure to both NHC and NHC-TP in the bone marrow was similar to that seen in the plasma suggesting that sufficient exposure was achieved.

Based on the guidance in ICH S2 (R1) the applicant has performed two *in vivo* studies, Pig-a mutagenicity and Big Blue® (cII Locus) transgenic rodent assays, which look at mutagenicity as the end-points. Equivocal results were seen in the Pig-a assay based on the fact that 1/3 criteria for a positive results was fulfilled, a statistical increase relative to the concurrent control. However, the mutation rates were within the 95% upper limit of the historical control data range and did not demonstrate a statistically significant dose-related trend when evaluated with an appropriate trend test and thus fulfilled 2/3 criteria for negative response. Whilst TK was not included in the study, there is sufficient evident from another study (Study TT#20-9027) from the same facility and using the same test-article batch and dose levels that there was exposure in excess of that seen clinically in these rats. The AUC and C_{max} values measured at the top dose of 500 mg/kg dose are 3.1 and 8.5-fold the clinically measured levels. Given that the cells used for the mutagenicity analysis are cells from the plasma, it is reasonable to assume that the exposure for this analysis is sufficient. Although a statistical increase relative to the concurrent control is seen, the biological significance of this remains unclear considering that the values seen, even at the top dose, are well within the historical control range. The statistical significance seen may be based on random chance and not biologically relevant. However, the range of the historical negative control data for the in vivo Pig-a mutation assay is higher than the normal background rates of $\leq 5*10^{-6}$ which are referenced for this assay (Gollapudi et al. Mut. Res. 783 (2015) 23-35). It was considered plausible that the range was more variable when the facility started with the assay and decreased with more experience and proficiency. However, the applicant clarified that the historical control database is based on studies which were all conducted in a single year in 2017 with no studies conducted in the intervening period until the molnupiravir study in 2020.

In the case of the Big Blue® (cII Locus) transgenic rodent assay a negative result was seen after mutation analysis of liver and bone marrow tissue. With the Big Blue® (cII Locus) transgenic rodent assay the choice of tissue for the analysis is not limited to particular organs/tissues. The choice of a fast proliferating tissue such as bone marrow and a slower growing tissue such as liver is in line with guidance; however, the levels of exposure in these tissues was unclear. Further data presented by the applicant indicate that when the exposure to NHP is normalised for dose the exposure in the bone marrow is similar to that in the plasma. Normalised NHC-TP tissue levels suggest that the NHC-TP levels are highest in the bone marrow and liver compared to the other tissues examined, including the lung, kidney and spleen. Whilst no TK was collected as part of the study, in a Dose Range Finder Assay in Fischer 344 Male Rats (TT #20-9027), the exposure

measured at the top dose of 500 mg/kg after 7 days dosing suggests a margin of exposure of 3.1 and 8.5-fold the clinically measured levels based on AUC and C_{max} values respectively. It is accepted that the exposure achieved is the MTD feasible for this study considering the clinical observations seen and that exposures in excess of that reached clinically in these tissues have been likely achieved. The study was fully compliant with the OECD 488 guideline with the number of plaques analysed for each animal was in excess of that required by the guideline considering the background mutation rates in the tissues analysed. Overall, the choice of the bone marrow and liver for the mutation frequency analysis has been appropriately justified and the exposure achieved in these tissues is likely to have been in excess of that observed clinically.

The applicant has argued that the positive bacterial mutagenicity results are a result of NHC-TP incorporation into the DNA of bacteria, which would not occur in eukaryotic cells. However, as discussed previously there is data in the literature describing positive mutagenicity findings in eukaryotic cells (Zhou *et al*; 2021). Although there are issues with the study, it does raise a relevant point that has not been addressed by the applicant, which is that NHC-TP could be metabolised by ribonucleotide reductase to the 2-deoxyribonucleotide form that could be incorporated into DNA. As discussed above in the PK section the applicant has data to suggest that NHC-TP is ultimately converted to cytidine and uridine; however, no data has been provided as to potential formation of 2'deoxy NHC-TP, especially in rapidly proliferating cells. In response to a question regarding this issue, the applicant indicated that the formation of 2′ -deoxy- NHC has not been detected when radiolabelled molnupiravir was incubated with hepatocytes of rat, dog, monkey or human origin and that the *in vivo* mutation assay at the cII Locus in Big Blue® Transgenic F344 Rats is sufficient to address the concern in line with the relevant guideline ICH S2R1. They indicated that they are not aware of any rationale for species differences in mammalian pyrimidine metabolism pathways and considering the conservation of this pathway across all species, the justification is accepted. There are no known mutations in animals or humans in ribonucleotide reductase that lead to increased activity.

In the absence of evidence of measurable levels of 2'deoxyNHC formation, data on the rate of its incorporation into cellular DNA is of limited value for risk assessment. Furthermore, as suggested by the applicant, should 2'deoxyNHC formation occur *in vivo*, its potential to introduce mutagenic changes would be assessed in the *in vivo* Big Blue® mutation assay, which was performed in compliance with the OECD 488 guideline and with likely sensitivity to detect weak mutagenic compounds.

A second Big Blue® (cII Locus) transgenic rodent assay study, which collected tissue from the testis (bone marrow and liver in addition), was initiated but terminated after the in-life portion because of the negative results in the first study. ICH S2(R1) indicates that testing for mutation in germ cells (e.g., sperm cells) is not warranted when negative results are observed in somatic cells. The applicant has argued that germ cells are less sensitive to mutagenic chemicals relative to somatic cells, that base excision repair in male germ cells is more effective than in somatic cells and that no unique germ cell mutagens have been identified to date. Furthermore, they have indicated there were no findings on organ weight, gross and histomorphologic evaluation of the reproductive organs in the repeat dose toxicity studies or effects on male and female fertility parameters in the fertility studies. Whilst the argumentation of the applicant as to why no mutagenic effect should be expected on the male germ cells is reasonable, a pharmacokinetic study in wild type Fisher 344 rats detected the presence of NHC and NHC-TP in the testes of male rats. A male germ cell mutation assay in the Big Blue rat model has been mandated by the FDA in which the rats will be treated for 28 days followed by a 70-day recovery period before mutation analysis. Whilst in the first instance it may seem preferable to complete the halted Study TT #20-9047, it is acknowledged that the design of the proposed study with 28 days treatment followed by a 70-day recovery, is superior to that of the 28 days treatment followed by a 28-day recovery in Study #20-9047 for analysing mutational effects across a full sperm cycle in rats.

The outcome of this study is not currently available and its results could potentially inform as to a mutagenic risk to the sperm. Therefore, should the results of this study not be available prior to authorisation it would appear appropriate as a precautionary measure to include an advisement in Section 4.6 of the SmPC for males to use contraception and not to father children for 3 months after treatment.

Reproductive and Developmental Toxicity

The fertility studies performed in rats do not indicate an effect on fertility parameters or early embryo-fetal development.

In both rats and rabbits, developmental toxicity was noted in the EFD studies, however, in both species this occurred in the presence of maternal toxicity. Malformations, increased levels of post-implantation loss and decreased fetal weight effects in rats were seen in the preliminary study in rats at the top dose of 1000 mg/kg. At this dose level, effects on maternal weight were particularly pronounced in the period of GD6 to GD 10. Two of the animals had to be euthanised because of excessive body weight loss (-11.7% or -15.7%) on GD 10 and body weight gain for the group in this time period was 4.4 g compared to 23.4 g in the control group (all other dose levels were comparable to control). No test-article related malformations were seen in rats at doses up to 500 mg/kg in either the pEFD or definitive EFD study; however, effects on fetal weight were evident in both studies, which were largely similar in magnitude and occurred in the presence of maternal toxicity. In rabbits, no test-article attributed malformations were reported in either pEFD or definitive EFD study and the developmental toxicity noted is limited to decreased fetal weight alone. However, it is noted that in the definitive rabbit EFD study, particularly at 750 mg/kg, the number of malformations is higher (albeit at low incidence) but the incidence of these findings was seen to be within the range of the historical control data for similar studies at the test facility. At the NOAEL in rats for both maternal and developmental toxicity, there is a margin of exposure of 0.8-fold. The effect on fetal weight was noted at a margin of exposure of 2.9-fold, while the post-implantation loss and malformations at 7.5-fold. The margins above the NOAEL are based on the TK from the pEFD study due to the sampling error in the definitive study at the 500 mg/kg dose level and the absence of a 1000 mg/kg group in the same study. The exposures measured at 100 and 250 mg/kg in the definitive study are largely comparable to the respective similar dose groups in the pEFD study; therefore, extrapolation is considered acceptable. In addition, there are no data regarding the placental transfer of molnupiravir and the extent of embryo/fetal exposure to NHC. A PPND study in rats has been performed with no significant molnupiravir related findings observed at any dose level with the top dose providing an exposure margin of 1.6-fold at the RHD. Based on the observed NHC levels measured in the offspring, the transfer into milk appears low.

The applicant has indicated that the observed developmental toxicity at the 1000 mg/kg dose level in the preliminary EFD study in rats is unlikely to be fully explained by the maternal toxicity observed, as there is no direct evidence of a causal association between the developmental toxicity and maternal toxicity. This can be agreed, as it appears likely that the maternal toxicity may have exacerbated the developmental toxicity, but it unlikely to have resulted in the malformations noted. However, the applicant does not consider these malformation findings a result of mutagenicity, as the *in vivo* mutagenicity studies have concluded that molnupiravir is not an *in vivo* mutagen and these studies are more sensitive to detect such effects than EFD studies. Furthermore, they have argued that there are significant differences in the developmental toxicity noted with molnupiravir, compared to other nucleoside analogues. Molnupiravir only produced malformations and embryo-fetal lethality at exposures 8-fold higher than the clinical exposure, with these findings present only in rats and not in rabbits at even higher exposure levels. In contrast, the nucleoside analogues have been shown to induce malformations and embryo-fetal lethality at doses/exposures similar to or below those

used in the clinic, and in multiple species. Effects with these compounds were also seen on fertility and PPND studies, which were not evident with molnupiravir.

2.4.7. Conclusion on the non-clinical aspects

Overall, the provided nonclinical package could be considered sufficient to support the MAA for Lagevrio.

2.5. Clinical aspects

2.5.1. 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.

- **Tabular overview of clinical studies**

This report covers the clinical data submitted as of 22 October 2021. Specifically:

- MK4482-004 – a final CSR was submitted.
- MK4482-006 – an interim report was submitted that included the primary analysis.
- MK4482-002 – an interim report was submitted for Part 1 (interim analysis #2; IA2); for Part 2 the applicant submitted a statistical summary and tabulations of the safety and efficacy data available at the time of interim analysis IA3/IA4, which were described in a Clinical Overview.

Additional data were included from MK4482-001, -005 and -007 as shown in the table; these studies involve a different patient population vs. that in -006 and -002.

Study	Phase/ Population	Study Results Included in Application
MK-4482-002 (P002)	Phase 2 (Part 1) Phase 3 (Part 2) non-hospitalised	Phase 2 (Part 1): IA results (all Part 1 participants who completed Day 29) for safety, efficacy, virology, and PK Phase 3 (Part 2): IA[a] results (50% of randomised participants who completed Day 29) for safety, efficacy and virology
MK-4482-006 (P006)	Phase 2a/ non-hospitalised	Final results for safety, efficacy, virology and PK
MK-4482-001 (P001)	Phase 2/ hospitalised	Phase 2: IA results for safety (through Day 29), efficacy (through Day 29; primary endpoint), virology, and PK
MK-4482-007 (P007)	Phase 2a/ hospitalised	Preliminary (blinded) summary of safety
MK-4482-005 (P005)	Phase 1/2/ hospitalised	Preliminary (blinded) summary of safety
MK-4482-004 (P004)	Phase 1/ healthy participants	Final results for safety and PK
[a] The IA for P002 (Phase 3) includes both IA3 and IA4.		

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Pharmacokinetic data were obtained from healthy subjects in MK4482-004 and from subjects with COVID-19 who were enrolled into the efficacy trials MK4482-001, MK4482-002 and MK4482-006.

Molnupiravir (EIDD-2801) is the 5'-isopropyl ester prodrug of the active antiviral ribonucleoside analogue N-Hydroxycytidine (NHC; EIDD-1931). Some reports refer to EIDD-2801 and EIDD-1931.

- In MK4482-004 powder in bottle (PIB) and capsules were used and their bioavailability was compared but not in a crossover fashion.
- MK4482-004 evaluated the dry filled capsule (DFC) containing 25, 100 and 200 mg. No changes to the DFC formulation were made after dose and formulation selection in this study.
- Molnupiravir is to be supplied commercially as a Swedish Orange opaque size 0 dry filled hard capsule containing 200 mg of the active substance.

MK-4482-004 was a 3-part study conducted during 2020 in healthy male (84%) and female subjects (16%) aged from 19-60 years (mean 40 years) enrolled at a single site in the UK.

Part 1 (Single Ascending Dose)

Part 1 comprised 8 dose-escalation cohorts and two formulations:

- Cohort 1: 50 mg EIDD-2801 or placebo (powder-in-bottle [PIB] formulation)
- Cohort 2: 100 mg EIDD-2801 or placebo (PIB formulation)
- Cohort 3: 200 mg EIDD-2801 or placebo (PIB formulation)
- Cohort 4: 400 mg EIDD-2801 or placebo (PIB formulation)
- Cohort 5: 600 mg EIDD-2801 or placebo (PIB formulation)
- Cohort 6: 800 mg EIDD-2801 or placebo (PIB formulation)
- Cohort 7: 1200 mg EIDD-2801 or placebo (capsule formulation)
- Cohort 8: 1600 mg EIDD-2801 or placebo (capsule formulation)

Following oral administration of 600 mg or 800 mg EIDD-2801, **EIDD-2801** was quantifiable but in low concentrations in samples from all subjects at 0.5 h after 800 mg. Following single doses up to 800 mg (PIB formulation), **EIDD-1931** appeared rapidly in plasma, with a T_{max} of 0.5 to 1.5 h.

Table 1: Summary of the Plasma Pharmacokinetic Parameters for EIDD-1931 following single oral dose of 50 to 800 mg EIDD-2801 (Powder-in-bottle) for Protocol EIDD-2801-1001-UK

Matrix: Plasma; Analyte: EIDD-1931; Profile Day: 1

	EIDD-2801 PIB (fasted)					
Parameter	50 mg (N = 6)	100 mg (N = 6)	200 mg (N = 6)	400 mg (N = 6)	600 mg (N = 6)	800 mg (N = 6)
AUC_{last} (h*ng/mL)	415 (27.4) [6]	917 (27.5) [6]	1810 (20.0) [6]	4000 (20.2) [6]	6120 (21.6) [6]	8720 (10.4) [6]
$DAUC_{last}$ (h*ng/mL/mg)	8.30 (27.4) [6]	9.17 (27.5) [6]	9.05 (20.0) [6]	9.99 (20.2) [6]	10.2 (21.6) [6]	10.9 (10.4) [6]
AUC_{0-inf} (h*ng/mL)	432 (26.5) [6]	932 (27.0) [6]	1830 (19.6) [6]	4010 (20.2) [6]	6130 (21.4) [6]	8740 (10.4) [6]
$DAUC_{0-inf}$ (h*ng/mL/mg)	8.64 (26.3) [6]	9.32 (27.0) [6]	9.13 (19.6) [6]	10.0 (20.2) [6]	10.2 (21.4) [6]	10.9 (10.4) [6]
$\%AUC_{extrap}$ (%)	3.34 (66.6) [6]	1.42 (55.8) [6]	0.931 (68.3) [6]	0.288 (28.2) [6]	0.247 (65.3) [6]	0.245 (40.1) [6]
C_{max} (ng/mL)	223 (46.2) [6]	454 (42.2) [6]	926 (12.6) [6]	1850 (22.7) [6]	2720 (27.0) [6]	3640 (13.4) [6]
DC_{max} (ng/mL/mg)	4.47 (46.2) [6]	4.54 (42.2) [6]	4.63 (12.6) [6]	4.63 (22.7) [6]	4.53 (27.0) [6]	4.55 (13.4) [6]
t_{max} (h)	1.00 (0.317-1.00) [6]	1.00 (0.500-1.50) [6]	1.00 (0.500-1.00) [6]	1.00 (0.500-1.00) [6]	1.00 (1.00-1.00) [6]	1.00 (0.500-1.00) [6]
t_{last} (h)	5.00 (4.00-6.00) [6]	6.00 (6.00-6.00) [6]	7.50 (6.00-9.00) [6]	9.00 (9.00-12.0) [6]	9.00 (9.00-12.0) [6]	12.0 (12.0-12.0) [6]
$t_{1/2}$ (h)	0.945 (12.1) [6]	0.907 (10.1) [6]	1.02 (16.4) [6]	1.03 (8.86) [6]	1.06 (10.3) [6]	1.29 (7.10) [6]
CL_F (L/h)	0.747 (72.8) [6]	1.11 (50.3) [6]	0.824 (104) [6]	1.36 (104) [6]	2.35 (51.5) [6]	2.06 (17.9) [6]

AUC_{inf} = area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC_{last} = area under the plasma concentration-time curve from time 0 to the last measurable non-zero concentration (t_{last}); CL/F = apparent clearance following an extravascular dose; CLR = renal clearance; C_{max} = maximum observed concentration; CV = coefficient of variation (%); n = number of subjects with valid observations; PIB = powder-in-bottle; $t_{1/2}$ = apparent terminal elimination half-life; t_{last} = time of the last quantifiable concentration; t_{max} = time of the maximum observed concentration; $\%AUC_{extrap}$ = percentage of AUC_{inf} that is due to extrapolation from the last quantifiable concentration to infinity.
Parameter starting with 'D' letter signifies the corresponding parameter was normalized by dose administered.
Geometric mean (CV) [n] statistics presented; for t_{max} and t_{last}, median (min-max) [n] statistics presented.

Following single doses of 1200 and 1600 mg (capsule formulation), median T_{max} was delayed relative to the lower doses and occurred at 1.75 and 1.50 h, respectively.

Table 2: Summary of the Plasma Pharmacokinetic Parameters for EIDD-1931 Following Single Oral Doses of 1200 to 1600 mg EIDD-2801 (Capsule) for Protocol EIDD-2801-20021-UK

Matrix: Plasma; Analyte: EIDD-1931; Profile Day: 1

	EIDD-2801 capsule (fasted)	
Parameter	1200 mg (N = 6)	1600 mg (N = 6)
AUC_{last} (h*ng/mL)	13800 (11.7) [6]	20700 (31.4) [6]
$DAUC_{last}$ (h*ng/mL/mg)	11.5 (11.7) [6]	12.9 (31.4) [6]
AUC_{0-inf} (h*ng/mL)	13800 (11.8) [6]	20700 (31.4) [6]
$DAUC_{0-inf}$ (h*ng/mL/mg)	11.5 (11.8) [6]	12.9 (31.4) [6]
$\%AUC_{extrap}$ (%)	0.196 (37.9) [6]	0.238 (32.1) [6]
C_{max} (ng/mL)	4500 (17.9) [6]	6350 (20.6) [6]
DC_{max} (ng/mL/mg)	3.75 (17.9) [6]	3.97 (20.6) [6]
t_{max} (h)	1.75 (1.00-2.50) [6]	1.50 (1.00-2.00) [6]
t_{last} (h)	12.0 (12.0-24.0) [6]	24.0 (15.0-24.0) [6]
$t_{1/2}$ (h)	1.81 (73.5) [6]	4.59 (71.6) [6]
CL_F (L/h)	3.90 (29.8) [6]	4.08 (18.5) [6]

AUC_{inf} = area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC_{last} = area under the plasma concentration-time curve from time 0 to the last measurable non-zero concentration (t_{last}); CL/F = apparent clearance following an extravascular dose; CLR = renal clearance; C_{max} = maximum observed concentration; CV = coefficient of variation (%); n = number of subjects with valid observations; PIB = powder-in-bottle; $t_{1/2}$ = apparent terminal elimination half-life; t_{last} = time of the last quantifiable concentration; t_{max} = time of the maximum observed concentration; $\%AUC_{extrap}$ = percentage of AUC_{inf} that is due to extrapolation from the last quantifiable concentration to infinity.
Parameter starting with 'D' letter signifies the corresponding parameter was normalized by dose administered.
Geometric mean (CV) [n] statistics presented; for t_{max} and t_{last}, median (min-max) [n] statistics presented.

Maximum observed plasma concentrations of EIDD-1931 were between 229- and 912-fold higher vs. EIDD-2801 in subjects who had any quantifiable EIDD-2801 concentrations. The geometric mean EIDD-1931:EIDD-2801 ratio based on C_{max} (MRCmax) at doses from 600 to 1600 mg EIDD-2801 was between 476 and 610. Between-subject variability for plasma NHC, as assessed by geometric CV, was generally low (<25%) to moderate (25% to 40%) for AUC_{0-12}, AUC_{last}, AUC_{0-inf} and C_{max}.

Part 2 (Food Effect)

Subjects were randomised to a treatment crossover sequence in a 1:1 ratio:

- Sequence 1: 200 mg EIDD-2801 (capsule formulation) in the fed state (within 30 minutes of a high fat breakfast) followed by 200 mg EIDD-2801 (capsule formulation) in the fasted state.
- Sequence 2**:** 200 mg EIDD-2801 (capsule formulation) in the fasted state followed by 200 mg EIDD-2801 (capsule formulation) in the fed state (as above).

There was a 14-day washout period between doses.

Following oral administration of 200 mg EIDD-2801 in the fed state, T_{max} for **EIDD-1931** occurred later, with a median value of 3 h and a range of 2 to 4 h. The first quantifiable concentrations occurred between 0.5 and 1.5 h. Generally, the slower absorption and later T_{max} in the fed state was reflected in a lower geometric mean C_{max}, with values of 575 ng/mL in the fed state compared to 893 ng/mL in the fasted state. The GLSM ratio for C_{max} in the fed state compared to the fasted state was 0.644 and the 90% CI did not include unity. The $AUC_{0\text{-}inf}$ and AUC_{last} were similar in the fed and fasted state. The ratios of GLSMs were 0.955 and 0.959, respectively, and the 90% CIs included unity.

Table 3: Assessment of the Effect of Food on the Pharmacokinetic Parameters of eIDD-1931 Following Single Oral Doses of 200mg EIDD-2801 (Capsule) for Protocol EIDD-2801-1001-UK

Matrix: Plasma; Analyte: EIDD-1931, Profile Day: 1

Parameter	Treatment	n	GLSM	Fed versus Fasted Ratio of GLSMs (90% CI)
$AUC_{0\text{-}inf}$ (h*ng/mL)	200 mg EIDD-2801 capsule (fasted)	10	1980	
	200 mg EIDD-2801 capsule (fed)	10	1890	0.955 (0.881, 1.03)
AUC_{last} (h*ng/mL)	200 mg EIDD-2801 capsule (fasted)	10	1950	
	200 mg EIDD-2801 capsule (fed)	10	1870	0.959 (0.881, 1.04)
C_{max} (ng/mL)	200 mg EIDD-2801 capsule (fasted)	10	893	
	200 mg EIDD-2801 capsule (fed)	10	575	0.644 (0.535, 0.775)
t_{max} (h)[a]	200 mg EIDD-2801 capsule (fasted)	10	1.00	
	200 mg EIDD-2801 capsule (fed)	10	3.00	1.75 (1.00, 2.50)

[a] The n, median, and Hodges-Lehmann estimate of median difference (90% CI) from the Wilcoxon signed-rank test presented.
$AUC_{0\text{-}inf}$ = area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC_{last} = area under the plasma concentration-time curve from time 0 to the last measurable non-zero concentration (t_{last}); CI = confidence interval; C_{max} = maximum observed concentration; GLSM = geometric least squares mean; n = number of subjects with valid observations; NC = not calculated; t_{max} = time of the maximum observed concentration
Model: ln(parameter) = treatment sequence + period + treatment + subject(treatment sequence) + random error, with subject(treatment sequence) fitted as a random effect
The GLSMs, ratios of GLSMs and corresponding CIs were obtained by taking the exponential of the LSMs, differences and corresponding CIs on the natural log (ln) scale.

Administration of EIDD-2801 capsule formulation provided similar systemic exposure to EIDD-1931 (based on $AUC_{0\text{-}inf}$ and AUC_{last}) as the PIB formulation at the same dose. However, C_{max} was up to 24% lower and T_{max} was up to 0.75 h later following administration of the capsule formulation.

Part 3 (Multiple Ascending Dose)

Part 3 comprised 7 dose-escalation cohorts, all of which received capsules:

- Cohort 1: 50 mg EIDD-2801 or placebo BID (capsule formulation)
- Cohort 2: 100 mg EIDD-2801 or placebo BID (capsule formulation)
- Cohort 3: 200 mg EIDD-2801 or placebo BID (capsule formulation)
- Cohort 4: 300 mg EIDD-2801 or placebo BID (capsule formulation)
- Cohort 5: 400 mg EIDD-2801 or placebo BID (capsule formulation)
- Cohort 6: 600 mg EIDD-2801 or placebo BID (capsule formulation)
- Cohort 7: 800 mg EIDD-2801 or placebo BID (capsule formulation)

The first dose each day was given in the fasted state. Otherwise, there were no restrictions on taking capsules with food. A single dose was administered on the morning of Day 6 for the collection of steady-state PK blood samples.

EIDD-1931 appeared rapidly in plasma and was generally quantifiable from between 0.25 and 0.5 h on Day 1 at all dose levels. Half of those administered 200 mg BID and all except 1 administered ≥300 mg BID had quantifiable pre-dose samples on Day 6. Generally, T_{max} occurred between 1.00 and 2.50 h on Days 1 and 6.

Table 4: Summary of Plasma Pharmacokinetic Parameters for EIDD-1931 on Day 1 Following the Fist of Multiple Oral Doses of 50 to 800 mg EIDD-2801 (Capsule) for Protocol EIDD-2801-1001-UK

Matrix: Plasma; Analyte: EIDD-1931; Profile Day: 1

	EIDD-2801 capsule BID (fasted)						
Parameter	50 mg (N = 6)	100 mg (N = 6)	200 mg (N = 6)	300 mg (N = 6)	400 mg (N = 6)	600 mg (N = 6)	800 mg (N = 6)
AUC_{last} (h*ng/mL)	444 (17.3) [6]	835 (19.9) [6]	1640 (15.5) [6]	3080 (17.4) [6]	3790 (19.5) [6]	6110 (26.9) [6]	8180 (21.5) [6]
$DAUC_{last}$ (h*ng/mL/mg)	8.88 (17.3) [6]	8.35 (19.9) [6]	8.18 (15.5) [6]	10.3 (17.4) [6]	9.48 (19.5) [6]	10.2 (26.9) [6]	10.2 (21.5) [6]
$AUC_{inf,obs}$ (h*ng/mL)	461 (15.7) [6]	855 (19.8) [6]	1660 (15.3) [6]	3090 (17.4) [6]	3800 (19.5) [6]	6680 (17.6) [5]	8200 (21.6) [6]
$DAUC_{inf,obs}$ (h*ng/mL/mg)	9.22 (15.7) [6]	8.55 (19.8) [6]	8.32 (15.3) [6]	10.3 (17.4) [6]	9.51 (19.5) [6]	11.1 (17.6) [5]	10.3 (21.6) [6]
$\%AUC_{extrap,obs}$ (%)	3.36 (43.6) [6]	2.19 (42.6) [6]	1.34 (90.5) [6]	0.395 (22.1) [6]	0.327 (34.4) [6]	0.201 (18.8) [5]	0.214 (52.4) [6]
AUC, (h*ng/mL)	461 (15.7) [6]	854 (19.8) [6]	1660 (15.3) [6]	3080 (17.3) [6]	3800 (19.5) [6]	6110 (26.9) [6]	8190 (21.5) [6]
DAUC, (h*ng/mL/mg)	9.22 (15.7) [6]	8.54 (19.8) [6]	8.31 (15.3) [6]	10.3 (17.3) [6]	9.50 (19.5) [6]	10.2 (26.9) [6]	10.2 (21.5) [6]
$\%AUC_{extrap}$ (%)	3.51 (43.8) [6]	2.17 (41.9) [6]	1.25 (104) [6]	0.119 (277) [6]	0.103 (317) [6]	0.00785 (37.0) [6]	0.00933 (47.7) [6]
C_{max} (ng/mL)	223 (19.4) [6]	395 (18.5) [6]	766 (16.3) [6]	1280 (15.2) [6]	1530 (23.2) [6]	2160 (31.4) [6]	2770 (13.3) [6]
DC_{max} (ng/mL/mg)	4.47 (19.4) [6]	3.95 (18.5) [6]	3.83 (16.3) [6]	4.27 (15.2) [6]	3.81 (23.2) [6]	3.60 (31.4) [6]	3.47 (13.3) [6]
t_{max} (h)	1.00 (1.00-1.00) [6]	1.25 (1.00-2.03) [6]	1.50 (1.00-1.50) [6]	1.50 (1.00-1.50) [6]	1.50 (1.00-2.00) [6]	1.75 (1.00-6.00) [6]	1.75 (1.50-2.50) [6]
t_{last} (h)	6.00 (4.00-6.00) [6]	6.00 (6.00-6.03) [6]	6.00 (6.00-9.07) [6]	9.00 (9.00-11.9) [6]	9.03 (9.00-11.9) [6]	11.9 (11.9-12.0) [6]	11.9 (11.9-11.9) [6]
$t_{1/2}$ (h)	0.937 (14.0) [6]	0.918 (9.08) [6]	0.960 (10.4) [6]	1.09 (17.7) [6]	1.03 (13.1) [6]	1.16 (3.50) [3]	1.18 (7.28) [6]
CL_{ss} (L/h)	0.848 (64.2) [6]	1.16 (94.6) [6]	0.833 (80.7) [6]	1.09 (40.4) [6]	1.20 (65.8) [6]	1.95 (21.3) [6]	2.78 (19.5) [6]

Table 5 Summary of Plasma Pharmacokinetic Parameters for EIDD-1931 on Day 6 Following Multiple Oral Doses of 50 to 800 mg EIDD-2801 (Capsule) for Protocol EIDD-2801-1001-UK

Matrix: Plasma; Analyte: EIDD-1931; Profile Day: 6

	EIDD-2801 capsule BID (fasted)						
Parameter	50 mg (N = 6)	100 mg (N = 6)	200 mg (N = 6)	300 mg (N = 6)	400 mg (N = 6)	600 mg (N = 6)	800 mg (N = 6)
AUC_{last} (h*ng/mL)	414 (16.3) [6]	947 (15.7) [6]	1720 (26.0) [6]	3880 (16.3) [6]	3730 (21.6) [6]	7250 (28.1) [6]	8450 (18.5) [5]
$DAUC_{last}$ (h*ng/mL/mg)	8.29 (16.2) [6]	9.47 (15.7) [6]	8.58 (26.0) [6]	9.92 (16.3) [6]	9.31 (21.6) [6]	12.1 (28.1) [6]	10.6 (18.5) [5]
AUC, (h*ng/mL)	432 (14.9) [6]	968 (15.3) [6]	1730 (25.2) [6]	2960 (16.2) [6]	3710 (21.6) [6]	7110 (28.2) [6]	8330 (17.9) [5]
DAUC, (h*ng/mL/mg)	8.65 (14.9) [6]	9.68 (15.3) [6]	8.65 (25.2) [6]	9.88 (16.2) [6]	9.28 (21.6) [6]	11.9 (28.2) [6]	10.4 (17.9) [5]
$\%AUC_{extrap}$ (%)	3.78 (50.8) [6]	1.82 (81.7) [6]	---	0.370 (NC) [6]	0.367 (NC) [6]	---	---
RA_{AUC}	0.938 (7.80) [6]	1.13 (9.25) [6]	1.04 (18.0) [6]	0.961 (14.7) [6]	0.977 (11.7) [6]	1.16 (12.2) [6]	1.09 (11.8) [5]
C_{max} (ng/mL)	188 (8.67) [6]	434 (14.0) [6]	742 (32.1) [6]	1100 (20.6) [6]	1470 (20.9) [6]	2340 (20.9) [6]	2970 (16.8) [5]
DC_{max} (ng/mL/mg)	3.76 (8.67) [6]	4.34 (14.0) [6]	3.71 (32.1) [6]	3.68 (20.6) [6]	3.67 (20.9) [6]	3.74 (20.9) [6]	3.71 (16.8) [5]
RA_{Cmax}	0.843 (16.0) [6]	1.10 (11.4) [6]	0.969 (23.8) [6]	0.861 (14.3) [6]	0.962 (18.5) [6]	1.04 (20.0) [6]	1.09 (7.15) [5]
t_{max} (h)	1.00 (1.00-1.50) [6]	1.25 (1.00-1.50) [6]	1.50 (0.500-1.50) [6]	1.50 (1.00-2.00) [6]	1.50 (1.00-1.50) [6]	1.75 (1.50-2.50) [6]	1.50 (1.00-2.02) [5]
t_{last} (h)	6.00 (4.00-6.00) [6]	6.00 (6.00-9.00) [6]	9.00 (6.00-12.0) [6]	12.0 (9.00-24.0) [6]	12.0 (9.00-24.0) [6]	24.0 (24.0-24.0) [6]	24.0 (15.1-36.0) [5]
$t_{1/2}$ (h)	0.968 (15.5) [6]	0.970 (15.8) [6]	1.24 (36.4) [6]	1.71 (47.1) [6]	1.20 (9.58) [5]	NC (NC) [1]	7.08 (154) [4]
C_{trough} (ng/mL)	0.0891 (184) [6]	0.230 (170) [6]	1.03 (322) [6]	5.47 (114) [6]	5.13 (109) [6]	18.7 (41.3) [6]	16.7 (42.8) [5]
CL_{ss} (L/h)	0.777 (73.1) [6]	0.945 (52.3) [6]	1.02 (80.9) [6]	1.04 (47.5) [6]	1.43 (41.8) [6]	2.31 (44.5) [6]	2.27 (90.0) [5]

AUC_{last} = area under the plasma concentration-time curve from time 0 to the last measurable non-zero concentration (t_{last}); AUC, = area under the plasma concentration-time curve during a dosing interval beam pointbox; CL/F = apparent clearance following an extravascular dose; CLR = renal clearance; C_{max} = maximum observed concentration; C_{trough} = plasma concentration at the end of the dosing interval; C_{trough} = plasma concentration at the end of the dosing interval; CV = coefficient of variation (%); n = number of subjects with valid observations; NC = not calculated; RA_{AUC} = observed accumulation ratio based on AUC_{τ}; RA_{Cmax} = observed accumulation ratio based on C_{max}; $t_{1/2}$ = apparent terminal elimination half-life; t_{last} = time of the last quantifiable concentration; t_{max} = time of the maximum observed concentration

Parameter starting with 'D' letter signifies the corresponding parameter was normalized by dose administered.

Geometric mean (CV) [n] statistics presented for t_{max} and t_{last} median (min-max) [n] statistics presented.

On Day 6, similar to Day 1, EIDD-1931 concentrations generally declined in a monophasic manner following administration of ≤400 mg BID and were mostly below the LLOQ by ≤12 h. One subject administered 300 mg BID, 1 administered 400 mg BID and all except 2 administered ≥600 mg BID had quantifiable levels up to 24 h and the emergence of a second slower elimination phase was apparent, giving an increase of geometric mean t1/2 with dose. Following 800 mg BID the elimination phase was quantifiable, with a geometric mean t1/2 of 7.08 h (range 1.49 to 19.1 h).

Ctrough was estimated by extrapolation from the last observed concentration where concentrations at the end of the dosing interval were below the LLOQ. Geometric mean Ctrough was 5.47 ng/mL after 300 mg BID and increased to 18.7 and 16.7 ng/mL after 600 and 800 mg BID, respectively. Across all cohorts and days,

C_{max} for EIDD-1931 was between 81.6- and 672-fold higher than for EIDD-2801 (where measurable). There was no evidence of accumulation of NHC in plasma.

Although this was not a crossover study, the extent of absorption based on plasma NHC concentrations appeared to be similar between the PIB and capsule formulations but the rate of absorption appeared to be slightly slower for the capsule formulation compared to the PIB formulation, which was reflected in a slightly later median T_{max} and lower GM C_{max}.

Distribution

The plasma protein binding of molnupiravir was not assessed since it is not stable in plasma. The binding of NHC at 2, 20 and 100 µM in CD-1 mouse, SD rat, beagle dog, cynomolgus monkey and human plasma was measured by rapid equilibrium dialysis for 6 h at 37°C. The unbound fraction of NHC was approximately 1 in all matrices and at all concentrations tested.

Excretion

After single doses, the amount of **EIDD-1931** excreted in urine increased supra-proportionally with dose and there was a similar trend toward increased renal clearance (CLR). After BID dosing, up to 3.61% of the administered dose was excreted in urine as EIDD-1931 when assessed by geometric mean percentage of the dose administered recovered in urine over the dosing interval ($Fe_{0-\tau}$). The majority (generally >90% of the total amount excreted) was excreted in the first 4 h. The GM CLR ranged from 0.777 to 2.78 L/h across Days 1 and 6. CLR and $Fe_{0-\tau}$ were similar across cohorts and days at doses ≤200 mg BID. At >200 mg BID, there was a trend for CLR and $Fe_{0-\tau}$ to increase with increasing dose. Over the 4-fold dose range from 200 to 800 mg BID, the amount excreted in urine during a dosing interval ($Ae_{0-\tau}$) increased by approximately 16- and 11-fold on Days 1 and 6, respectively. The inter-subject variability in renal PK parameters was generally high (>40%).

Table 6: Summary of the Cumulative Urinary Excretion Parameters of EIDD-1931 on Day 6 Following Multiple Oral Doses of 50 to 800 mg EIDD-2801 (Capsule) for Protocol EIDD-2801-1001-UK

Matrix: Urine; Analyte: EIDD-1931; Profile Day: 6

		EIDD-2801 capsule BID (fasted)						
Parameter	Timepoint	50 mg (N = 6)	100 mg (N = 6)	200 mg (N = 6)	300 mg (N = 6)	400 mg (N = 6)	600 mg (N = 6)	800 mg (N = 6)
$Ae_{0-\tau}$ (mg)	0 to 4 h	0.328 (63.2) [6]	0.833 (48.3) [6]	1.50 (88.4) [6]	2.91 (64.4) [6]	3.06 (48.0) [6]	14.8 (40.1) [6]	16.9 (95.3) [5]
	0 to 8 h	0.336 (64.5) [6]	0.913 (47.8) [6]	1.75 (85.1) [6]	3.12 (63.6) [6]	5.31 (47.4) [6]	16.3 (40.0) [6]	18.8 (81.9) [5]
	0 to 12 h	0.336 (64.5) [6]	0.915 (48.0) [6]	1.76 (85.5) [6]	3.14 (63.4) [6]	5.32 (47.5) [6]	16.4 (39.9) [6]	18.9 (81.6) [5]
	0 to 48 h	0.336 (64.5) [6]						
$Fe_{0-\tau}$ (%)	0 to 4 h	0.832 (63.2) [6]	1.09 (48.3) [6]	0.955 (88.4) [6]	1.23 (64.4) [6]	1.61 (48.0) [6]	3.13 (40.1) [6]	2.68 (95.3) [5]
	0 to 8 h	0.854 (64.5) [6]	1.16 (47.8) [6]	1.11 (85.1) [6]	1.32 (63.6) [6]	1.69 (47.4) [6]	3.46 (40.0) [6]	2.98 (81.9) [5]
	0 to 12 h	0.854 (64.5) [6]	1.16 (48.0) [6]	1.12 (85.5) [6]	1.33 (63.4) [6]	1.69 (47.5) [6]	3.48 (39.9) [6]	3.00 (81.6) [5]
	0 to 48 h	0.854 (64.5) [6]						

$Ae_{0-\tau}$ = amount of the dose administered recovered in urine over the time interval t1 to t2; CV = coefficient of variation (%);
$Fe_{0-\tau}$ = percentage of the dose administered recovered in urine over the time interval t1 to t2; n = number of subjects with valid observations; NC = not calculated
Geometric means (CV) [n] statistics presented.

Metabolism

There has been no human ADME study.

The applicant conducted a semi-quantitative analysis of pooled human urine samples obtained at 0-12 h on Day 1 in study MK4482-004. NHC, cytidine, uridine and NHC-glucuronide were all detected in urine obtained after dosing with 100 mg or 800 mg.

The levels of NHC and NHC-glucuronide in urine increased approximately 18- and 13-fold, respectively, in the 800 mg BID dose group compared to the 100 mg BID dose group. Uridine increased approximately 6-fold in

the 800 mg BID dose. The fold-increase in cytidine could not be calculated because little to no cytidine was detected at the lower dose.

The applicant's conclusions were that the molnupiravir, being the 5'-isobutyrate ester prodrug of NHC, is converted to NHC by esterases (including CES1 and CES2) in intestinal and liver microsomes as well as plasma. After cellular uptake, NHC is triphosphorylated by host kinases to the active moiety NHC-TP. It was concluded from the human and nonclinical data that the majority of molnupiravir is converted to NHC, NHC-TP and (or ultimately to) uridine and/or cytidine which then mix with the endogenous nucleoside pool.

Dose proportionality

On Day 6 in MK4482-004, the increases in EIDD-1931 AUC_T with dose were slightly supra-proportional, with a slope >1 and a 90% CI that did not include unity (1.08 [90% CI: 1.02 to 1.14]). However, between-treatment pairwise analysis using an ANOVA model and ln-transformed dose-normalised AUC_T indicated that the 90% CI for the ratio of GLSMs spanned unity for the majority of comparisons up to 800 mg BID. When assessed using C_{max}, statistical analysis indicated a dose-proportional increase in exposure to EIDD-1931 with increasing dose, with a slope of 0.971 and a 90% CI (0.915 to 1.03) that included unity.

Pharmacokinetics in target population

A population PK model of NHC was developed initially using plasma concentration data collected after single and repeated MK-4482 administration in healthy individuals and patients with COVID-19 enrolled in MK-4482-P001, MK-4482-P002, MK-4482-P004 and MK-4482-P006. The dataset included 2952 NHC concentrations from 100 healthy participants, 189 inpatients with COVID-19 and 260 outpatients with COVID-19.

Modelling used NONMEM, Version 7, Level 3. The first-order conditional estimation with interaction method was used during all stages of model developing where possible. The forward selection followed by backward elimination approach was used for covariate evaluation. The final model was a linear 2-compartment model with sigmoid absorption (implemented using a zero-order input process into a depot compartment followed by first-order absorption into the central compartment) and first-order elimination. Inter-individual variability (IIV) was estimated for the elimination clearance (CL/F), central volume of distribution (VC/F) and the duration of the zero-order absorption process (D1), although the last 2 IIV terms were only estimated in participants from MK-4482-P004 and MK-4482-P001 who contributed more than 3 samples.

Covariates included in the final model as statistically significant predictors of PK parameters were:

- A less-than-proportional power function of body weight on CL/F;
- A less-than-proportional power function of BMI on VC/F;
- A 31.3% decrease in VC/F in females compared to males;
- A 568% increase in duration of D1 following a high-fat meal compared to fasting or a standard meal;
- A 64.4% decrease in D1 for oral solution or suspension compared to capsule;
- A 26.5% decrease in D1 for inpatients compared to healthy or outpatient participants.

Attempts were made to harmonise the body size effects on CL/F and VC/F at the stage of the model refinement. The results suggested that the effect of body size on CL/F could be interchangeably described by body weight or by BMI if associated with sex. However, the effect of body size on VC/F was better described by BMI associated with sex, compared to body weight alone. Therefore, for reasons of parsimony, the effects

identified during covariate analysis were not modified. Parameter estimates for the final model are presented in the table below.

Table 7: Parameter Estimates and Standard Errors for the Final Plasma NHC Pharmacokinetic Model

Parameter		Final Parameter Estimate		Magnitude of Variability	
		Population Mean	%RSE	Final Estimate	%RSE
CL/F	Apparent central clearance in 80-kg participants (L/h)	76.9	2.01	41.1 %CV	14.9
	Power of body weight effect (-)	0.421	20.4		
VC/F	Apparent central volume in 28-kg/m² BMI male participants (L)	72.0	6.40	40.0 %CV	35.8
	Proportional shift in female participants (-)	0.313	18.1		
	Power of BMI effect (-)	0.753	28.4		
Q/F	Apparent distribution clearance (L/h)	3.35	6.73	NE	NA
VP/F	Apparent peripheral volume (L)	70.0	14.8	NE	NA
KA	First-order absorption rate constant (1/h)	0.830	2.81	NE	NA
D1	Zero-order absorption duration (h)	0.802	4.83	42.8 %CV	15.9
	Proportional shift due to high-fat meal (-)	5.68	10.4		
	Proportional shift in oral solution (-)	-0.644	5.71		
	Proportional shift in hospitalized patients (-)	-0.265	22.4		
PHF	Probability of unknown high-fat meal (-)	0.250	FIXED	NE	NA
Residual Variability in Phase 1 Studies		0.123	9.58	35.1 %CV	NA
Residual Variability in Phase 2 Studies		0.268	5.33	51.7 %CV	NA
Minimum Value of the Objective Function = 38916.167					

Abbreviations: BMI, body mass index; %CV, coefficient of variation expressed as a percent; IIV, interindividual variability; NA, not applicable; NE, not estimated; NHC, β-d-N4-hydroxycytidine; %RSE, relative standard error expressed as a percent.
Note: Shrinkage estimates: 9.0% for IIV in CL/F, 36.6% for IIV in VC/F, and 39.0% for IIV in D1.
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Goodness of fit (GOF) plots indicated that the final model described the data reasonably well. All model parameters were estimated precisely (%RSE < 29% for fixed effects and < 36% for random effects) and without correlation. Based upon the final PK model, shrinkage in the Bayesian estimates of CL/F was small (9.0%), suggesting that individual predictions of CL/F, and thus, individual exposures can be considered reliable. However, shrinkage in VC/F and D1 were reasonably high (36.6% and 39.0%, respectively). Therefore, C_{max} predictions should be considered with caution.

Simulations were performed based on the final PK model using covariate data from the participants included in the analysis dataset and their individual Bayesian estimates of PK parameters. Simulations assumed hypothetical 800 mg BID dosing for 5.5 days for all individuals in the analysis dataset. Numerical integration was performed in NONMEM to compute the trough concentration prior to the last dose (Ctrough), C_{max} and AUC_{0-12} after the last dose for each individual. C_{max} was calculated for participants in which the absorption of NHC could be assessed (individuals for whom IIV was estimated on more than just CL). The model-predicted distribution of exposure metrics is shown by study in the tables below, first in nmol/L and then by ng/mL. The tables are specific to the recommended posology of 800 mg BID for 5 days (10 doses).

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Table 8: Distribution of Model-Predicted NHC Exposures (Molar Units) After 5.5 days of 800 mg Twice Daily Dosing, by Study

Variable		MK-4482-P001	MK-4482-P002	MK-4482-P004	MK-4482-P006	Overall	Patient: With COVID-19*
Maximum Concentration (nmol/L)	Mean (SD)	9530 (3110)	NA	10600 (2140)	NA	9910 (2840)	9530 (3110)
	Geom. mean (%CV)	8990 (36.9)		10400 (20.7)		9460 (32.6)	8990 (36.9)
	Median	9260		10600		9870	9260
	P5, P95	4580, 15600		7570, 14800		5050, 15400	4580, 15600
	n	178		100		278	178
Trough Concentration (nmol/L)	Mean (SD)	230 (550)	413 (1470)	102 (69.1)	185 (472)	286 (954)	302 (1050)
	Geom. mean (%CV)	110 (123)	132 (141)	87.7 (55.7)	117 (73)	113 (113)	120 (124)
	Median	88.9	102	83.2	102	95.6	97.9
	P5, P95	34.5, 860	41.8, 1280	42.3, 284	59.4, 286	39.2, 582	39.2, 860
	n	189	194	100	66	549	449
AUC_{0-12} (nmol x h/L)	Mean (SD)	32500 (16100)	38000 (36100)	29800 (6880)	34600 (12900)	34200 (21100)	35200 (23000)
	Geom. mean (%CV)	30100 (38)	33200 (46.9)	29100 (22.3)	33200 (27.6)	31300 (38.3)	31900 (41)
	Median	28800	30800	28700	32100	29900	30200
	P5, P95	18800, 56800	19600, 80900	20600, 39800	24400, 46100	19600, 56800	19600, 65200
	n	189	194	100	66	549	449

Abbreviations: AUC_{0-12}, area under the NHC concentration versus time curve from 0 to 12 h postdose; %CV, coefficient of variation expressed as a percent; Geom., geometric; n, number of individuals; NA, not applicable; NHC, β-d-N4-hydroxycytidine; Px, x^{th} percentile; SD, standard deviation.

* Excludes data from Study MK-4482-P004.

Table 9: Distribution of Model-Predicted NHC Exposures (Mass Units) After 5.5 days of 800 mg Twice Daily Dosing, by Study

Variable		MK-4482-P001	MK-4482-P002	MK-4482-P004	MK-4482-P006	Overall	Patient: With COVID-19*
Maximum Concentration (ng/mL)	Mean (SD)	2470 (807)	NA	2740 (554)	NA	2570 (737)	2470 (807)
	Geom. mean (%CV)	2330 (36.9)		2690 (20.7)		2450 (32.6)	2330 (36.9)
	Median	2400		2750		2560	2400
	P5, P95	1190, 4030		1960, 3840		1310, 3980	1190, 4030
	n	178		100		278	178
Trough Concentration (ng/mL)	Mean (SD)	59.6 (144)	107 (382)	26.5 (17.9)	47.9 (122)	68.9 (247)	78.4 (272)
	Geom. mean (%CV)	28.4 (123)	34.3 (141)	22.7 (55.7)	30.4 (73)	29.4 (113)	31.1 (124)
	Median	23.1	26.4	21.6	26.6	24.8	25.4
	P5, P95	8.94, 223	10.8, 333	11, 73.7	15.4, 74.1	10.2, 151	10.2, 223
	n	189	194	100	66	549	449
AUC_{0-12} (ng x h/mL)	Mean (SD)	8430 (4170)	9860 (7810)	7720 (1780)	8980 (3340)	8870 (5480)	9130 (5970)
	Geom. mean (%CV)	7790 (38)	8620 (46.9)	7540 (22.3)	8600 (27.6)	8120 (38.3)	8260 (41)
	Median	7450	8000	7450	8320	7740	7830
	P5, P95	4880, 14700	5080, 21000	5350, 10300	6320, 12700	5070, 14700	5060, 16900
	n	189	194	100	66	549	449

Abbreviations: AUC_{0-12}, area under the NHC concentration versus time curve from 0 to 12 h postdose; %CV, coefficient of variation expressed as a percent; Geom., geometric; n, number of individuals; NA, not applicable; NHC, β-d-N4-hydroxycytidine; Px, x^{th} percentile; SD, standard deviation.

* Excludes data from Study MK-4482-P004.

The impact of the covariate effects included in the final PK model was evaluated based on the geometric mean ratio (GMR) of exposure metrics. The intrinsic factor effects on MK-4482 PK were compared to standard bioequivalence limits (0.8 to 1.25).

For all sub-groups of age, body weight, sex, racial classification, ethnicity, patient hospitalisation status, renal function and hepatic function, the GMRs of AUC0-12 were within the 0.8 to 1.25 bioequivalence range. For BMI ≥40 kg/m^2, the GMR fell just below this range.

Overall, the applicant concluded from this analysis that, within their observed ranges, none of the evaluated intrinsic or extrinsic factors substantially influenced NHC exposures, as most effect sizes were well below 2-fold changes.

The selected PK model was deemed acceptable to predict individual exposure metrics for later use in pharmacodynamics analyses.

During the assessment, the POPPK analysis was updated several times. The last received POPPK analysis report is dated March 24 2022 and it includes data from healthy subjects (MK-4482-P004), the Phase 2a study in non-hospitalised patients with COVID-19 (MK-4482-P006), the study in hospitalised patients with COVID-19 (Phase 2 portion of MK-4482-P001) and the pivotal study in non-hospitalised patients with COVID-19 (MK-4482-P002).

There were 8093 sample records associated with 2036 subjects identified initially. Following data exclusions, the analysis was based on 4202 records from 1207 subjects. Exclusions related to data from study 008, records of NHC-TP, records from those who received placebo, duplicates of sampling date and time, dosing history problems, missing and non-imputable covariate information, values > ULOQ or < LLOQ, data from subjects with a study conduct issue and data points associated with an absolute value of the conditional weighted residuals > 5.

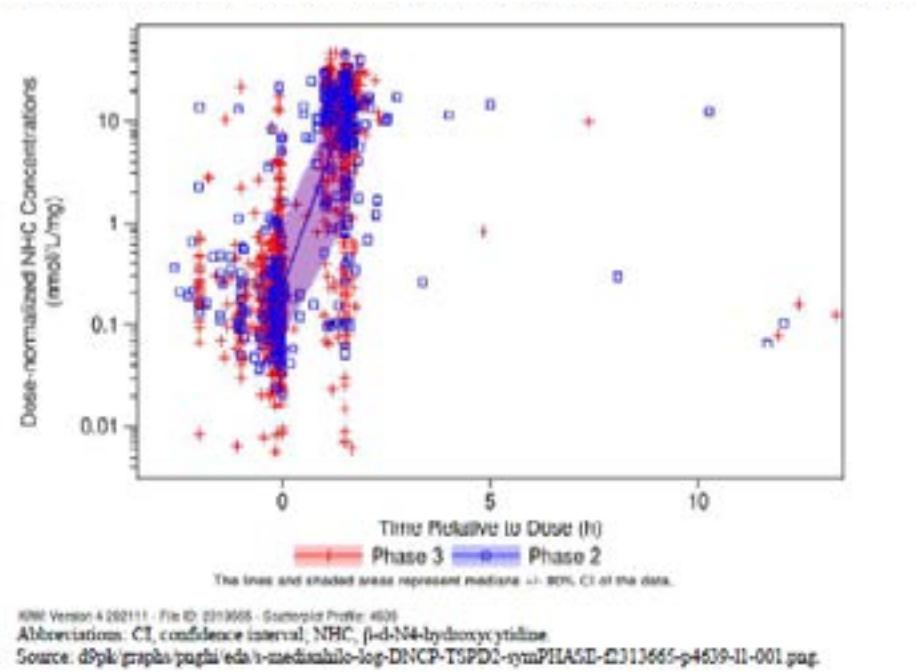
The final population comprised 100 healthy subjects, 196 hospitalised patients with COVID-19 and 911 non-hospitalised patients with COVID-19 (including 651 from the Phase 3 portion of MK-4482-P002. The population included 624 males (51.7%) and 583 females (48.3%) with a median (range) age of 46 years (18 to 91 years) and a median (range) body weight of 85 kg (36.1 to 172 kg). Recruitment occurred worldwide, with the majority of participants coming from Europe (41%), followed by Latin America (29.3%), North America (20.5%), Africa (7.04%) and Asia Pacific (2.15%). The majority of participants identified as white (66.7%) and non-Hispanic or Latino (59.2%). The analysis included individuals with normal renal function (45%), mild impairment (48.1%) or moderate impairment (6.96%). Based on the use of a modified Child-Pugh score most participants had normal hepatic function (94.8%, n = 1144) or mild hepatic impairment (4.97%, n = 60). Only 3 (0.25%) had moderate hepatic impairment.

As indicated in other sections, the dose of molnupiravir varied, as did the timing of sampling. In patients with COVID-19, samples were collected prior to the 9th or 10th dose and at different times post-dose depending on the study (1.5 h post-dose in MK-4482-P002).

POPPK modelling was performed using the computer program NONMEM, Version 7, Level 3. The PK model selected in the analysis conducted at the end of Phase 2 of MK-4482-P002 was refined. While the absorption and variability models were reassessed, the disposition model and covariate effects that were selected in the previous analysis were assumed to apply to the extended dataset used in this analysis. A univariate stepwise backward elimination analysis was conducted to test the statistical significance of the covariate effects selected in the previous analysis.

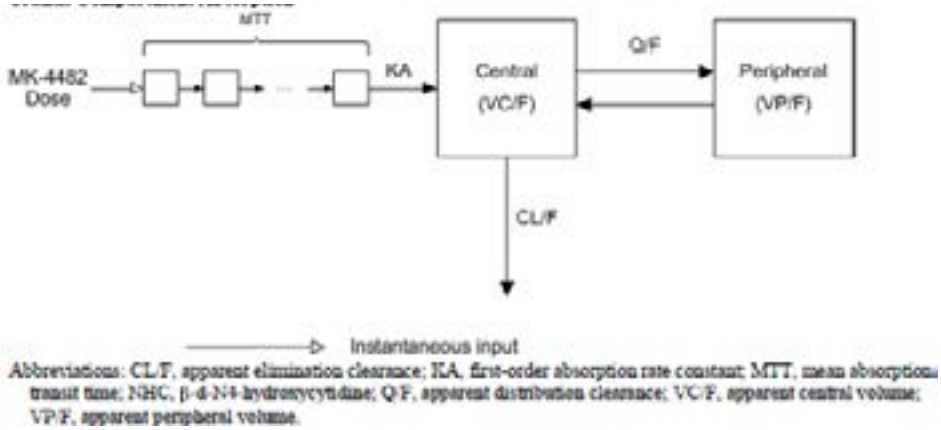
While the variability was generally larger in patients with COVID-19, the PK of NHC in plasma were generally similar across studies. In particular, the distribution of NHC plasma concentrations was consistent in the Phase 2 and Phase 3 portions of MK-4482-P002 (see first figure below).

The PK of NHC in plasma were described by a linear 2-compartment model with absorption captured by a series of transit compartments and with first-order elimination (see second figure below).



Abbreviations: CI, confidence interval; NHC, β-d-N4-hydroxycytidine.
Source: d9pk\graphs\paghi\eda\s-medianhalo-log-DNCP-TSPD2-symPHASE-f2313665-p4639-11-001.pag.

Figure 2: Dose-Normalised NHC Plasma Concentrations Versus Time Relative to Dose in Study MK-4482-P002, by Phase



Abbreviations: CL/F, apparent elimination clearance; KA, first-order absorption rate constant; MTT, mean absorption transit time; NHC, β-d-N4-hydroxycytidine; Q/F, apparent distribution clearance; VC/F, apparent central volume; VP/F, apparent peripheral volume.

Figure 3: Schematic of the Pharmacokinetic Model of Plasma NHC Following MK-4482 Administration Based on Transit Compartment Absorption

Inter-individual variability (IIV) was estimated for the apparent elimination clearance (CL/F) and central volume (VC/F), and inter-occasion variability was estimated on the mean transit time (MTT) of absorption. Variability in VC/F and MTT was only estimated in those who contributed more than 2 samples (MK-4482-P004 and MK-4482-P001). Distinct residual variability models were implemented for healthy participants and patients with COVID-19. All fixed and random effects model parameters were estimated precisely (relative standard error expressed as a percent [%RSE] 24.1%) and without correlation.

Table 10: Parameter Estimates and Standard Errors for the Final Pharmacokinetic Model

Parameter		Final Parameter Estimate		Magnitude of Variability	
		Population Mean	%RSE	Final Estimate	%RSE
CL/F	Apparent central clearance in 80-kg participants (L/h)[a]	70.6	1.97	43.4 %CV	8.00
	Power of body weight effect (-)[a]	0.412	14.0		
VC/F	Apparent central volume in 28-mg/m² BMI male participants (L)[b]	63.9	5.07	62.9 %CV	24.1
	Proportional shift in female participants (-)[b]	-0.330	11.8		
	Power of BMI effect (-)[b]	0.997	13.1		
Q/F	Apparent distribution clearance (L/h)	2.99	5.70	NE	NA
VP/F	Apparent peripheral volume (L)	68.3	14.6	NE	NA
MTT	Mean transit time (h)[c]	0.435	5.39	NE	NA
	Proportional shift due to high-fat meal (-)[c]	4.22	8.29		
	Proportional shift in oral solution (-)[c]	-0.616	5.49		
NN	Number of transit compartments (-)	7.84	16.5	NE	NA
KA	First-order absorption rate constant (1/h)	0.797	2.57	NE	NA
F1	Relative bioavailability (-)	1.00	FIXED	NE	NA
Interoccasion Variability in MTT[d]		NA	NA	39.8 %CV	17.6
Residual Variability in Phase 1		0.0652	11.9	25.5 %CV	NA
Residual Variability in Phase 2/3		0.347	4.66	48.7 %CV	NA
Minimum Value of the Objective Function = 56166.984					

Abbreviations: BMI, body mass index; %CV, coefficient of variation expressed as a percent; IIV, interindividual variability; IOV, interoccasion variability; NA, not applicable; NE, not estimated; NHC, β-d-N4-hydroxycytidine; %RSE, relative standard error expressed as a percent.

[a] The typical apparent clearance ($\widehat{CL/F}$) for an individual with weight $WTKG$ can be calculated as follows:

$$\widehat{CL/F} = 70.6 \times (WTKG/80)^{0.412}$$

[b] The typical apparent central volume of distribution ($\widehat{VC/F}$) for a male ($SEXF$=0) and female ($SEXF$ = 1) individual with body mass index weight BMI can be calculated as follows:

$$\widehat{VC/F} = 63.9 \times (1 - 0.33 \times SEXF) \times (BMI/28)^{0.997}$$

[c] The typical duration of the mean transit time of absorption ($\widehat{MTT}$) for an individual receiving MK-4482 as a capsule or suspension ($FSOL$=0) or an oral solution ($FSOL$=1) in fasted conditions (HFM=0) or after a high-fat meal (HFM=1) can be calculated as follows:

$$\widehat{MTT} = 0.435 \times (1 + 4.22 \times HFM) \times (1 - 0.616 \times FSOL)$$

[d] The different occasions for IOV in MTT were: Occasion 1 and Occasion 2.

Shrinkage estimates: 9.3% for IIV in CL, 27.9% for IIV in VC, 27.6% for IOV in MTT: Occasion 1, and 7.8% for IOV in MTT: Occasion 2.

Based upon the previous analysis, the covariate effects included in the final model as statistically significant predictors of the PK parameters were:

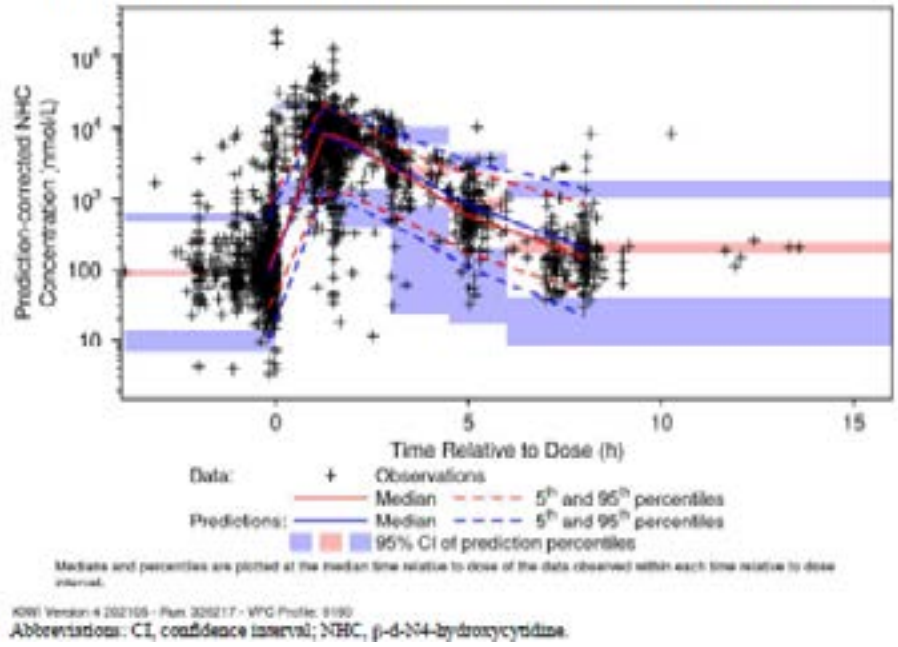
- less-than-proportional power function of body weight on CL/F
- less-than-proportional power function of body mass index (BMI) on VC/F
- 33% decrease in VC/F in females compared to males
- 422% increase in MTT following a high-fat meal compared to fasting or a standard meal
- 61.6% decrease in MTT for oral solution compared to capsule or suspension

The effect of hospitalisation status on absorption identified in the previous analysis was not found to be statistically significant = 0.001) following the refinement of the PK model.

Based upon the parameterisation and estimates of this final model, CL/F was predicted to increase from approximately 58.2 to 83.4 L/h when body weight increased from 50 to 120 kg, while VC/F was predicted to be 45.7, 63.9 and 79.8 L in males with a BMI of 20 kg/m2, 28 kg/m2 and 35 kg/m2. At equal BMIs, females are predicted to have a 33% lower VC/F than males. The typical effect of a high-fat meal prior to dosing would multiply MTT by 5.22, suggesting that high-fat food has a substantial effect on MK-4482 absorption kinetics. Similarly, formulation was found to impact MTT, as shown by the 61.6% decrease for oral solution

compared to capsule or suspension. Each of these effects of meals on absorption affected the rate, but not the extent of absorption, so overall exposure was not impacted by meal status.

The prediction-corrected visual predictive checks showed that in patients with COVID-19, the model predictions tracked the median and the variance in observed NHC concentrations generally well, with a slight under-prediction at the lower end of the concentration range, which may be related to the inclusion of outlier observations in the analysis dataset.



Abbreviations: CI, confidence interval; NHC, β-d-N4-hydroxycytidine.

Figure 4: Visual Predictive Check Plots for the Final Pharmacokinetic Model in Patients With COVID-19

Observed data in all dose groups of the COVID-19 patient studies were well described by the final PK model, based upon stochastic simulations in a virtual population with characteristics sampled from the actual analysis dataset.

Based upon pharmacodynamic analyses reported separately, efficacy and safety were more strongly related to overall exposures of NHC rather than peak or trough concentrations. Therefore, the effect of intrinsic and extrinsic factors was evaluated on the basis of the NHC GMR AUC0-12 predicted assuming a hypothetical 800 mg Q12h dosing regimen for 5 days. Distribution of trough concentration (Ctrough) and maximum concentration (C_{max}) are provided for completeness but were not used for evaluation of clinical relevance.

The clinical relevance of the predicted intrinsic and extrinsic factor effects was judged based on a comparison of whether or not the full 90% confidence interval (CI) of the associated GMR fell within bounds of [0.7, 2.0] set based upon efficacy and safety analyses.

For all sub-groups of age, body weight, BMI, sex, racial classification, ethnicity, patient hospitalisation status, renal function, hepatic function, formulation, meal status and use of remdesivir, the GMRs of AUC0-12 and the associated 90% CI limits were within the 0.7 to 2.0 comparability range. Therefore, based on the pre-defined criteria, the applicant concluded that no clinically important change in exposure was identified for any

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intrinsic or extrinsic factor, indicating that the same 800 mg Q12h dose is appropriate for all of these subpopulations.

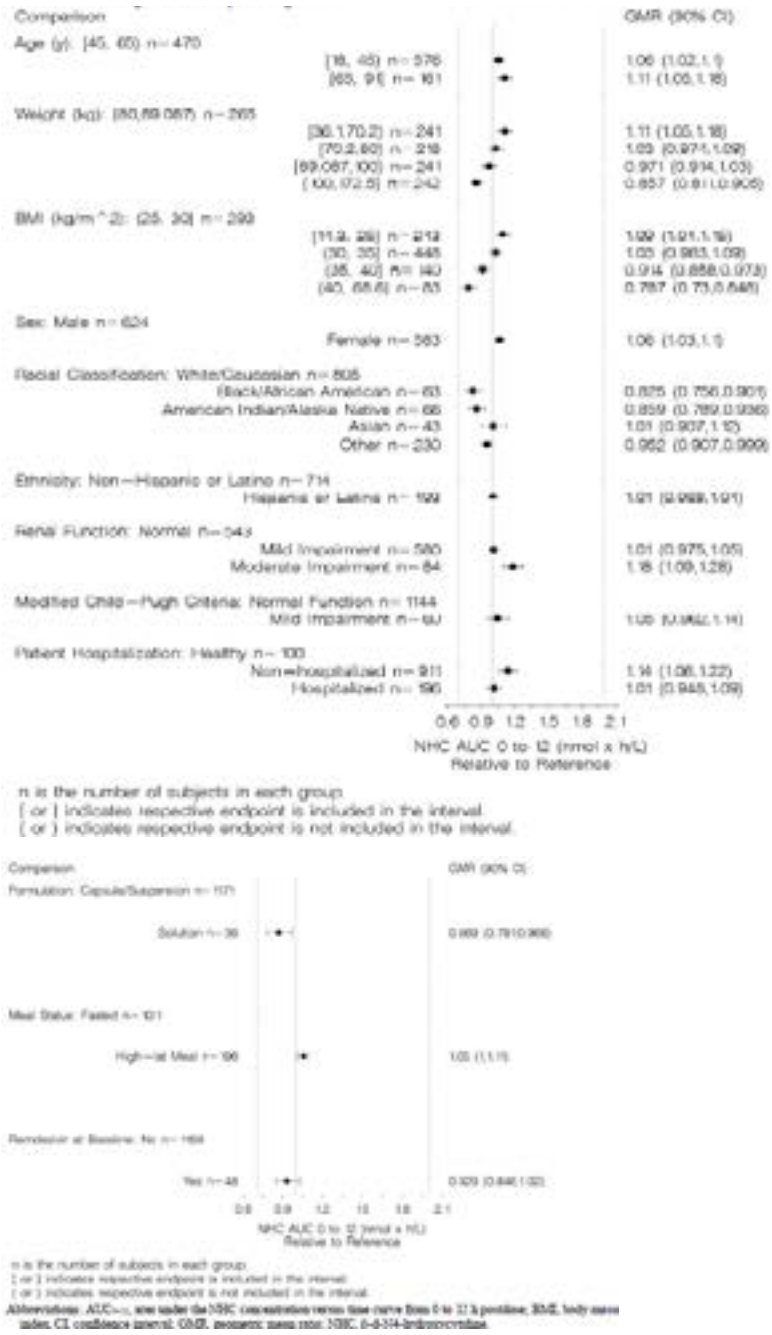

Figure 5: Forest Plot of Geometric Mean Rations (90% Confidence Intervals) for Model-Estimated AUC_{0-12} After 5 Days of MK-4482 800 mg Twice Daily Dosing

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The applicant's conclusions from this final POPPK analysis were as follows:

A linear 2-compartment model with absorption captured by a series of transit compartments and with first-order elimination was found to adequately describe the plasma PK of NHC after single and repeated Q12h dosing of MK-4482 in healthy adults and adult patients with COVID-19.

No statistical differences in NHC PK were found between healthy participants and patients with

COVID-19.

A high-fat meal delayed the absorption of MK-4482, but did not alter the extent of absorption. This resulted in decreased NHC peak concentrations (27.3%) and increased trough concentrations (59%) but did not significantly affect NHC AUC0-12. These alterations are not clinically relevant.

Body size was a statistically significant predictor of CL/F (through a less-than-proportional relationship with body weight) and VC/F (through a less-than-proportional relationship with BMI). Increases in body size metrics were generally associated with decreases in C_{max}, Ctrough and AUC0-12 of small magnitudes that are not expected to be clinically significant nor to warrant any dose adjustment.

Age was not a statistically significant predictor of NHC PK parameters and did not meaningfully affect NHC exposures over the range of observed age (18 to 91 years).

Females had a 33% lower VC/F than males, but sex did not statistically significantly affect NHC exposures. The small increases (15%) in C_{max}, Ctrough and AUC0-12 observed in females compared to males were most likely driven by differences in body size.

No statistically significant effect of ethnicity or self-identified racial group on NHC PK was found.

Estimated glomerular filtration rate was not a statistically significant predictor of NHC elimination. Mild renal impairment did not substantially affect NHC exposures. The effect of moderate renal impairment (observed in 84 participants) was modest on AUC0-12 (18% increase) and larger on Ctrough (45% increase). Overall, the effects of mild and moderate renal impairment are not clinically relevant.

Based upon 60 patients with mild hepatic impairment, hepatic function was not a statistically significant predictor of NHC PK and did not have a clinically relevant influence on NHC exposure.

Based upon 48 patients who received remdesivir, this was not a statistically significant predictor of NHC PK and did not have a clinically relevant influence on NHC exposure.

Overall, molnupiravir can be administered in adults without dose adjustment based upon age, sex, body size, food, and (mild to moderate) renal or (mild) hepatic impairment.

Special populations

No studies have been conducted in special populations.

This application concerns adults only. Age among adults was not a significant covariate in the POPPK analysis based on data collected up to the time of IA2 in studies MK4482-001 and -002. The availability of PK data from subjects aged >65 years at the time of updating the POPPK report is shown in the table.

Table 11: Summary of Elderly Subjects by Molnupiravir Study Included in the IA4 Population PK Data

Study Number	Age 65-74 Years (Older Subjects Number /Total Number)	Age 75-84 Years (Older Subjects Number /Total Number)	Age 85+ Years (Older Subjects Number /Total Number)
MK-4482-001	44/196	12/196	4/196
MK-4482-002 (Phase 2)	27/194	5/194	0/194
MK-4482-002 (Phase 3)	24/360	5/360	1/360
MK-4482-004	0/100	0/100	0/100
MK-4482-006	3/66	1/66	0/66
Total	98/916	23/916	5/916

Interactions

No clinical drug-drug interaction studies have been conducted. The following in-vitro data are relevant:

Molnupiravir and NHC as victims

Molnupiravir is hydrolysed to NHC via the high capacity esterases CES1 and CES2 *in vitro*. Following uptake of NHC into cells, host kinases and phosphatases involved in the endogenous pyrimidine nucleoside pathways anabolise and catabolise NHC to and from NHC-TP. NHC-related material is likely converted to endogenous pyrimidine nucleosides (uridine and/or cytidine) and their respective phosphate metabolites. The mitochondrial amidoxime reducing components (mARC1 and mARC2) have been reported to convert NHC to cytidine *in vitro* and cytidine deaminase readily converts NHC to uridine *in vitro*. Drug-drug interactions (DDIs) resulting from interference with these pathways seems unlikely. Molnupiravir is not a substrate for BCRP and MDR1 P-gp *in vitro*.

Molnupiravir and NHC as perpetrators

The potential for molnupiravir or NHC to be reversible inhibitors of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4 was evaluated using pooled human liver microsomes. At 100 µM, neither inhibited 50% of the marker activity of any CYP tested (i.e. IC_{50} values were all greater than 100 µM). At concentrations of 10 and 50 µM, neither demonstrated time-dependent inhibition of any CYP tested.

Since molnupiravir levels are expected to rapidly decline because of hydrolysis to NHC during absorption/first pass, a Gastroplus model was used to estimate maximum portal vein concentrations for molnupiravir and NHC of 1.6 and 24 µM, respectively. Since the CYP IC_{50} values *in vitro* were >100 µM, if inhibition were to occur it would be well above 10x the NHC plasma C_{max} and well above the maximum NHC portal vein concentrations. The data indicate that molnupiravir and NHC are unlikely to cause DDIs due to inhibition of CYPs in the intestine and liver during absorption or in the systemic circulation.

Molnupiravir and NHC did not inhibit OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2K and MRP2 with IC_{50} values greater > 100 µM. Molnupiravir and NHC also did not inhibit MDR1 P-gp and BCRP when assayed in a membrane vesicle format, which afforded testing up to 1000 µM. Molnupiravir and NHC did not produce an induction response in CYP1A2, 2B6 and 3A4 mRNA or enzyme activity.

2.5.2.2. Pharmacodynamics

Mechanism of action

After oral administration, molnupiravir is converted to NHC. After uptake of NHC into host cells, it is phosphorylated by host cell enzymes to form the active moiety NHC-TP. NHC-TP is a competitive alternative substrate to natural ribonucleotides for virally encoded RdRps. The process whereby the mutation rate is increased by exposure to a drug is referred to as Viral Decay Acceleration and results in viral ablation due to the mechanism of error catastrophe.

Primary pharmacology

In-vitro studies have shown that NHC has activity against several RNA viruses, including SARS-CoV-2, in multiple cell types (including Vero E6, HuH-7, Calu-3 lung epithelial cells and A549-ACE2 cells. The antiviral activity of NHC did not correlate with cellular cytotoxicity concentrations since CC_{50} values were greater than the highest concentration evaluated (i.e. SI values >3 in most studies).

Table 12: NHC Antiviral Activity Against SARS-CoV-2, SARS-CoV, and MERS-CoV in Cell Lines and Primary Human Bronchial/Tracheal Epithelial Cell

Virus	Strain	Cell line	EC_{50} (μM)	CC_{50} (μM)	SI	Source/Reference
SARS-CoV-2	2019-nCoV/USA-WA1/2020; GenBank Ac. No. MN985325.1	Calu-3 2B4[a]	0.08	>10	>125	Sheahan et al, 2020 [Ref. 4.3: 05K8L0]
		Vero E6	0.3	>10	>33	
SARS-CoV-1	Urbani	Vero76	<0.4	144	>360	NIAID Antiviral Testing Program [Ref. 4.3: 06FR0T]
SARS-CoV-1	SARS-CoV-GFP[b]	HAE-3D[c]	<1	>100	>100	PI0001 (EIDD Report 25.038) [Sec. 2.6.3.1]
SARS-CoV-1	SARS-CoV-GFP[b]	HAE	0.14	>100	>714	Sheahan et al, 2020 [Ref. 4.3: 05K8L0]
MERS-CoV	MERS-nLUC[d]	Calu-3 2B4[a]	0.15	>10	>67	Sheahan et al, 2020 [Ref. 4.3: 05K8L0]
MERS-CoV	GenBank Ac. No. JX869059[e]	DBT-9	0.56	>200	>357	Agostini et al, 2019 [Ref. 4.3: 05JF05]
MERS-CoV	Human β-CoV[b], Novel 2912	Vero E6	<0.8	20	>25	NIAID Antiviral Testing Program [Ref. 4.3: 06FR0T]

Ac. No.=Accession Number; CC_{50}=half-maximal cytotoxicity concentration; cDNA=complementary DNA; EC_{50}=half-maximal effective concentration; GFP=green fluorescent protein; HAE=human airway epithelium; MERS-CoV=Middle east respiratory syndrome-associated coronavirus; NHC=EIDD-1931 or N-hydroxycytidine; NIAID=National Institute of Allergy and Infectious Diseases (USA); nLUC=nanoluciferase; SARS-Cov-1=Severe acute respiratory syndrome-associated coronavirus-1; SI=selectivity index.

[a] Calu-3 2B4 is a human lung epithelial cell line.
[b] SARS-CoV engineered to express green fluorescent protein
[c] HAE organoid model.
[d] MERS-nLUC is a recombinant MERS-CoV engineered to express nanoluciferase.
[e] cDNA-derived clone.

Table 13: NHC Antiviral Activity Against SAS-CoV-2 in Multiple Susceptible Cell Lines

Laboratory	Cell Line	EC_{50} (μM)	CC_{50} (μM)	SI
Southern Research Institute	Vero E6 [a]	1.44	>30	>20.8
		2.03	>30	>14.8
		1.23	>30	>24.4
		0.97	>20	>20.6
HD Biosciences	Huh-7 [b]	2.08	>40.34	>19.4
		2.25	>40.34	>17.9
University of Texas Medical Branch (Galveston)	A549-ACE2 [c]	0.691	ND	ND
		0.672	ND	ND
Hackensack Meridian Health	A549-ACE2 [d]	2.66	>36	>15.5
		2.03	>36	>17.7
		2.16	>10	>4.62
		28.98 [f, g]	>36	>1.24
		1.44	>36	>25.0
Hackensack Meridian Health	VeroE6-TMPRSS2 [e]	0.32	ND	ND
		0.94	4.62	4.91
		1.08 [f]	19.3	17.9
		1.14	>10	>8.77
		0.49	4.39	8.96
Utah State University	Vero E6 [h]	0.78	>100	>130

ACE = angiotensin-converting enzyme 2; CC_{50}=half-maximal cytotoxicity concentration; EC_{50}=half-maximal effective concentration; HMH = Hackensack Meridian Health; μM=micromolar; ND = not determined; NHC=EIDD-1931 or N-hydroxycytidine; SARS-CoV-2=severe acute respiratory syndrome associated-coronavirus-2; SI=selectivity index; UTMB = University of Texas Medical Branch (Galveston).

[a] The SRI assay used Vero E6 cells and the SARS-CoV-2 USA_WA1/2020 strain virus.

[b] The HD Biosciences assay used Huh-7 cells and the hCoV-229E virus.

[c] The UTMB assay used A549-ACE2 cells and an N-luciferase-derived SARS-CoV-2 USA_WA1/2020 strain virus.

[d] This HMH assay used A549-ACE2 cells and mNeonGreen SARS-CoV-2 (icSARS-CoV-2-mNG), a reverse genetic variant of 2019-nCoV/USA_WA1/2020.

[e] This HMH assays used VeroE6-TMPRSS2 cells and mNeonGreen SARS-CoV-2 (icSARS-CoV-2-mNG), a reverse genetic variant of 2019-nCoV/USA_WA1/2020.

[f] This assay was performed using a 384-well format.

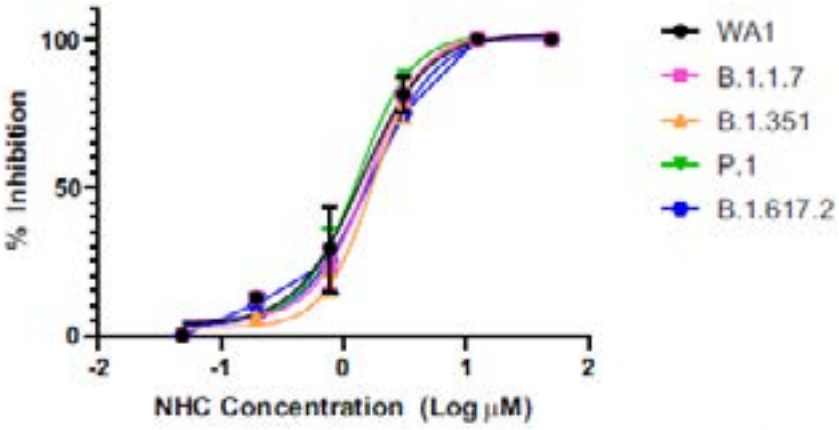
[g] This assay shows an inflection point of approximately 2.6 μM. The reported EC_{50} value may be shifted ten-fold due to a low maximum effective concentration.

[h] The Utah State University assay used Vero E6 cells and SARS-CoV-2 USA-WA1/2020.

Source: Adapted from Nonclinical Study Reports PD005, PD007, and PD008 [Sec. 2.6.3.1].

NHC showed in-vitro activity against SARS-CoV-2 variants of concern (VOCs) B.1.1.7 (Alpha), B.1351 (Beta), P.1 (Gamma) and B.1.617.2 (Delta).

In another study, the antiviral activity of NHC and remdesivir were compared against the WA1 (USA-WA1/2020) isolate using a cytopathic effect protection assay in Vero E6 cells. NHC inhibited SARS-CoV-2 variants B.1.1.7 (Alpha), B.1.351 (Beta) and P.1 (Gamma) with IC_{50} values of 1.59 μM, 1.77 μM and 1.32 μM, respectively, compared with 1.41 μM for WA1. In addition, NHC inhibited the SARS-CoV-2 variant B.1.617.2 (Delta) with an IC_{50} of 1.68 μM.



B.1.1.7 = SARS-CoV-2 Alpha variant or SARS-CoV-2 Isolate hCoV-19/USA/CA_CDC_5574/2020; B.1.351 = SARS-CoV-2 Beta variant or SARS-CoV-2 hCoV-19/South Africa/KRISP-EC-K005321/2020; B.1.617.2 = SARS-CoV-2 Delta variant or SARS-CoV-2 Isolate hCoV-19/USA/PHC658/2021; CA = California; CDC = (US) Centers for Disease Control and Prevention; CPE = cytopathic effect; μM = micromolar; NHC = N-hydroxycytidine; P.1 = SARS-CoV-2 Gamma variant or SARS-CoV-2, hCoV-19/Japan/TY7-501/2021; SARS-CoV-2 = severe acute respiratory syndrome-associated coronavirus 2; SEM = standard error of the mean; USA = United States of America; WA1 = SARS-CoV-2, Isolate USA-WA1/2020.

Data points represent the mean ± SEM percent inhibition of viral CPE by NHC against each SARS-CoV-2 virus variant tested. The SARS-CoV-2 variants B.1.1.7 (Alpha), B.1.351 (Beta), and P.1 (Gamma) were evaluated at the same time while the B.1.617.2 (Delta) variant was assessed separately.

Figure 6: Antiviral Activity on NHC Against SARS-CoV-2 Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2) Variants of Concern

As new variants emerged, additional studies reported the activity of NHC against Lambda, Mu and Omicron variants. The in-vitro activity of NHC was determined against C.378 Lambda and B.1.621 Mu variants using CPE in Vero E6 cells at ADARC at Columbia University. NHC IC_{50} values were 0.92 μM and 0.98 μM for C.37 (Lambda) and 1.05 μM and 1.94 μM for B.1.621 (Mu) compared to the historical IC_{50} value of 1.41 μM for WA1.

Table 14: N-Hydroxycytidine Antiviral Activity Against SARS-CoV-2 Variants Lambda and Mu in Vero E6 Cells

	IC_{50} (μM)				
		Lambda C.37		Mu B.1.621	
Compound	WA1 (USA)	Assay 1	Assay 2	Assay 1	Assay 2
NHC	1.41	0.98	0.92	1.94	1.05

B.1.621=SARS-CoV-2 Mu variant or SARS-CoV-2 Isolate hCoV-19/USA/WI-UW-4340/2021; C.37=SARS-CoV-2 Lambda variant or SARS-Related Coronavirus 2 Isolate hCoV-19/Peru/un-CDC-2-406994S/2021; CA=California; CDC=(US) Centers for Disease Control and Prevention; CPE=cytopathic effect; IC_{50}=half-maximal inhibitory concentration; NHC=N-hydroxycytidine; SARS-CoV-2=severe acute respiratory syndrome-associated coronavirus 2; SEM=standard error of the mean; USA or US=United States of America; WA1=SARS-CoV-2, Isolate USA-WA1/2020.

Viruses are described in [Table 4]. IC_{50} values were calculated from a four-parameter dose-response curve in GraphPad Prism 8.0. The dose-response data for NHC are shown in [Figure 1]. The SARS-CoV-2 variants C.37 (lambda) and B.1.621 (Mu) were evaluated at the same time while the data shown for WA1 is historical (Nonclinical Study Report PD010). The assay was performed twice. Assay 1 was performed with NHC lot 0003002; Assay 2 was performed with lot 0003005.

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The available data from sponsored studies and published studies for the Omicron variants are summarised in the next table.

Table 15: Molnupiravir and NHC Antiviral Activity Against SARS-CoV-2 Variants

Study	Cell Type	SARS-CoV-2 Variant	Molnupiravir EC_{50} (μM)	NHC EC_{50} (μM)
MSD Nonclinical Study Report PD015[a] [Ref. 4.2.1.1: PD015MS04482]	Vero E6	Omicron (BA.1)	ND	1.06
				1.12
		Omicron (BA.1.1)	ND	3.35
				1.86
Vangeel et al. 2022 [Ref. 4.3: 07YNFR]	Vero E6-GFP	Alpha	3.6	2.3
		Omicron	1.9	ND
Bojkova et al. 2022 [Ref. 4.3: 07YNGB]	Caco-2	Delta	ND	0.81
		Omicron-1[b]	ND	3.87
		Omicron-2[b]	ND	2.85
	Calu-3	Delta	ND	0.49
		Omicron-1[b]	ND	0.94
		Omicron-2[b]	ND	0.71
Dabrowska et al. 2021 [Ref. 4.3: 07YGG0]	A549 (ACE2/TMPRSS2)	Delta	1.3	0.17
		Omicron	0.23	0.07
Rosales et al. 2022 [Ref. 4.3: 07YJSK]	HeLa	Delta	ND	12.8
		Omicron	ND	10.4
	Vero E6/TMPRSS2	Delta	ND	1.81
		Omicron	ND	0.25
Takashita et al. 2022 [Ref. 4.3: 07YNHS]	Vero E6/TMPRSS2	Delta	ND	0.83
		Omicron (B.1.1.529)	ND	0.43
Li et al. 2022 [Ref. 4.3: 07YKW6]	Calu-3	WT	1.97	ND
		Omicron	0.76	ND
Takashita et al. 2022 [Ref. 4.3: 07Z526]	Vero E6/TMPRSS2	Omicron (BA.2)	ND	0.67

B.1.1.529=SARS-CoV-2 Omicron variant; EC_{50}=half-maximal effective concentration; GFP=green fluorescent protein; ND=not determined; NHC=β-D-N4-hydroxycytidine; SARS-CoV-2=severe acute respiratory syndrome-associated coronavirus 2; USA or US=United States of America; WT=wild-type.

[a] MSD Nonclinical Study Report PD015 describing study performed by Dr. Ho's lab at Aaron Diamond AIDS Research Center (ADARC), Division of Infectious Diseases, Columbia University Irving Medical Center (CUIMC), New York, New York, USA.

[b] SARS-CoV-2 Omicron (B.1.1.529) isolates Omicron 1 = FFM-ID20100/2021, EPI_ISL_6959671, GenBank ID OL800702; and Omicron 2 = FFM-ZAF0398/2021, EPI_ISL_6959681, GenBank ID OL800703).

Study PD015 addressed B.1.1.529 and BA.1.1 variants. This study in VeroE6 cells used authentic virus and a CPE assay. In two separate experiments, NHC had IC_{50} values of 0.63 μM and 1.10 μM for SARS-CoV-2 WA1 and 1.10 μM for the delta variant. NHC had IC_{50} values of 1.06 μM and 1.12 μM for omicron (B.1.1.529) and 3.35 μM and 1.86 μM for omicron BA.1.1.

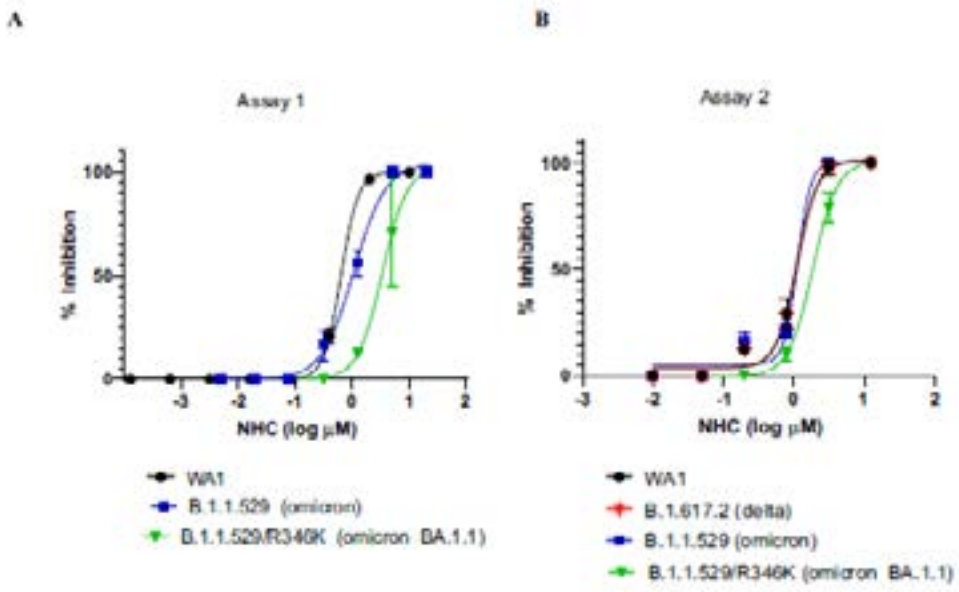
Table 16: N-Hycroxycytidine Antiviral Activity Against SARS-CoV-2 Omicron B.1.1.529 and Omicron BA.1.1 Variants in Vero E6 Cells

SARS-CoV-2 Virus	NHC IC_{50} (μM)	
	Assay 1	Assay 2
WA1 (USA)	0.63	1.10
Omicron B.1.1.529	1.06	1.12
Omicron B.1.1.529 BA.1.1 (R346K)	3.35	1.86
Delta B.1.617.2	ND	1.10

B.1.1.529=SARS-CoV-2 omicron variant; B.1.617.2=SARS-CoV-2 delta variant; IC_{50}=half-maximal inhibitory concentration; ND=not determined; NHC=N-hydroxycytidine; SARS-CoV-2=severe acute respiratory syndrome-associated coronavirus 2; USA or US=United States of America; WA1=SARS-CoV-2, Isolate USA-WA1/2020.

Amino acid single letter code: K=lysine; R=arginine.

Viruses are described in [Table 4]. IC_{50} values were calculated from a four-parameter dose–response curve in GraphPad Prism 8.0. The dose-response data for NHC are shown in [Figure 1].



B.1.1.529=SARS-CoV-2 omicron variant; B.1.617.2=SARS-CoV-2 delta variant; CPE=cytopathic effect; NHC=N-hydroxycytidine; SARS-CoV-2=severe acute respiratory syndrome-associated coronavirus 2; SEM=standard error of the mean; USA or US=United States of America; WA1=SARS-CoV-2, Isolate USA-WA1/2020.

Amino acid single letter code: K=lysine; R=arginine.

The panels show antiviral assay results for NHC against each SARS-CoV-2 variant. Data points represent the mean ± SEM percent inhibition of viral CPE by NHC against each SARS-CoV-2 virus variant tested. CPE was scored as described in section [5.3.1]. Viruses tested are described in [Table 4]. **Panel A** shows data for Assay 1; **panel B** shows data for Assay 2. IC_{50} values are shown in tabular form in [Table 5].

Figure 7: Antiviral Activity of NHC Against the SARS-CoV-2 Omicron (B.1.1.529) and Omicron BA.1.1 Variants

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One study (see Takashita *et al*. in the table) showed that the BA.2 variant was fully susceptible to NHC (EC_{50}: 0.67±0.22 µM).

In a non-infectious SARS-CoV-2 reporter replicon assay NHC was similarly active (EC_{50} values <1.6-fold) against replicons with remdesivir resistance-associated amino acid substitutions in NSP12 (polymerase). Two remdesivir-resistance mutations (F476L and V553L) did not confer cross-resistance to NHC in an in-vitro virus replication assay.

In vivo studies have included several viruses and animal models. Briefly:

Molnupiravir 500 mg/kg significantly reduced infectious SARS-CoV-2 levels in lung tissue from infected mice when given pre-exposure and post-exposure.

The ability of molnupiravir to mitigate SARS-CoV-2 infection and block transmission was examined in a ferret model of intranasal infection with 1 × 105 pfu of SARS-CoV-2. Treatment with twice-daily molnupiravir significantly reduced the SARS-CoV-2 viral load in the upper respiratory tract and completely suppressed viral spread to untreated contact animals.

In Syrian hamsters infected with 1 × 105 $TCID_{50}$ units of the B.1-G (Wuhan strain), B.1.1.7 (Alpha) or B.1.351 (Beta) variants of SARS-CoV-2, treatment with molnupiravir 200 mg/kg BID gave statistically significant reductions in viral RNA copies per mg of lung tissue and in infectious virus lung titres regardless of variant.

Two studies have evaluated molnupiravir against SARS-CoV-2 Omicron variants in animal infection models.

Rosenke *et al*. assessed the efficacy of MOV against Alpha, Beta, Delta and Omicron (B.1.1.529; EPI_ISL_7171744) variants in the Syrian hamster COVID-19 model.

Molnupiravir inhibited virus replication in the lungs of hamsters infected with Alpha, Beta and Delta VOCs and inhibited virus replication in the upper and lower respiratory tract of hamsters infected with the Omicron variant.

Lieber *et al*. evaluated molnupiravir against Alpha, Beta, Gamma, Delta and Omicron (B1.1.529, BA.1) VOCs in primary human airway epithelium organoids (in vitro), the ferret model of upper respiratory disease and a lethal Roborovski dwarf hamster efficacy model of severe COVID-19-like acute lung injury. All VOCs tested were inhibited by molnupiravir *in vitro* with results similar to those for the WA1 variant. Dwarf hamsters infected with Omicron showed significant virus load reduction in molnupiravir-treated males but not females.

Secondary pharmacology

NHC was tested for inhibition potential against a panel of ion channels, including hERG (CYL5038). There was no observed inhibition of function of any ion channel tested with NHC at 10 µM in this study (the clinical C_{max} is 10.8 µM when dosing with 800 mg BID). The applicant has not conducted a TQT study but ECGs were obtained in MK4482-004.

Relationship between plasma concentration and effect

MK4482-001 Part 1 and 002 Part 1 (interim analysis #2 in each study)

For the exposure-response (ER or PK/PD) analyses, Bayesian individual exposure estimates were derived from the POPPK model. The following viral load (VL) endpoints were explored:

- Change from baseline at EOT (Day 5), Day 10, 15, 29
- Decline slope from baseline to EOT (taking Day 3 measure into calculation)
- Percentage of subjects BLOQ at EOT, Day 10, 15, 29

E-R relationships were modelled testing several functional forms (E_{max}, sigmoidal E_{max}, Linear) and all models included a covariate effect term for baseline VL. Models were evaluated for all P001/P002 data and for subsets defined by study or time since symptom onset (TSSO). Overall, results were consistent with a virologic effect during the 5-day treatment with durability.

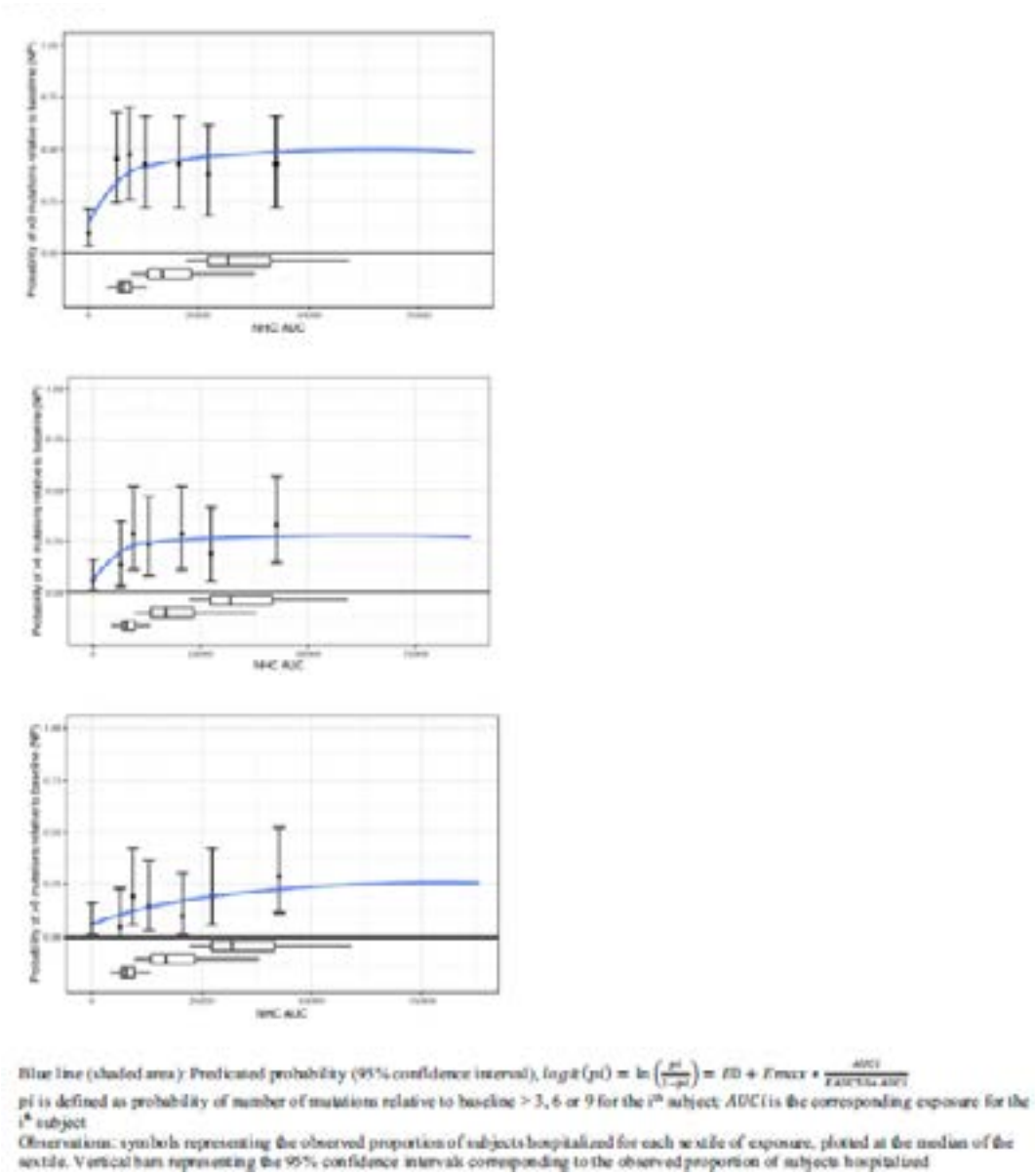
E-R Relationship Identified (X denotes at 0.05 level; x denotes marginal result at 0.10 level, x not significant)

		P001/002 *N=520	P002 *N=276	TSSO ≤5 days in P001/002 *N=58 from P001 *N=186 from P002
Mutation	Mutation Rate Above Threshold of 3		Not tested due to small sample size	
	Mutation Rate Above Threshold of 6			
	Mutation Rate Above Threshold of 9			
Viral RNA	CFB on Day 5			
	CFB on Day 10			
	CFB on Day 15			
	CFB on Day 29			
	Decline slope from baseline to Day 5			
	Proportion of BLOQ at Day 5			
	Proportion of BLOQ at Day 10			
	Proportion of BLOQ at Day 15			
	Proportion of BLOQ at Day 29			
Clinical Efficacy	Hospitalization Rate	Not Relevant		Not Relevant

*N reflects the number of subjects with available exposures + placebo subjects

Figure 8: E-R Relationship

There were 195 participants in P001 and P002 with a baseline result and at least one on-treatment result from NGS. The mutation rate ER dataset included 180/195 with plasma NHC PK measures or from placebo arms. An increased SARS-CoV-2 mutation rate was observed in participants receiving any molnupiravir dose compared to placebo, consistent with the proposed mechanism of action. The highest mutation rate post-treatment was observed in the 800 mg group, with the drug effect saturating at 800 mg. The presence of mutations was not correlated with TSSO to start of treatment.



Blue line (shaded area): Predicated probability (95% confidence interval), $logit(pi) = \ln\left(\frac{pi}{1-pi}\right) = E0 + Emax * \frac{AUCi}{EAUC50+AUCi}$

pi is defined as probability of number of mutations relative to baseline > 3, 6 or 9 for the i^{th} subject; $AUCi$ is the corresponding exposure for the i^{th} subject

Observations: symbols representing the observed proportion of subjects hospitalized for each sextile of exposure, plotted at the median of the sextile. Vertical bars representing the 95% confidence intervals corresponding to the observed proportion of subjects hospitalized

Figure 9: Binned Data and Logistic Regression Model-Estimated Exposure-Response Relationship for Probability of Mutation Rate >3 (top), 6 (middle) or 9 (bottom) per 10,000 bases Relative to Baseline in P001/002

The VL PK/PD dataset for P001 and P002 at IA2 included 520 with plasma NHC PK measures and VL measures at baseline and EOT. Exploratory data analyses identified several challenges, including a strong

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influence of baseline VL on change from baseline (CFB) or VL initial decline slope and baseline VL of BLOQ resulting in a zero or positive CFB post treatment. The figure shows the relationship between baseline and CFB at EOT for VL during treatment, where data falling on the dashed line is at the theoretical maximal observable VL drop based on assay LOQ.

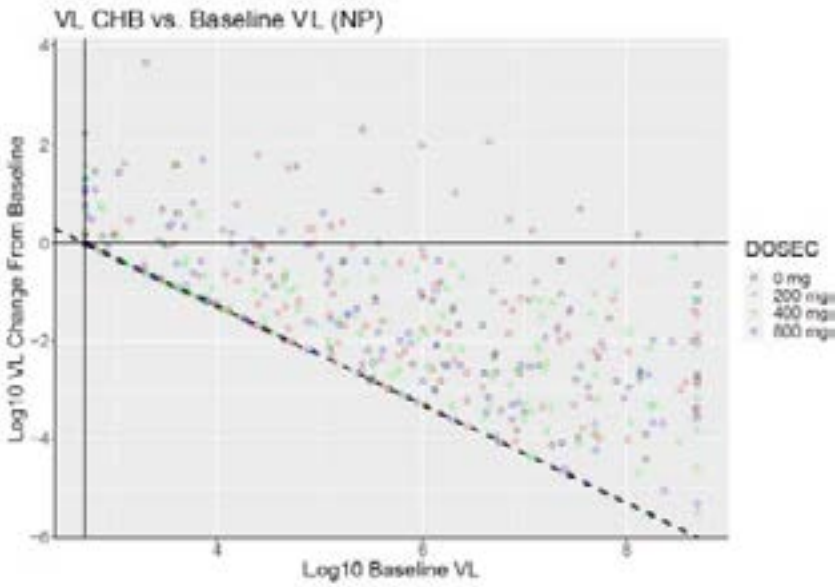

Figure 10: Association between Viral Load Change from Baseline on day 5 and the Baseline Viral Load for NP SARS-CoV-2 RNA viral load

The TSSO at baseline was strongly associated with baseline VL, which would strongly influence the magnitude of VL change that could be demonstrated post treatment. For VL change from baseline or decline slope, exploratory analyses indicated that TSSO was an influential factor on potential drug effects observed. Dose-dependence was suggested in the VL profiles, particularly for data from P002 and/or in subsets with shorter TSSO. The apparent influence of TSSO in VL profiles is shown below.

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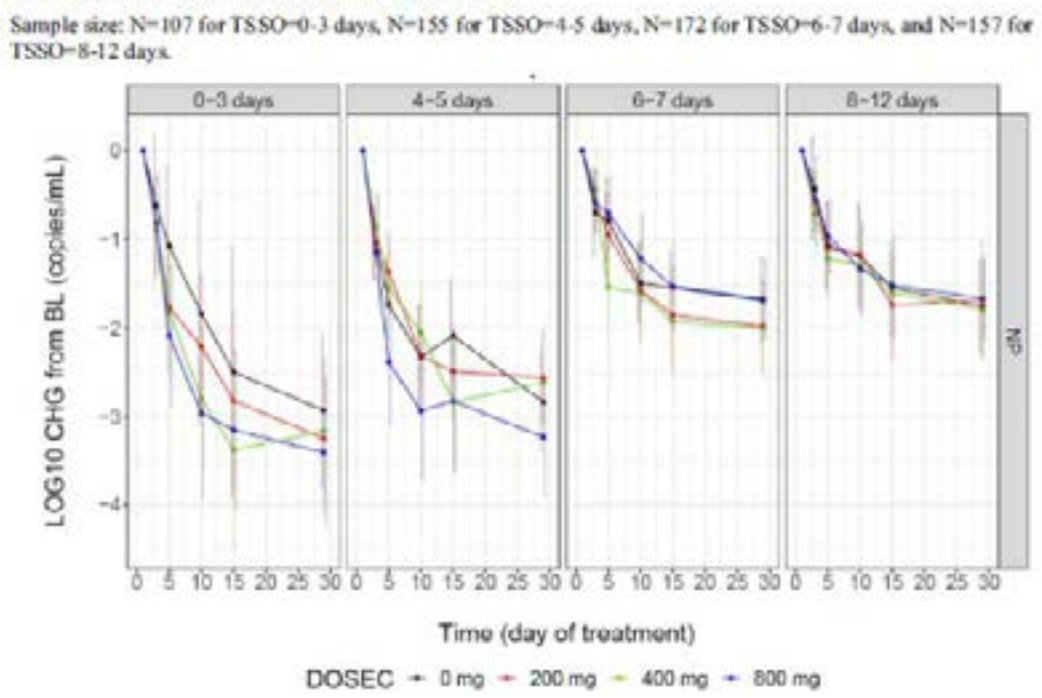

Figure 11: Mean Viral Load Change from Baseline Profiles in the Combined P001 and P002 Data, Stratified by Time since Symptom Onset (TSSO) in 4 Buckets

At 800 mg, VL change from baseline vs. placebo in P002 was 0.47 and 0.25 (log_{10} copies/ml) at Day 5 and Day 10, respectively. In the subgroup of TSSO <=5 days in P002, VL drop from baseline vs. placebo was 0.71 and 0.60 (log_{10} copies/ml) at Day 5 and Day 10, respectively. Dose-response curves simulated from the ER models predict a larger drug effect at 800 mg than at 400 or 200 mg, with this result most evident in shorter TSSO data.

The potential for ER in drug effects on the time to achieve negative VL was modelled using data on subjects with BLOQ measures at EOT, Day 10, 15 and 29. Results suggested a larger separation from placebo during the 5-day treatment period in P002 or in the subpopulation of TSSO ≤5 days. The proportion with negative VL appeared to increase over placebo in the post-treatment period. For subsets of P002 only or TSSO ≤5 days, separation appeared to occur prior to Day 10 (as early as Day 3) and the 400 and 800 mg doses separated further from placebo than the 200 mg dose. The confidence intervals for these curves were largely overlapping even when the central tendency separated.

In Part 1 of P002 there were 11 hospitalisations through Day 29 but 3/11 received ≤ 3 doses of 800 mg molnupiravir before hospitalisation so no PK samples were collected. The rate of hospitalisation was 1.3% (3/225) in participants receiving ≥ 5 doses of molnupiravir (all doses combined) vs. 5.4% (4/74) in participants receiving placebo. Logistic regression did not identify a significant relationship in the full P002 population, and a marginal trend was identified in those with TSSO≤ 5 days (N=182, p-value=0.098), suggesting the importance of early treatment. Mutation rate and probability of BLOQ exposure-response models yielded ER curvature consistent with nearing saturation, while change from baseline and slope of viral decline exposure-response could be equally well described by E_{max} or linear relationships. The applicant concluded that the E-R analyses with mutation rate, VL endpoints and P002 clinical efficacy suggest that 800 mg provides an effect near the plateaus of the dose response curve, particularly for TSSO ≤5 days.

The applicant also conducted mechanistic viral dynamics modelling (VDM) to explore the pattern of drug effect on VL profiles. The model mathematically represents the cellular infection process by the SARS-CoV-2 virus and the induced innate and adaptive immunity responses. The treatment effect was assumed to inhibit viral infection rate by reducing the infectivity consistent with the catastrophic mutational error mechanism of action. A simplified drug effect of 95% reduction of viral infectivity during treatment was implemented. The nasal swab longitudinal virology data from two published ferret challenge studies were used to inform the viral replication parameters of the model. To translate the model to humans, the infected cell death rate, innate immunity effector cell number and scaling factor between viral titre and viral load were adjusted to capture the central tendencies in P001/P002.

Results suggested that when the treatment is started on day 1-3 post infection it slows the growth of the virus to give a lower peak VL relative to no treatment and a shortened duration of measurable VL. After day 5 or 6, the VL drug effect becomes minimal and is similar to the profile with no treatment.

Updated E-R analysis including study 002, Part 2

During the procedure the applicant provided an updated E-R report dated 24 March 2022, which includes the full data from study 2 Part 2.

This final report on pharmacometrics was prepared following completion of the Phase 3 non-hospitalised study (P002 Part 2) and aimed to further characterise exposure-dependency in molnupiravir drug effects, to evaluate the appropriateness of the 800 mg Q12H dose and to describe molnupiravir exposures associated with safety and efficacy.

E-R models were developed for the occurrence of hospitalisation or death during the 29-day study period and for viral load. An extensive effort to build placebo response models was undertaken prior to attempting to model the drug effect or exposure-dependency in response for each model developed. Additionally, models were investigated to characterise the link between viral load and the primary clinical outcome.

Participants with high baseline viral load were at greater risk for more severe symptomology, hospitalisation, need for supplemental oxygen and mechanical ventilation and death vs. those with lower baseline viral load. There was an even stronger relationship with sustained high viral loads as measured on Day 5 or Day 10 with these outcomes. Molnupiravir likely influences outcomes by reducing viral loads more quickly than the natural immune response alone.

The applicant states that change from baseline measures relative to placebo are typically reported to more clearly separate drug effects from the natural viral load time course. However, this additional change from baseline is not itself the driver of clinical outcome. Rather it is the resulting absolute viral load (natural immune response + drug effect) that likely influences the outcome. This suggests that the magnitude of drug effect on viral load needed to avoid hospitalisation or death will likely vary across individuals depending on the magnitude of their viral replication and their immune response.

In the placebo model of the primary clinical outcome, influential factors were baseline viral load, baseline disease severity, age, weight, clade and comorbidities of active cancer and diabetes. Baseline viral load and baseline disease severity were also consistently identified as covariates in the placebo models for virologic endpoints. The clinical outcomes modelling was based on empirical relationships in a logistic regression structure that did not attempt to mechanistically link effects on virology with those on outcome.

Drug effect in the primary outcome model was best represented as an additive term on the other covariate terms. This is consistent with the likely varying nature of the magnitude of drug effect on viral load needed to avoid negative outcomes. It also suggests that the observed drug benefit in terms of the relative risk

reduction for clinical outcomes may vary with the population studied even when the specific drug effect term is not altered. To illustrate this potential effect, the logit equation solution for a series of hypothetical patients is calculated in the table below.

Table 17: Calculation of Probability of Hospitalisation (p(H)) for a Series of Hypothetical Patients if Untreated (placebo) or Treated with MOV (at the typical median exposure) using the final clinical outcomes E-R Model equation

Hypothetic Patient Characteristics	logit placebo	drug effect	logit MOV	p(H), placebo	p(H), MOV	Fractional reduction with MOV
40 yr, delta, 70 kg, mild symptoms,bVL=5 log	-4.535	-0.647	-5.182	0.011	0.006	-0.474
40 yr, gamma, 70 kg, mild symptoms,bVL=7	-2.408	-0.647	-3.055	0.083	0.045	-0.455
65 yr, gamma, 70 kg, mild symptoms,bVL=7	-1.308	-0.647	-1.955	0.213	0.124	-0.417
65 yr, gamma, 70 kg, mod symptoms,bVL=7	-0.448	-0.647	-1.095	0.390	0.251	-0.357
65 yr, gamma, 150 kg, mod symptoms,bVL=7	0.992	-0.647	0.345	0.729	0.585	-0.197
65 yr, gamma, 150 kg, mod symptoms, active cancer,bVL=7	2.751	-0.647	2.104	0.940	0.891	-0.052

for all, AUC = 32900 (median value at 800 mg)

With identical drug effect value in all scenarios, the % reduction in probability of hospitalisation with MOV treatment relative to placebo decreases as the complexity of the patient with regards to other influential factors increases. This simple exploration suggests that caution is warranted in comparing relative risk reduction values between studies or among groups without a careful understanding of how the other influential factors may differ in these comparisons.

In study 2 Part 2 the relative risk reduction was larger at the interim analysis than in the all randomised 3 analysis. To check for the potential that drug effect was altered over the course of the trial conduct, enrolment bin was evaluated as a covariate on the E-R model. It was not found to be significant, suggesting that shifts in other influential covariates over the study may account for the difference in efficacy.

Although modest, a shift towards MOV participants skewing older, with higher bVL and with higher prevalence of active cancer relative to placebo later in the trial, relative to the opposite skews earlier in the trial, may have influenced the observed results. The potential role of other influential factors is an important consideration in making cross trial comparisons.

As an external validation, the placebo primary outcome event rate was projected for a patient population similar to that studied in the nirmatrelvir/ritonavir trial using the placebo model developed from the MOV trial data. The prediction from this exercise was 7.2% hospitalisation or death, which is similar to the 6.4% rate reported for this trial. The outcome rate was also projected for MOV treatment in this population and the results suggested that the risk reduction would have been larger than in the population studied in the MOV trial. Of note, the Day 5 VL drop relative to placebo in patients with TSSO ≤5 days was -0.695 log10 in the nirmatrelvir/ritonavir trial compared to -0.35 log10 for MOV in the MOV trial. Although the nirmatrelvir/ritonavir VL drug effect was larger, the difference was smaller relative to the reported differences in risk reduction.

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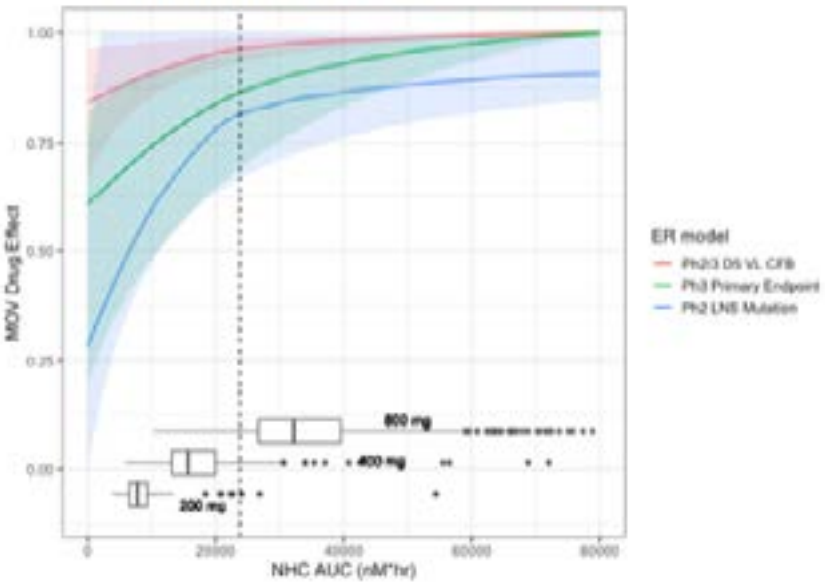
A key limitation in the exposure-response analyses is the need to exclude participants for whom PK data are missing, generally due to PK samples having not been collected at the EOT visit, or for whom no baseline VL sample was obtained. For this reason, the observed results described in this report do not exactly match those reported in the clinical study report for P002 where these participants were included. The 15 excluded participants in the ER analyses from the MOV arm who were hospitalised in Phase 3 resulted in the absolute hospitalisation rates for MOV from the ER models being lower than observed in the full clinical results without this exclusion. For this reason, the E-R modelling results should be interpreted with a focus on the learnings regarding the relative impact of exposure on response rather than a focus on absolute values predicted.

After accounting for other influential covariates, the exposure-dependency in the clinical outcomes and in the virologic response was well characterised during model development. Consistent with results from E-R analyses at the end of Phase 2, the Phase 3 E-R results continue to support that plasma NHC AUC0-12 is the preferred PK parameter for driving response. Strong exposure-dependency with AUC became non-significant or less significant when trough concentration (C12hr) was used as the exposure parameter in the model. The active moiety NHC-TP in PBMC tissue cells has been shown to have a longer half-life and to accumulate with Q12H dosing and NHC AUC in plasma was shown to have a consistent strong correlation with NHC-TP PK measures in PBMCs. Taken together, all these findings strongly support that NHC AUC in plasma is the appropriate PK driver for assessing exposure-response relationships.

The mechanism of action of introducing errors into the viral RNA is also a cumulative process of accumulation of substitutions which render the new virus produced to be non-infectious. Consistent with findings from the end of Phase 2 analysis, drug effect is obtained on Day 10 viral load similar to that seen on Day 5. Furthermore, the investigation of the hospitalisation benefit associated with these virologic pharmacodynamic markers supports the importance of reduced viral load at Days 5 and 10 as strong drivers of clinical outcomes.

Longer times after treatment end (Day 15) had weaker evidence for exposure-response, which may reflect washout of drug effect, but could also have been due to the generally low viral load values at that stage post-infection being too low to demonstrate a drug effect, if present.

In contrast to findings from the end of Phase 2 E-R analysis, the E-R analysis from the Phase 3 analysis supports a consistent interpretation regarding the shape of the E-R relationships across all the response measure. Normalised exposure-response curves for the primary clinical outcome in Phase 3, the Day 5 CFB VL response from Phase 2 and 3, and the LNS mutation rate (measure of mechanism of action) from Phase 2 are overlaid in the figure, illustrating this consistency in E-R shape.



AUC=area under the concentration-time curve, CFB=change from baseline, E-R=exposure-response, LNS= low frequency nucleotide substitutions ; MOV=molnupiravir, MK-4482, EIDD-2801; NHC=N-hydroxycytidine, EIDD-1931; PopPK=population PK; Q12H=every 12 hours; VL=viral load

Y-axis is a relative scale (from 0 to 1) and reflects the predicted drug effect relative to the model estimated Emax value for each E-R model. Three different efficacy responses were simulated for a range of exposures using their corresponding E-R models. The efficacy was normalized to a [0, 1] scale using a min-max normalization method where the corresponding emax value is considered as maximum efficacy. The red, green, and blue lines and shaded regions show the mean and 90% C.I. of the drug effect for various efficacy responses. The shaded uncertainty bands are created by accounting for the uncertainty in the drug effect model parameter estimates (Emax and EC50). The dashed vertical line represents the AUC value (23800 nM*hr) that corresponds to the 0.7 lower clinical bound. All other covariates were fixed to the mean values for continuous covariates and to the most prevalent category for the categorical covariates.

The solid line within the box represents the median. The lower and upper hinges represent the 25th and 75th percentiles, respectively. The whiskers extend to the most extreme values within 1.5 times the interquartile range.

Figure 12: Normalised E_{max} E-R Relationships for Hospitalisation or Death (Phase 3), Day 5 Viral Load CFB (Phase 2 and Phase 3), LNS Error count (Phase 2) Compared to AUC Distribution at 200, 400, and 8000 mg Q12H from PopPK Results

All of these E-R relationships were best represented by an E_{max} structural model with reasonable consistency in the estimated AUC50s (within ~4-fold) across the models of 19900, 10260, and 4390 nM*hr for hospitalisation, Day 5 VL CFB, and LNS mutation rate, respectively. Most patients at 800 mg achieve exposures associated with near maximal response. The viral load E-R models indicate that maximal response is essentially obtained at 800 mg, while the hospitalisation E-R model suggests that small gains in drug benefit would be seen if doses are increased over 800 mg. However, the available results suggest that additional clinical benefit from increased doses above 800 mg would at best be modest in magnitude and the results support the 800 mg dose.

The results support plasma NHC AUC exposures as the primary PK measure to judge the clinical relevance of PK effects on efficacy, as well as most relevant PK measure for safety.

Given that exposure findings in the comparability bounds (0.7 to 2.0) for MOV are based on NHC AUC and are proposed based on the totality of the E-R results, the lower bound of 0.7 corresponds to plasma NHC AUC0-12 of approximately 23,800 nM*hr (that is, 70% of the geometric mean of model predicted AUC0-12 for patients with COVID-19) for which subpopulations can be expected to derive meaningful clinical benefit from dosing with 800 mg Q12h without the need for dose adjustment. This bound would maintain subpopulation exposures above the AUC50 from the hospitalisation E-R mode. The upper bound of 2.0 corresponds to

plasma NHC AUC012 of approximately 68,000 nM*h (that is, 2 times the geometric mean of model predicted AUC012 for patients with COVID-19) that ensures that subpopulations are maintained within the range of clinical experience, as 48 achieved plasma NHC AUC012 greater than this threshold in the molnupiravir trials without notable alteration in the safety profile.

In summary, the applicant has concluded from the updated E-R analyses that:
☐ There is strong empirical/statistical evidence of an exposure-response relationship in viral load change from baseline on Day 5 and 10 in the virologic data from non-hospitalised patients enrolled ≤ 5 days following symptom onset pooled across the Phase 2 and 3 studies. The magnitude of antiviral effect for the 800 mg dose was greater than that predicted for the 200 mg and 400 mg doses.

☐ Significant exposure-response in the probability of hospitalisation or death was identified in the Phase 3 data (P002 Part 2). The AUC50 was estimated to be 19900 nM*hr. A number of influential factors were identified that affected hospitalisation rate beyond drug exposures, including baseline viral load, baseline disease severity, age, weight and comorbidities of active cancer and diabetes.

☐ The shape of the exposure-response relationships identified for drug effects on viral load and for drug effects on hospitalisation rate were similar and overall supported a conclusion that exposures from an 800 mg dose fall near the plateau of the E-R curves.

☐ Overall, the exposure-response results support the MOV dose of 800 mg Q12H.

☐ The E-R results support clinical equivalence bounds of 0.7, 2.0 for the NHC AUC in plasma as defining the range of exposures with meaningful drug benefit and demonstrated acceptable tolerability.

2.5.3. Discussion on clinical pharmacology

Pharmacokinetics

Nonclinical and clinical investigations indicated that molnupiravir is a prodrug. After oral administration, the human plasma levels of molnupiravir are low and measurable levels after 800 mg BID for 5 days are transient. The data reflect rapid conversion of molnupiravir to NHC such that the NHC T_{max} after an 800 mg oral dose of molnupiravir occurs at about 1 h.

The nonclinical data indicate that conversion from molnupiravir to NHC is mainly via non-specific esterases in the intestine and liver, suggesting that clinically significant drug-drug interactions are unlikely to occur at the level of conversion of molnupiravir to the circulating active substance NHC. The mechanism of action of NHC (see next section) relies on its cellular uptake from plasma and serial phosphorylation by host cell kinases to the triphosphate (NHC-TP).

With so little molnupiravir detected in plasma, the absolute bioavailability of parent drug is assumed to be negligible. The absolute bioavailability of NHC after oral dosing of humans with molnupiravir has not been determined. Absolute bioavailability of NHC after oral dosing of dogs and rats was estimated to be from 52-100%.

Molnupiravir does not show significant pH-dependent solubility over gastrointestinal pH values so gastric pH reducing agents are not predicted to affect NHC PK. After 200 mg single doses administered using capsules, there was no significant effect of food on NHC AUC (i.e. extent of absorption) but there was a delay in absorption, giving a longer T_{max} and lower C_{max}.

Since the food effect is not expected to affect antiviral activity, dosing was without regard to food in the efficacy studies and there are no restrictions on dosing conditions in the SmPC.

After 800 mg BID dosing of healthy subjects using capsules for 5 days, the elimination phase for NHC was quantifiable, with a geometric mean $t_{1/2}$ of 7.08 h (range 1.49 to 19.1 h). There was no accumulation in plasma. Between-subject variability, as assessed by geometric CV, was generally low (<25%) on Days 1 and 6 for NHC AUCτ and C_{max}. Moreover, in-vitro data suggest that NHC is not protein bound.

There has not been an ADME study but it is clear that only small quantities of NHC were recovered from urine along with some NHC glucuronide. It was concluded from the human and nonclinical data that the majority of molnupiravir is converted to NHC, NHC-TP and (or ultimately to) uridine and/or cytidine, which then mix with the endogenous nucleoside pool. Considering these conclusions on metabolism and excretion, the applicant did not conduct studies to examine the effect of renal or hepatic impairment on NHC PK. However, in response to queries raised and the POPPK findings, as well as the exclusion of subjects with severe renal impairment from clinical studies, the applicant has agreed to commit to assess the effects of renal and hepatic impairment on NHC PK.

The initial POPPK analysis indicated that there was little difference in NHC C_{max}, C_T and AUC between healthy subjects and subjects infected with COVID-19 or between hospitalised and non-hospitalised populations. The applicant updated the POPPK analysis during the procedure. The updated analysis of predicted NHC AUC_{0-12} would support not recommending dose adjustments.

There have been no clinical drug-drug interaction studies. With such low clinical exposures to molnupiravir itself, no clinically important interactions are expected for parent drug as victim or perpetrator.

NHC is not a substrate of P-gp or BCRP and it did not inhibit these transporters at 100x the clinical C_{max}. At concentrations up to 100 µM (10x C_{max}) in some experiments, NHC did not inhibit any of the major CYP isoenzymes or transporters (i.e. IC_{50} values were all greater than 100 µM). Also, at molnupiravir concentrations up to 5x clinical C_{max} (with an assumption that most was likely converted to NHC during the experiment) and NHC concentrations up to 2x clinical C_{max}, there was no induction of CYP1A2, 2B6 or 3A4. There were some limitations on the maximum concentrations that could be tested due to cytotoxicity in some experimental conditions.

The SmPC recommends that if a dose is missed and this is noticed within 10 h, then the missed dose should be taken, followed by the next dose on time, which means that two doses could be taken as little as 2 hours apart. On request, the applicant provided a justification for this 10-hour window based on POPPK modelling and simulations of plasma levels of NHC with 800 mg given 2, 4 or 6 hours apart. Exposures (C_{max} and AUC_{0-12}) were most similar to 12-hour dosing when the 9th dose was delayed by 6 hours. An 8-hour delay increased the AUC_{0-12} and C_{max} slightly (GMR 1.2 and 1.1, respectively) and a 10-hour delay gave GMRs of 1.5 and 1.4, respectively, assuming the fasted condition. If all subjects were dosed with a high-fat meal, delaying the previous dose by 10 hours results in GMRs of 1.8 for both parameters vs. 12-hour dosing. Overall, based on POPPK NHC estimates in plasma, it was agreed that missed doses may be taken within 10 hours of their regularly scheduled time.

The applicant was also requested to provide advice on repeat dosing in case of vomiting. The current statement in the SmPC recommends no repeat dosing. The applicant provided a justification for this advice, which was accepted.

Pharmacodynamics

The in-vitro virologic data indicate that NHC is active against a range of RNA viruses, including SARS-Cov-1 and SARS-CoV-2, MERS-CoV and influenza viruses.

The EC_{50} values for SARS-CoV-2 isolates, which have been determined in various laboratories and cell lines, have generally ranged from <1 µM up to ~3 µM. In Vero E6 cells, NHC inhibited SARS-CoV-2 variants B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma) and B.1.617.2 (Delta) with IC_{50} values of 1.59 µM, 1.77 µM, 1.32 µM and 1.68 µM, respectively, compared with 1.41 µM for the "wild type" strain WA1. NHC was also active against the Lambda (C.37) and Mu (B.1.621) variants, with mean IC_{50} values of 0.92 µM and 0.98 µM for C.37 (Lambda) and 1.05 µM and 1.94 µM for B.1.621 (Mu).

Additional data on activity of molnupiravir against the omicron variant and sub-variants as assessed in Vero E6 cells suggest that activity is maintained against B.1.1.529 and BA.1.1. One published study (Takashita *et al*. 2022) showed that the BA.2 variant was fully susceptible to NHC (EC_{50}: 0.67±0.22 µM). A report from Takashita *et al*. showed antiviral activity of MOV against Omicron variants BA.2.12.1, BA.4 and BA.5. In addition, studies at Columbia University showed that molnupiravir/NHC has similar antiviral activity against BA.2, BA.4 and BA.5 compared with the original WA-1 isolate.

Based on the different mechanism of action and on in-vitro studies using SARS-CoV-2 replicons encoding defined mutations, the activity of NHC is not affected by NSP12 (polymerase) mutations that confer reduced susceptibility to remdesivir. Molnupiravir did not antagonise remdesivir *in vitro*.

In-vivo nonclinical studies provided support for the potential efficacy of oral molnupiravir dosing to treat SARS-CoV-2. See the nonclinical report for further details.

The decision to proceed to Part 2 of MK4482-002 with 800 mg BID was based on initial exposure-response (E-R) analyses, mainly driven by Part 1 of this study and Part 1 of MK4482-001 in hospitalised patients. The modelling of E-R for effect on viral load led the applicant to conclude that:

i. The largest overall magnitude of antiviral effect was observed for the 800 mg dose;

ii. The effects were more pronounced for those enrolled ≤ 5 days following symptom onset;

iii. The TSSO at baseline was strongly associated with baseline VL;

iv. 800 mg BID gives an antiviral effect that is near the plateau of the dose-response curve.

The applicant updated the exposure-response analyses using the study 2 Part 2 data. However, the analyses necessarily exclude participants for whom PK data are missing. The 15 excluded participants in the ER analyses from the MOV arm who were hospitalised in Phase 3 resulted in the absolute hospitalisation rates for MOV from the ER models being lower than observed in the full clinical results without this exclusion. The final conclusion of the applicant is that there is an exposure-response relationship in viral load change from baseline on Day 5 and 10 in non-hospitalised patients enrolled ≤ 5 days following symptom onset. It is concluded that the predicted effect of the 800 mg dose is greater than that predicted for 200 mg and 400 mg doses. A number of influential factors were identified that affected hospitalisation rate beyond drug exposures, including baseline viral load, baseline disease severity, age, weight and comorbidities of active cancer and diabetes.

Serial passage experiments suggested that there is a reasonable barrier to NHC resistance. Data from clinical studies have shown an increased SARS-CoV-2 mutation rate in virus obtained during treatment and after

treatment in subjects who received molnupiravir dose compared to placebo, consistent with the proposed mechanism of action (viral error catastrophe). The highest mutation rate post-treatment was observed in the 800 mg group, with the drug effect saturating at 800 mg. The presence of mutations did not correlate with TSSO to start of treatment.

2.5.4. Conclusions on clinical pharmacology

There are no outstanding issues. The applicant committed to monitor emergence of new variants and will assess the in-vitro activity of molnupiravir against these.

2.5.5. Clinical efficacy

The applicant's studies that enrolled outpatients with COVID-19 were:

- MK4482-006, which was a dose-finding study with a virologic primary endpoint
- MK4482-002, with dose-finding and confirmatory parts with a clinical primary endpoint

MK4482-001 was a study in hospitalised patients that was stopped at the end of Phase 2 due to lack of clinical effect.

2.5.5.1. Dose response studies

MK4482-006

This was a randomised double blind, placebo-controlled escalating dose study. Eligible adult subjects were to start treatment within ≤168 h of time since symptom onset (TSSO). Laboratory confirmation required a positive molecular or non-molecular test conducted at any CLIA-certified laboratory from a sample collected ≤96 hours prior to study entry. Subjects were to have at least one of fever OR signs/symptoms of respiratory illness as defined and listed in the protocol. Eligible subjects were not in need of hospitalisation or immediate medical attention in the opinion of the investigator. No medications with possible anti-SARS-CoV-2 activity were allowed within 30 days prior or during the study and subjects were not to have been vaccinated against SARS-CoV-2. There was staged enrolment starting with 200 mg BID for 5 days and increasing by study arm to 800 mg BID. Dosing was without regard to food except those subjects fasted overnight before the PK sampling days.

Study Part	Treatment Description	Treatment Display Code
Part 1	Part1: Molnupiravir 200 mg BID	A
	Part 1: Placebo	B
Parts 2/3/4/5/6/7/8/9	Parts 2-9: Molnupiravir 400 or 800 mg BID	C/E/G/I/K/M/O/Q
	Parts 2-9: Placebo	D/F/H/J/L/N/P/R
Pooled Treatment	Molnupiravir 200 mg BID	1
	Molnupiravir 400 mg BID	2
	Molnupiravir 800 mg BID	3
	Placebo	9

In Part 1, randomisation was stratified by time (days) from symptom onset defined by:

- Early presentation: randomisation 0 to ≤60 h from symptom onset
- Late presentation: randomisation >60 to ≤168 h from symptom onset

Randomisation was not stratified in subsequent study parts.

The primary efficacy objective was to determine if molnupiravir reduces the time to viral RNA negativity, defined by RT-PCR applied to nasopharyngeal (NP) swabs. The NP swabs were also used for determination of infectivity at a central laboratory.

The RT-PCR assay was based on the US CDC 2019-nCoV EUA assay, which uses primers specific to the N1 region of the SARS-CoV2 RNA with LLOQ of 1018 copies/mL. The infectivity assay was that described by Sheahan (2020) in Vero E6 cell monolayers. A positive culture resulted when viral RNA was >1,000 copies/mL at Day 2 or increased from Day 2 to Day 5 by 0.5 $\log_{10}$ copies/mL.

The GenoSure SARS CoV-2 RdRp assay (next-generation sequencing [NGS] assay) was used to amplify and sequence the complete RdRp coding region of the SARS-CoV-2 RNA. Minor variants detected at 1%.

The following analysis sets were defined for this study:

Intent-to-Treat (ITT) = all randomised.

Modified Intent-to-Treat (mITT) = all treated with at least 1 post-baseline viral RNA assessment.

Per Protocol (PP) = no important protocol deviations and completed the Day 28 follow-up visit.

Results

Subject disposition is shown in the figure and the populations analysed are shown in the table.

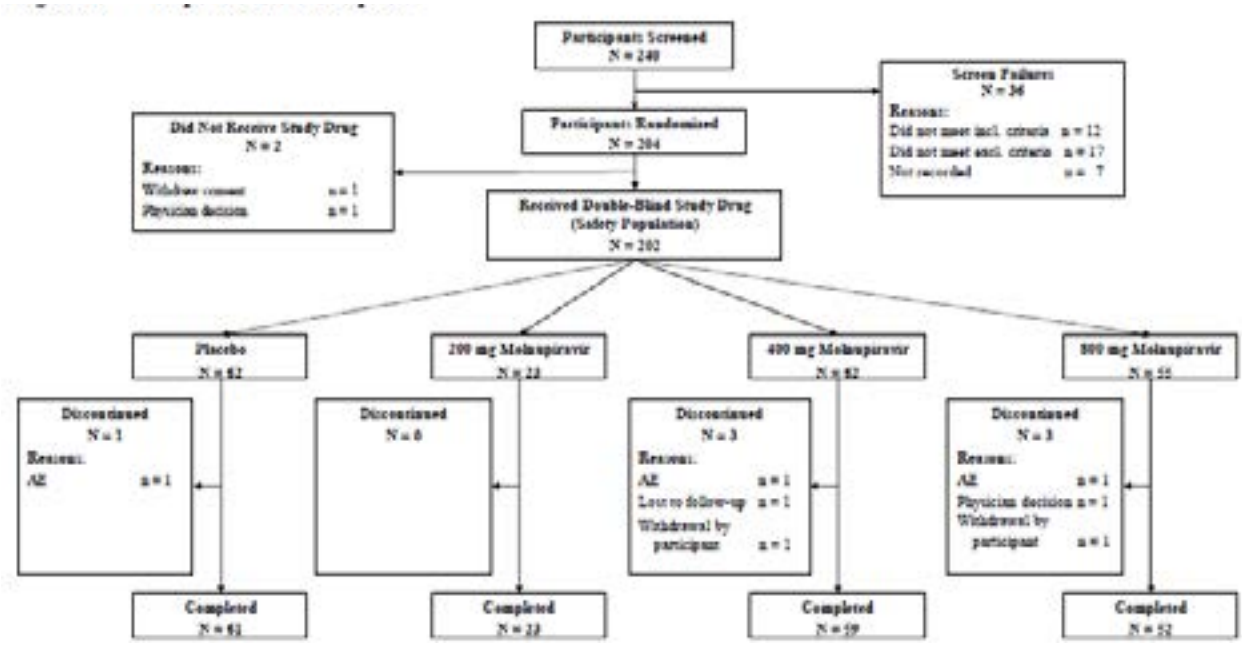


Figure 13: Disposition of Participants

Table 18: Summary of Participant Populations (Randomised Participants)

Category	Molnupiravir 200 mg (N=23) n (%)	Molnupiravir 400 mg (N=64) n (%)	Molnupiravir 800 mg (N=55) n (%)	All Molnupiravir (N=142) n (%)	Placebo (N=62) n (%)
Number of Subjects Randomized (ITT)	23	64	55	142	62
Number of Subjects in the Safety Population [a]	23	62	55	140	62
Number of Subjects in the mITT Population [a]	23 (100.0)	61 (98.4)	53 (96.4)	137 (97.9)	61 (98.4)
Number of Subjects in the PK Population [a]	18 (78.3)	27 (43.5)	28 (50.9)	73 (52.1)	0
Number of Subjects in the PP Population [a]	23 (100.0)	58 (93.5)	52 (94.5)	133 (95.0)	61 (98.4)

The 800 mg group had the lowest mean viral load at baseline at 5.80 log_{10} copies/mL, compared with viral loads of 6.69, 6.38 and 6.11 log_{10} copies/mL in the 200 mg, 400 mg and placebo groups, respectively.

The majority had at least 1 risk factor for severe illness from COVID-19 (60.7% in the combined molnupiravir group and 57.7% in the placebo group). The most common risk factor was smoking (30.7% molnupiravir and 32.3% placebo).

Results for the primary endpoint of time to clearance of viral RNA in NP swabs showed a median of 14 days with 800 mg molnupiravir and 15 days with placebo. The proportion with SARS-CoV-2 RNA negativity by EOS was greater with 800 mg molnupiravir (92.5%) vs. placebo (80.3%) and the proportion with undetectable SARS-CoV-2 RNA was greater in the 800 mg group vs. placebo group on two days (p=0.0373 on Day 5 and p=0.0343 on Day 28).

Table 19: Summary of Time to Undetectable SARS-CoV-2 Viral RNA (Full mITT Population)

	Molnupiravir 200 mg (N=23)	Molnupiravir 400 mg (N=61)	Molnupiravir 800 mg (N=63)	All Molnupiravir (N=137)	Placebo (N=61)
Number (%) Participants with Response	21 (91.3)	48 (78.7)	49 (92.5)	118 (86.1)	49 (80.3)
Number (%) Participants Censored	2 (8.7)	13 (21.3)	4 (7.5)	19 (13.9)	12 (19.7)
Time to Response (days)					
Median (95% CI)	22.0 (15.0, 28.0)	27.0 (15.0, 28.0)	14.0 (13.0, 14.0)	15.0 (14.0, 20.0)	15.0 (15.0, 27.0)
Log Rank p-value	0.5551	0.7270	0.0128	0.4216	

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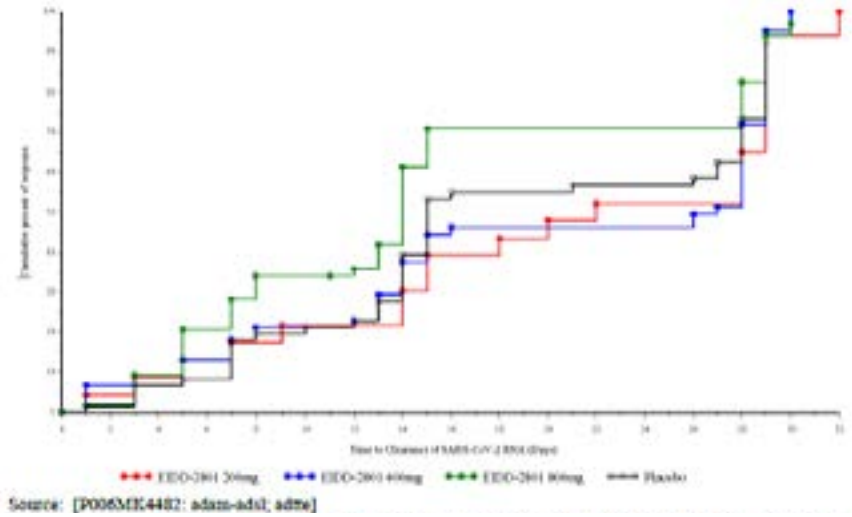

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Figure 14: Kaplan-Meier Plot of Time to Clearance of SARS-CoV-2 RNA by Treatment (Full mITT Population)

At baseline, the proportions with positive SARS-CoV-2 infectivity results varied across treatment groups. The proportion with positive cultures decreased faster in the 800 mg dose group compared with lower doses and placebo such that the change from baseline in viral load showed a larger decrease in the 800 mg group compared with other groups from Days 3 to 28.

Table 20: Summary of SARS-CoV-2 Infectivity Results (Full mITT Population)

	Molnupiravir 200 mg	Molnupiravir 400 mg	Molnupiravir 800 mg	All Molnupiravir	Placebo
Category	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**
Day 1					
Number of Participants with Positive Infectivity	11/22 (50.0)	18/43 (41.9)	20/52 (38.5)	49/117 (41.9)	25/53 (47.2)
p-value [a]	>.9999	0.6816	0.4320	0.6167	
p-value [b]					0.3144
Day 3					
Number of Participants with Positive Infectivity	4/22 (18.2)	5/43 (11.6)	1/53 (1.9)	10/118 (8.5)	9/54 (16.7)
p-value [a]	>.9999	0.5691	0.0161	0.1225	
p-value [b]					0.0095
Day 5					
Number of Participants with Positive Infectivity	1/22 (4.5)	0/42 (0.0)	0/53 (0.0)	1/117 (0.9)	6/54 (11.1)
p-value [a]	0.6658	0.0335	0.0270	0.0043	
p-value [b]					0.0025
Day 7					
Number of Participants with Positive Infectivity	1/21 (4.8)	0/47 (0.0)	0/52 (0.0)	1/120 (0.8)	2/56 (3.6)
p-value [a]	>.9999	0.4990	0.4960	0.2379	
p-value [b]					0.092

Analysis of nucleotide changes in the RdRp region at levels ≥1% of the viral population compared with the Wuhan consensus sequence indicated an increased mutation rate in molnupiravir-treated subjects compared with those given placebo. The result indicated a mean of 10.9 nucleotide changes in the RdRp among molnupiravir-treated subjects compared with 5.7 in the placebo group (p=0.024).

An analysis of mutations leading to amino acid changes in the RdRp gene demonstrated that the amino acid changes occurred throughout the protein sequence. There were no apparent differences across treatment groups in the pattern and/or position in the RdRp of the amino acid changes observed.

Based on published data, infectious SARS-CoV-2 virus can only be cultured when the SARS-CoV-2 RNA viral load as measured by RT-PCR is above approximately 10^6 copies/mL. The agreement between SARS-CoV-2 viral load and SARS-CoV-2 infectivity was explored for baseline and all study samples.

Table 21: Agreement Between SARS-CoV-2 Infectivity and SARS-CoV-2 Viral Load at Baseline (All Participant Data)

	SARS-CoV-2 Viral Load		
SARS CoV-2 Infectivity by RT-PCR	Negative (BLQ)	Positive	Kappa Statistic
Negative	13 (7.5%)	82 (47.4%)	0.1251
Positive	0	78 (45.1%)	

Table 22: Agreement Between SARS-CoV-2 Infectivity and SARS-CoV-2 Viral Load Assesments (All Participant Data)

	SARS-CoV-2 Viral Load		
SARS CoV-2 Infectivity by RT-PCR	Negative (BLQ)	Positive	Kappa Statistic
Negative	127 (18.6%)	450 (65.8%)	0.0811
Positive	0	107 (15.6%)	

Samples that had negative infectivity had much lower viral load at baseline and throughout the study. For both analyses, infectivity results were negative for every sample that had a negative SARS-CoV-2 RNA result.

Infectivity results were only positive for 45.1% of samples that had a positive SARS-CoV-2 RNA result at baseline and 15.6% of all samples that had a positive SARS-CoV-2 RNA result throughout the study. The kappa statistics of 0.1251 at Baseline and 0.0811 overall indicate a very low level of agreement between the assays.

The proportion with any (IgG, IgM, IgA, total Ig or composite) antibody to SARS-CoV-2 at baseline were 15.0%, 30.0%, 35.3% and 18.2% in the molnupiravir and placebo groups, respectively. The proportions increased over time and by Day 28 nearly all participants were seropositive (at least 96.5%). There were no obvious differences in the proportions of participants with IgG on Days 7 and 28 between those treated with placebo vs molnupiravir.

There was a clear effect of antibody status at baseline on infectivity. In the seronegative subjects, 59% molnupiravir and 55.8% placebo subjects had a positive infectivity result at baseline compared to 3% and 11% in respective groups who were seropositive at baseline. Among baseline seronegative subjects all except one treated with 800 mg achieved negative infectious virus on Day 3 vs. 20.9% treated with placebo. On Days 5 and 7, all subjects treated with 400 mg or 800 mg had negative infectious virus compared to 14.0% and 4.7% of those treated with placebo.

Table 23: Summary of SARS-CoV-2 Infectivity Results for Participants with Negative Composite Antibody Status at Baseline (Full mITT Population)

	Molnupiravir 200 mg	Molnupiravir 400 mg	Molnupiravir 800 mg	All Molnupiravir	Placebo
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Day 1 No. of participants with positive infectivity	9/17 (52.9)	17/29 (58.6)	20/32 (62.5)	46/78 (59.0)	24/43 (55.8)
Day 3 No. of participants with positive infectivity	2/17 (11.8)	5/29 (17.2)	1/32 (3.1)	8/78 (10.3)	9/43 (20.9)
Day 5 No. of participants with positive infectivity	0/17 (0.0)	0/29 (0.0)	0/32 (0.0)	0/78 (0.0)	6/43 (14.0)
Day 7 No. of participants with positive infectivity	1/16 (6.3)	0/30 (0.0)	0/32 (0.0)	1/78 (1.3)	2/43 (4.7)

In the subgroup enrolled ≤4.5 days after onset of COVID-19 symptoms positive infectivity was 15.1% in the molnupiravir groups and 25.9% in the placebo group. In the subgroup enrolled >4.5 days after onset of COVID-19 symptoms, 3.1% of molnupiravir and 7.4% of placebo participants tested positive for infectious virus.

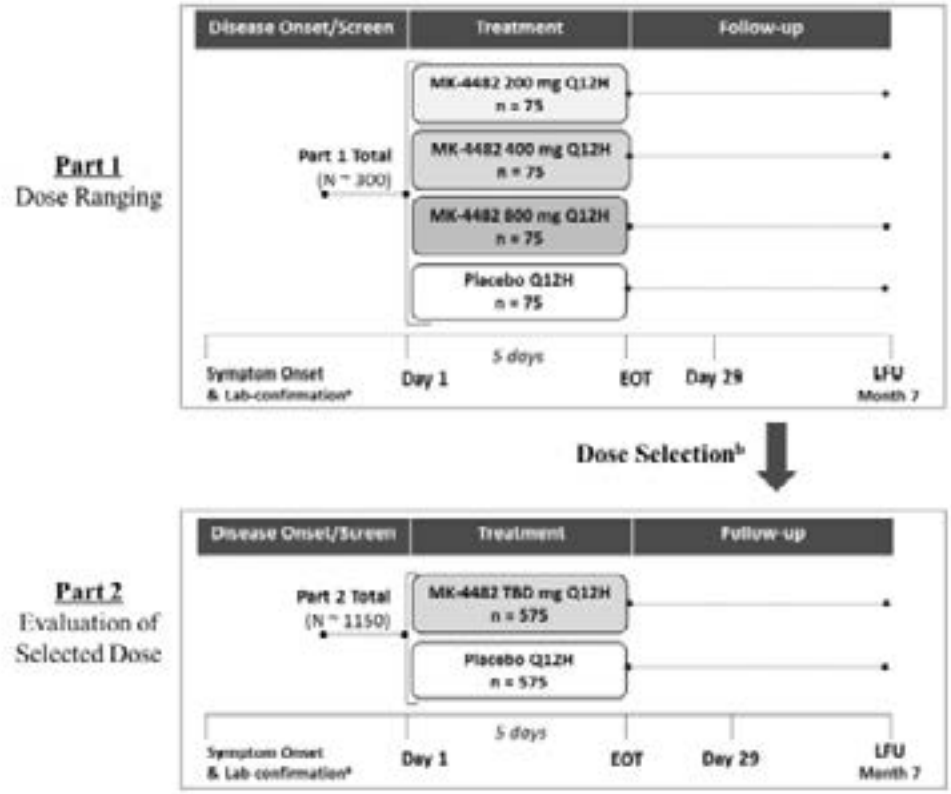
There were no consistent or meaningful differences between the treatment groups at any time during the study for COVID symptoms. There were 4 participants hospitalised during the study (2 in the 400 mg group, 1 in the 800 mg group and 1 in the placebo group).

Based on the 8-point WHO Ordinal Scale, all participants were ambulatory with no limitation of activities or with limitation of activities at baseline. The proportions rated as having limitation of activities at baseline varied from 63.6%, 75.4%, 90.2% and 74.1% in the 200 mg, 400 mg, 800 mg and placebo groups, respectively. The proportions rated as having limitation of activities decreased over time in all of the treatment groups to a similar degree.

2.5.5.2. Main studies

MK4482-002

The last (4th) amended protocol received was dated 15 August 2021. The study was in two parts.



EOT=end-of-treatment; LFU=Late Follow-up Visit; N=total number of participants in each study part; n=number of participants per intervention group; Q12H=administered once every 12 hours; TBD=to be determined based on dose selection in Part 1 of the study.

*Eligible participants had laboratory-confirmed SARS-CoV-2 infection with signs/symptoms attributable to COVID-19 for ≤7 days prior to randomization. Calculation of the 7-day symptom onset window did not include the date of randomization.

[b] Dose selection will be based on Part 1 interim analysis(es) in combination with the totality of data available across the molnupiravir clinical program prior to initiating Part 2.

Figure 15: Study Schema and Treatment Plan

- **Study participants**

Eligible subjects were adults with laboratory-confirmed SARS-CoV-2 infection with sample collection ≤7 days (Part 1) or ≤5 days (Part 2) prior to the day of randomisation. RT-PCR confirmation was the preferred method, but eligibility could be based on other molecular or antigen tests.

Eligible subjects were not vaccinated against COVID-19. They were to have initial onset of signs/symptoms attributable to COVID-19 ≤7 days (Part 1) or ≤5 days (Part 2) prior to randomisation. Signs/symptoms attributable to COVID-19 present at randomisation were to include at least one of: fever >38.0ºC, chills, cough, sore throat, shortness of breath or difficulty breathing with exertion, fatigue, nasal congestion, runny nose, headache, muscle or body aches, nausea, vomiting, diarrhoea, loss of taste or loss of smell.

Subjects were to have mild or moderate COVID-19 based on the following protocol definitions:

Mild COVID-19:

Must have **ALL** of the following:

- Respiratory rate <20 breaths per minute
- Heart rate <90 beats per minute
- SpO_2 >93% on room air or on supplemental oxygen for a reason other than COVID-19 which HAS NOT increased since onset of COVID-19 signs/symptoms

AND

Must **NOT** have shortness of breath **at rest** or **with exertion** as assessed by the investigator, respiratory failure, shock, or multi-organ dysfunction/failure (see definitions in Critical COVID-19 below)

Moderate COVID-19:

Must have **ONE or MORE** of the following:

- Shortness of breath **with exertion** as assessed by the investigator
- Respiratory rate >20 to <30 breaths per minute
- Heart rate ≥90 to <125 beats per minute

AND

Must have SpO_2 >93% on room air or on supplemental oxygen for a reason other than COVID-19 which HAS NOT increased since onset of COVID-19 signs/symptoms [or only on ≤4 liters/min supplemental oxygen for COVID-19 (but was not previously on supplemental oxygen), regardless of SpO_2]

AND

Must **NOT** have shortness of breath **at rest** as assessed by the investigator, respiratory failure, shock, or multi-organ dysfunction/failure (see definitions in Critical COVID-19 below)

Subjects with mild COVID-19 in Part 1 and all subjects in Part 2 were to have at least 1 characteristic or underlying medical condition associated with an increased risk of severe illness from COVID-19, listed in the protocol as:

- Age >60 years
- Active cancer (if associated with immunosuppression or significant morbidity/mortality)
- Chronic kidney disease (excluding dialysis or eGFR <30 mL/min/1.73 m^2)
- Chronic obstructive pulmonary disease
- Obesity (BMI 30 or higher)
- Serious heart conditions (heart failure, coronary artery disease, or cardiomyopathies)
- Diabetes mellitus

Immunocompromised state from solid organ transplant and sickle cell disease were high-risk conditions in Part 1 but were removed from Part 2.

Excluded subjects included those who:

- Were hospitalised or expected to need hospitalisation for COVID-19 within 48 h

- Had any of the following conditions:

• HIV with a recent viral load >50 copies/mL or CD4 <200 cell/mm³

• Chemotherapy required within 6 weeks before randomisation

• A neutrophilic granulocyte absolute count <500/mm3

• Autologous or allogeneic hematopoietic stem cell transplant recipient

- Had a platelet count <100,000/µL or received a platelet transfusion in the 5 days prior to randomisation.

- Had acute pancreatitis within 3 months prior to randomisation or a history of chronic pancreatitis.

The table shows concomitant therapies that were not permitted for the specific time frames listed.

Table 24: Prohibited and Allowed Therapies

COVID-19 Vaccines	• SARS-CoV-2 vaccines are prohibited any time prior to randomization and through Day 29.
COVID-19 Monoclonal Antibodies	• Monoclonal antibodies are prohibited for treatment of the current SARS-CoV-2 infection, including prior to randomization and through Day 29.
Other COVID-19 Therapeutics	• Sponsor-designated standard of care for treatment for COVID-19* is permitted (eg, corticosteroids) but may require additional safety monitoring as determined by the treating clinician. o If guidelines for local standard of care conflict with Sponsor-designated standard of care, site should consult with Sponsor. o Unless designated by the Sponsor as acceptable standard of care for COVID-19, concomitant use of other therapies intended as specific treatment for COVID-19 are prohibited from randomization through Day 29. If a participant is hospitalized during the study, other therapies intended as treatment for COVID-19 are permitted. • Supportive therapies (including but not limited to anti-pyretic and anti-inflammatory agents) to manage COVID-19 signs/symptoms are allowed.
Non-COVID-19 Investigational Agents	All non-COVID-19 investigational agents including devices are prohibited within 30 days prior to randomization and through Day 29.

- **Treatments**

The following treatments were administered as 200 mg capsules taken without regard to food:

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
MK-4482	Experimental	MK-4482	Drug	Capsule	200 mg	Part 1: 200 mg, 400 mg, 800 mg; Part 2:800 mg	Oral	Q12H 5 days (10 doses total)	Experimental	IMP	Central
Placebo	Placebo Comparator	Placebo Matching MK-4482	Drug	Capsule	0 mg	Part 1: N/A Part 2: N/A	Oral	Q12H 5 days (10 doses total)	Placebo	IMP	Central

N/A = not applicable; Q12H = every 12 hours.
The classification of Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) in this table is based on guidance issued by the European Commission and applies to countries in the European Economic Area (EEA). Country differences with respect to the definition/classification of IMP/NIMP may exist. In these circumstances, local legislation is followed.

- **Objectives and endpoints**

The primary and secondary objectives and endpoints were as shown in the table below.

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The primary endpoint was all-cause hospitalisation (defined in the protocol as ≥24 h of acute care in a hospital or similar acute care facility, including emergency rooms or facilities created to address hospitalisation needs during the COVID-19 pandemic) or death in the 28 days after the day of randomisation (i.e. to Day 29).

Two secondary endpoints were defined to document the effect of treatment on signs/symptoms associated with COVID-19 infection and on shifts in clinical status as measured on the WHO 11-point ordinal outcome scale through Day 29.

Objectives	Endpoints
Primary	
• To evaluate efficacy of MOV compared to placebo as assessed by the percentage of participants who are hospitalized and/or die from randomization through Day 29.	• Hospitalization or death
• To evaluate the safety and tolerability of MOV compared to placebo.	• Adverse events • Adverse events leading to discontinuation of study intervention
Secondary	
• To evaluate the efficacy of MOV compared to placebo as assessed by time to sustained resolution or improvement, and time to progression of each targeted self-reported sign/symptom of COVID-19 from randomization through Day 29.	• COVID-19 signs/symptoms
• To evaluate the efficacy of MOV compared to placebo as assessed by the odds of a more favorable response on the WHO 11-point ordinal scale on Day 3, EOT, Day 10, Day 15, and Day 29.	• WHO 11-point scale score

- **Sample size**

The sample size for Part 1 was not determined based on a specific hypothesis for a selected endpoint. The plan for 300 participants (75 per group) was deemed sufficient to provide reasonable precision to discriminate between treatment groups with regard to the virology endpoints.

In Part 2 the primary analysis was to include ~1550 subjects (~775 for each group) eligible for the MITT population. The study was to have overall power of 97% to demonstrate superiority of molnupiravir 800 mg over placebo at an overall one-sided, 2.5% alpha level, if the underlying treatment difference (molnupiravir minus placebo) in the primary endpoint is -6 percentage points.

The power and sample size were based on the following assumptions:

1) An underlying percentage hospitalised/dying of 12% for placebo and 6% for molnupiravir

2) A futility/efficacy interim analysis at 50% information

- **Randomisation**

Randomisation was performed centrally using an IRT system.

In Part 1, there was a 1:1:1:1 ratio for 3 molnupiravir doses or placebo with stratification by:

1. Time from symptom onset prior to the day of randomisation (≤5 days, >5 days)
2. At increased risk of severe illness from COVID-19 (yes, no)

At least 75% were to have at least one protocol-listed risk factor for severe COVID-19 and ≤50% were to have moderate COVID-19 as defined in the protocol.

In Part 2, there was a 1:1 ratio for molnupiravir 800 mg BID or placebo with stratification by:

1. Time from symptom onset prior to the day of randomisation (≤3 days, >3 days)

- **Blinding (masking)**

A double-blinding design was used with in-house blinding. A separate, small, cross-functional unblinded team of Sponsor personnel was convened for Part 2 of the study with the purpose of supporting preparation and submission of the MAA based on IA3/4.

- **Statistical methods**

Efficacy analysis populations

The MITT population was the primary population for the analysis of efficacy data for both parts of this study. The MITT population consisted of all randomised participants who received at least 1 dose of study intervention and excluded any subject hospitalised before start of study treatment. The MITT population for Part 2 did not include Part 1 participants.

A supportive analysis using the Per-Protocol population was to be performed for the primary efficacy endpoint in Part 2. The Per-Protocol population excluded participants with deviations from the protocol that could substantially affect the results of the primary efficacy endpoint. Inclusion in this population was determined prior to the final unblinding of the database.

Primary and sensitivity analyses

For the primary endpoint, superiority of molnupiravir compared to placebo was to be assessed using the stratified Miettinen and Nurminen method. For the primary analysis of this endpoint in the MITT population, incomplete data on Day 29 survival and hospitalisation status were treated as follows:

- Unknown Day 29 survival status was treated as failure.
- Early withdrawal from the study with known Day 29 survival status as alive but unknown Day 29 hospitalisation status was not treated as failure.

A sensitivity analysis treating unknown Day 29 survival status as failure and early withdrawal from the study with known Day 29 survival status as alive but unknown Day 29 hospitalisation status as failure was also planned.

A sensitivity analysis for the primary endpoint was planned to include only COVID-19 related hospitalisations or death by Day 29 in the MITT population using the stratified Miettinen and Nurminen method. An additional sensitivity analysis excluding hospitalisations that occurred early (within a certain time from randomisation) was also planned.

Two additional sensitivity analyses of time to hospitalisation/death and time to COVID-related hospitalisation/death were planned for the MITT population using the stratified log-rank test to compare MK-

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4482 with placebo and the same stratification factors as for the primary endpoint. Hazard ratios were based on the stratified Cox Proportional Hazards regression model.

The first table below summarises the main features of the planned efficacy analyses.

There were four interim analysis planned initially with details as shown in the second table below.

There were no adjustments for multiplicity other than controlling type I error for interim analyses of the primary endpoint in Part 2 of the study. The p-value boundary for efficacy at the final analysis was anticipated to be 0.0194, corresponding to an absolute difference of -0.03.

Primary Endpoints	**Efficacy**: Proportion of participants with hospitalization or death by Day 29. **Safety**: Number of participants with AEs, and discontinuing study intervention due to AEs
Key Secondary Endpoints	• Time to sustained resolution or improvement, and time to progression of each targeted self-reported sign/symptom of COVID-19 through Day 29 • Odds of a more favorable response on the WHO 11-point ordinal scale on Day 3, EOT, Day 10, Day 15, and Day 29
Statistical Methods for Key Efficacy Analyses	For the evaluation of the primary hypothesis, superiority of MK-4482 compared to placebo with respect to the percentage of participants with hospitalization or death by Day 29 will be calculated using the stratified Miettinen and Nurminen method [Miettinen, O. 1985].
Statistical Methods for Key Safety Analyses	P-values (Tier 1 endpoints) and 95% CIs (Tier 1 and Tier 2 endpoints) will be provided for between-treatment differences in the percentage of participants with AEs; these analyses will be performed using the unstratified Miettinen and Nurminen method [Miettinen, O. 1985].
Interim Analyses	**IA1 – Part 1 Dose Evaluation** This IA will be used to review data to inform dose selection models and analyses. **IA2 – Part 1[b] Dose Selection** This IA will be used to evaluate the dose/exposure-response to select the dose for Phase 3. **IA3 – Part 2 Sample Size Re-estimation** This IA will be an unblinded sample size re-assessment. The conditional power approach will be employed in which the overall sample size can be adjusted upwards if the interim result is sufficiently promising without inflation of the type I error. **IA4 – Part 2 Futility/Early Efficacy** The purpose of this IA is to allow for early stopping in the case of futility and to allow for the initiation of marketing authorization applications in the case of a positive efficacy finding. Additional details about interim analyses are in Section 9.7.
Multiplicity	There are no adjustments for multiplicity other than the type I error control for interim analyses described in Section 9.7.

Sample Size and Power	The total sample size for the primary efficacy assessment (Part 2) will be ~1550 participants (~775 for MK-4482 800 mg and ~775 for the placebo group). The study has overall power of 97% to demonstrate the superiority of MK-4482 over placebo at an overall one-sided, 2.5% alpha level, if the underlying treatment difference (MK-4482 minus placebo) in the percentage of participants who are hospitalized and/or die through Day 29 is -6 percentage points. Additional details and assumptions for sample size and power calculation are in Section 9.9.

[a] Stratification in Part 1 included: 1) Time from symptom onset prior to the day of randomization (≤5 days, >5 days); and 2) At increased risk of severe illness from COVID-19 (Appendix 10) (yes, no)

Interim Analysis	Timing	MK-4482-002 Primary Data for Analysis	Committee Action
IA1 – Part 1 Dose Evaluation	Targeted to occur during Phase 2 after ~300 participants complete EOT combined in MK-4482-001[a] and MK-4482-002.	PK, available virologic, safety & efficacy data through EOT	eDMC recommendation for discontinuation of the study or protocol modifications Sponsor sDMC review of interim safety data and review of preliminary virology data Review by an unblinded team to inform dose selection models and analyses
IA2 – Part 1[b] Dose Selection	Targeted to occur at the completion of Phase 2 after ~300 participants complete Day 29 (includes participants from IA1).	PK, safety & efficacy data through Day 29 and available virologic data	eDMC recommendation for discontinuation of the study or protocol modifications Sponsor sDMC approval of proposed MK-4482 dose for Part 2
IA3 – Part 2 Sample Size Re-estimation	Targeted to occur no earlier than at 30% of the full planned Part 2 enrollment and no later than IA4. Final timing to be based on enrollment timelines.	Primary efficacy endpoint at Day 29	Sample size re-estimation to be assessed by eDMC based on review of conditional power for primary endpoint with potential to increase Part 2 sample size
IA4 – Part 2 Futility/Early Efficacy	Targeted to occur during Phase 3 after ~775 participants complete Day 29 across the MK-4482 group and the placebo group (~50% of total enrollment).	Safety & efficacy data through Day 29	Futility and early efficacy to be assessed by eDMC per eDMC Charter and guided by statistical criteria

eDMC=external Data Monitoring Committee; EOT=End of Treatment; IA=Interim Analysis; PK=pharmacokinetics; sDMC=standing internal Data Monitoring Committee.

[a] MK-4482-001 is a companion MK-4482 dose-ranging study in hospitalized adults with COVID-19

[b] IA2 represents the analysis of the full Part 1 cohort of participants through Day 29.

IA3 – Part 2: Sample size re-estimation

IA3 was to occur no earlier than at 30% of the full planned Part 2 enrolment and no later than IA4. The conditional power approach was to be employed, in which the overall Part 2 sample size could be adjusted upwards by 450 participants to a total of 2000 if the interim result was sufficiently promising (conditional power >51% but <80%, assuming continuing the interim analysis trend) without inflation of the type I error [Chen, Y. H. J., et al 2004]. The potential increase in total Part 2 sample size was designed to maintain adequate study power in the event that the observed treatment effect at the interim analysis was smaller than the original assumption but still clinically meaningful. Based on enrolment timelines, the supplemental SAP stated that IA3 and IA4 were to be conducted at a single time point (once 50% of planned participants were enrolled and followed through the Day 29 visit). Based on an expected information fraction of 50%, the promising zone for adjusting the overall sample size upwards by 450 participants is between 0.0703 and 0.0299 in the 1-sided p-value scale.

IA4 – Part 2: Futility/Early Efficacy IA

IA4 was to occur when ~50% of participants in the molnupiravir group and the placebo group had completed the Day 29 visit. This interim analysis was to allow early stopping in the case of futility or initiation of MAAs in the case of a positive efficacy finding. There were no plans to discontinue enrolment prior to the planned final sample size in the case of a positive efficacy outcome.

The Gamma family spending function with $\gamma = -1$ was to be used to set both efficacy and futility boundaries for the primary endpoint as a guide for the eDMC in order to control overall type I error rate of 0.025, 1-sided. Assuming the information fraction of 50%, the non-binding futility boundary expressed on the absolute difference scale is -0.011. The boundary crossing probabilities for futility are 71% under H0 and 0.8% under H1 (absolute difference of -0.06). The p-value boundary for efficacy is 0.0094, corresponding to an absolute difference of -0.048. The boundary crossing probabilities for efficacy are 0.9% under H0 and 72% under H1 (absolute difference of -0.06). Had sample size re-estimation resulted in an increase in the total planned sample size to 2000, the p-value boundary for efficacy at the final analysis would have been 0.0184.

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The applicant provided a separate SAP dated 16 September 2021 (version 2). This document included summaries of changes from the protocol SAP (protocol amendment 04) and version 1 of the SAP (dated 16 June 2021).

Results – Part 1 (interim CSR; IA2)

- **Participant flow**

The study was conducted at 82 sites in 12 countries. There were 302 subjects randomised into Part 1, of which 299 were treated and included in the MITT population. The majority completed the 5-day treatment (94.6%) and Day 29 visit (96.7%) and few (3.3%) discontinued after Day 29. Based on the CSR dated 19 July 2021, the majority had not yet completed the 7-month LFU visit.

Table 25: Disposition of Participants - All Randomised Participants – MK-4482-002 IA2

	MK-4482 200 mg		MK-4482 400 mg		MK-4482 800 mg		MK4482 Combined		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Not Randomized											66	
Participants in population	75		77		76		228		74		302	
Status for Study Medication												
Started	74		77		74		225		74		299	
Completed	69	(93.2)	73	(94.8)	70	(94.6)	212	(94.2)	71	(95.9)	283	(94.6)
Discontinued	5	(6.8)	4	(5.2)	4	(5.4)	13	(5.8)	3	(4.1)	16	(5.4)
Adverse Event	0	(0.0)	0	(0.0)	3	(4.1)	3	(1.3)	1	(1.4)	4	(1.3)
Non-Compliance With Study Drug	2	(2.7)	1	(1.3)	0	(0.0)	3	(1.3)	1	(1.4)	4	(1.3)
Physician Decision	0	(0.0)	2	(2.6)	0	(0.0)	2	(0.9)	0	(0.0)	2	(0.7)
Withdrawal By Subject	1	(1.4)	1	(1.3)	1	(1.4)	3	(1.3)	1	(1.4)	4	(1.3)
Other	2	(2.7)	0	(0.0)	0	(0.0)	2	(0.9)	0	(0.0)	2	(0.7)
Status for Day 29 Milestone*												
Started	74		77		74		225		74		299	
Completed	71	(95.9)	75	(97.4)	71	(95.9)	217	(96.4)	72	(97.3)	289	(96.7)
Discontinued	3	(4.1)	2	(2.6)	3	(4.1)	8	(3.6)	2	(2.7)	10	(3.3)
Lost To Follow-Up	2	(2.7)	0	(0.0)	1	(1.4)	3	(1.3)	1	(1.4)	4	(1.3)
Withdrawal By Subject	1	(1.4)	2	(2.6)	2	(2.7)	5	(2.2)	1	(1.4)	6	(2.0)
Status for Trial Through LFU												
Started	75		77		76		228		74		302	
Discontinued	4	(5.3)	2	(2.6)	5	(6.6)	11	(4.8)	4	(5.4)	15	(5.0)
Death	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.3)
Lost To Follow-Up	2	(2.7)	0	(0.0)	1	(1.3)	3	(1.3)	1	(1.4)	4	(1.3)
Withdrawal By Subject	2	(2.7)	2	(2.6)	4	(5.3)	8	(3.5)	2	(2.7)	10	(3.3)
Status Not Recorded	71	(94.7)	75	(97.4)	71	(93.4)	217	(95.2)	70	(94.6)	287	(95.0)

Status Not Recorded = Ongoing
* Only participants who receive at least 1 dose will be included.

Important and not important protocol deviations associated with the pandemic were reported for 51 participants. No subject was excluded from the MITT analyses due to an important protocol deviation.

- **Baseline data**

The majority of participants was male (52.6%) and the mean age was 49.2 years (range 18 to 84 years) with 52% aged 18 to 50 years. The majority (66.9%) started treatment ≤5 days after COVID-19 sign/symptom onset across all groups and 75.2% had at least on factor for increased risk of severe COVID-19, most commonly due to obesity (48.7% BMI ≥30), age >60 years (23.5%) and diabetes mellitus (16.6%).

At baseline, COVID-19 severity was moderate for 57.0% and mild for 43.0%. SARS-CoV-2 baseline antibody testing was positive for 12.6% and 81.1% had detectable SARS-CoV-2 RNA (rather than a positive antigen detection test) in a baseline NP sample.

Subjects were not receiving supplemental oxygen at study entry, within minimum oxygen saturation at 94% on room air.

Table 26: Participant characteristics – Oxygen Saturation – Modified Intent-To-Treat Population – MK 4482-002 Part 1 – IA2

	MK-4482 200 mg	MK-4482 400 mg	MK-4482 800 mg	MK-4482 Combined	Placebo	Total
Participants in population	74	77	74	225	74	299
Participants with data	73	77	74	224	74	298
Mean	97	96.9	96.9	96.9	97.3	97
SD	1.58	1.51	1.55	1.54	1.61	1.56
Median	97	97	97	97	97	97
Range	(94, 100)	(94, 100)	(94, 100)	(94, 100)	(94, 100)	(94, 100)

- **Outcomes and estimation**

The number of primary endpoint events across intervention groups was low (total 11) with no statistically significant differences between molnupiravir groups vs. placebo or between molnupiravir dose levels. The 11 events reported all involved hospitalisation, with no deaths. All of the 11 subjects hospitalised had at least one of the protocol-listed risk factors for severe COVID-19 including obesity (n=8), >60 years of age (n=5) and diabetes mellitus (n=5).

Table 27: Incidence of Death or Hospitalisation Through Day 29 Modified Intent-To-Treat Population – MK-4482-002 IA2

Treatment	N	n (%)	Treatment vs. Placebo		
			Unadjusted Difference	Adjusted Difference in Rates % (95% CI)*	p-Value
MK-4482 200 mg	74	1 (1.4)	-4.1	-4.1 (-12.2, 2.5)	0.1676
MK-4482 400 mg	77	3 (3.9)	-1.5	-1.5 (-9.9, 6.2)	0.6668
MK-4482 800 mg	74	3 (4.1)	-1.4	-1.3 (-9.6, 6.4)	0.7141
Placebo	74	4 (5.4)			
Pairwise Comparison among MK Treatment Groups			Unadjusted Difference	Adjusted Difference in Rates % (95% CI)*	p-Value
MK-4482 400 mg vs. MK-4482 200 mg			2.5	2.5 (-3.9, 9.8)	0.3351
MK-4482 800 mg vs. MK-4482 200 mg			2.7	2.7 (-3.7, 10.1)	0.3121
MK-4482 800 mg vs. MK-4482 400 mg			0.2	0.3 (-7.3, 8.3)	0.9342

* Adjusted differences, the corresponding confidence intervals and p-values are based on Miettinen & Nurminen method stratified by randomization strata.
Unknown Day 29 survival status is treated as failure.

Post-hoc subgroup analyses of the primary endpoint for participants >60 years of age, time from COVID-19 symptom onset ≤5 days and increased risk for severe COVID-19 indicated improved outcomes with molnupiravir. Among those who started treatment within 5 days of symptom onset and were at increased risk of severe COVID-19, there were 4/107 (3.7%) hospitalised in the combined molnupiravir groups vs. 4/34 (11.8%) in the placebo group.

- **Ancillary analyses**

Time to sustained resolution or improvement and time to progression of each self-reported COVID-19 sign/symptom was similar across groups. The observed median time to sustained improvement or resolution was ≤12 days for all symptoms and the sustained resolution or improvement rate was generally comparable across the groups through Day 29. There were no clear trends in treatment effect between intervention groups as assessed by the WHO 11-point ordinal scale. With >94% having a baseline score of 2, 74.3% achieved a score of 0 or 1 by Day 29.

There were comparable decreases in mean SARS-CoV-2 RNA titres from to baseline across the groups.

Higher viral sequence mutation rates (per 10,000 bp) were observed at Day 5 in NP samples from molnupiravir-treated subjects (6.7 to 8.7) compared with placebo (2.0). The highest RNA mutation rate was at Day 5 in the 800 mg BID group. SARS-CoV-2 mutations observed post-baseline were distributed across the entire 30,000 bp genome with no increase of treatment-emergent mutations in the RdRp active site.

Results – Part 2 (based on IA3/4)

- **Participant flow**

Subjects were recruited across 5 continents with the majority in Latin America (~56%) followed by Europe (~23%). There were 775 subjects randomised and eligible for inclusion in IA4, of which 765 (98.7%) had received study treatment and 94.9% had completed assigned treatment. In addition, 95.0% completed the Day 29 visit. The most common reason for discontinuation was withdrawal by subject (2.7%). At the time of IA4, disposition was as shown below.

Table 28: Disposition of Participants – All Randomised Participants – MK-4482-002 Combined IA3/IA4

	MK-4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	387		388		775	
Status for Study Medication						
Started	386		379		765	
Completed	371	(96.1)	355	(93.7)	726	(94.9)
Discontinued	15	(3.9)	24	(6.3)	39	(5.1)
Adverse Event	5	(1.3)	13	(3.4)	18	(2.4)
Lost To Follow-Up	1	(0.3)	1	(0.3)	2	(0.3)
Non-Compliance With Study Drug	4	(1.0)	6	(1.6)	10	(1.3)
Withdrawal By Subject	4	(1.0)	2	(0.5)	6	(0.8)
Other	1	(0.3)	2	(0.5)	3	(0.4)
Status for Day 29 Milestone*						
Started	386		379		765	
Completed	369	(95.6)	358	(94.5)	727	(95.0)
Discontinued	17	(4.4)	21	(5.5)	38	(5.0)
Death	0	(0.0)	8	(2.1)	8	(1.0)
Lost To Follow-Up	5	(1.3)	3	(0.8)	8	(1.0)
Withdrawal By Subject	12	(3.1)	9	(2.4)	21	(2.7)
Other	0	(0.0)	1	(0.3)	1	(0.1)
Status for Trial Through LFU						
Discontinued	18	(4.7)	31	(8.0)	49	(6.3)
Death	0	(0.0)	9	(2.3)	9	(1.2)
Lost To Follow-Up	5	(1.3)	3	(0.8)	8	(1.0)
Randomized By Mistake Without Study Treatment	1	(0.3)	1	(0.3)	2	(0.3)
Withdrawal By Subject	12	(3.1)	17	(4.4)	29	(3.7)
Other	0	(0.0)	1	(0.3)	1	(0.1)
Status Not Recorded	369	(95.3)	357	(92.0)	726	(93.7)

LFU=Late Follow-up Visit
Status Not Recorded = Ongoing
* Only participants who receive at least 1 dose will be included.

As indicated in the statistical analysis plan, dated 16 September 2021, there were changes made compared to the description outlined in the protocol. The most important were as follows:

3.7	Added additional details for IA3 and IA4	IA3 and IA4 were combined into a single timepoint based on enrollment timelines. As such, the information fraction for the interim analysis for sample size re-estimation is fixed at 50% (timing was flexible between 30% and 50% per protocol).

Some other important changes are shown below:

3.5.1	Clarified that the MITT population will exclude participants who were hospitalized before first dose.	Participants who were hospitalized before first dose are not the target population of the study, therefore they are excluded from the MITT population.

3.6.1	Added details about the censoring rules for the analyses of time to hospitalization/death and time to COVID-19 related death or hospitalization	Further describes how to handle missing data in the analyses of time to hospitalization/death and time to COVID-19 related death or hospitalization
3.6.1	Added details about the censoring rules for the analysis of time to sustained resolution or improvement of each self-reported sign/symptom of COVID-19	Further clarifies the handling of missing data in the analysis of time to sustained resolution or improvement of each self-reported sign/symptom of COVID-19
3.6.1	Added details about the censoring rules for the analysis of time to progression of each self-reported sign/symptom of COVID-19	Further clarifies the handling missing data in the analysis of time to progression of each self-reported sign/symptom of COVID-19
3.6.1	Added detailed method for analyzing SARS-CoV-2 RNA titer	Provides detailed analysis methods for exploratory endpoint
3.6.1	Added text to specify details in using the proportional odds model for analyzing the WHO 11-point ordinal scale score	Provided details about collapsing the WHO 11-point ordinal scale score in order to use the proportional odds model for analysis

- **Baseline data**

There was an approximate equal gender split at baseline with a median age just over 40 years. Less than 15% of subjects were aged >60 years. Almost all subjects (99.2%) had at least 1 of the protocol-listed risk factors for severe illness from COVID-19, with the most common being obesity (BMI ≥30, 76.5%). The baseline COVID-19 severity was moderate for 43.4% and mild for 56.0%. All subjects had symptom onset within 5 days prior to randomisation and about half had onset within ≤3 days. The minimum oxygen

saturation at baseline was 93% and the applicant confirmed that no subject was receiving supplemental oxygen at study entry.

Table 29: All Randomised Participants – MK-4482-002 Combined IA3/IA4

	MK-4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	387		388		775	
Sex						
Male	187	(48.3)	217	(55.9)	404	(52.1)
Female	200	(51.7)	171	(44.1)	371	(47.9)
Age (years)						
18 to 49	274	(70.8)	271	(69.8)	545	(70.3)
50 to 64	82	(21.2)	80	(20.6)	162	(20.9)
65 to 74	24	(6.2)	24	(6.2)	48	(6.2)
≥75	7	(1.8)	13	(3.4)	20	(2.6)
≤60	336	(86.8)	333	(85.8)	669	(86.3)
>60	51	(13.2)	55	(14.2)	106	(13.7)
Participants with data	387		388		775	
Mean	43.2		44.2		43.7	
SD	13.5		14.3		13.9	
Median	41.0		43.0		41.0	
Range	18 to 87		18 to 88		18 to 88	
Time from Symptom Onset to Randomization						
≤3 Days	188	(48.6)	184	(47.4)	372	(48.0)
>3 Days	198	(51.2)	203	(52.3)	401	(51.7)
Unknown	1	(0.3)	1	(0.3)	2	(0.3)
Participants with data	386		387		773	
Mean	3.5		3.5		3.5	
SD	1.1		1.0		1.1	
Median	4.0		4.0		4.0	
Range	1 to 5		1 to 5		1 to 5	
Risk Factors for Severe Illness from COVID-19						
At least one risk factor	385	(99.5)	384	(99.0)	769	(99.2)
Age >60 years	51	(13.2)	55	(14.2)	106	(13.7)
Active Cancer	6	(1.6)	11	(2.8)	17	(2.2)
Chronic Kidney Disease	14	(3.6)	20	(5.2)	34	(4.4)
Chronic Obstructive Pulmonary Disease	7	(1.8)	22	(5.7)	29	(3.7)
Obesity (BMI ≥ 30)	306	(79.1)	287	(74.0)	593	(76.5)
Serious Heart Condition	47	(10.9)	36	(9.3)	78	(10.1)
Diabetes Mellitus	48	(12.4)	57	(14.7)	105	(13.5)
Baseline COVID Severity						
Mild	222	(57.4)	212	(54.6)	434	(56.0)
Moderate	162	(41.9)	174	(44.8)	336	(43.4)
Severe	2	(0.5)	0	(0.0)	2	(0.3)

Table 30: Participant Characteristics – Oxygen Saturation – Modified Intent-To-Treat Population – MK-4482-002 Part 2 – Combined IA3/IA4

	MK-4482 800 mg	Placebo	Total
Participants in population	385	377	762
Oxygen Saturation (%)			
Participants with data	385	377	762
Mean	96.8	96.8	96.8
SD	1.56	1.51	1.54
Median	97	97	97
Range	(93, 100)	(94, 100)	(93, 100)

At baseline, 85.5% had detectable SARS-CoV-2 RNA (by NP sample) and 18.2% had positive SARS-CoV-2 antibody results. The updated sequencing results gave data for 527/775 (68%).

The most common genotype clades at baseline were 21A (Delta, 36.9%), 21H (Mu, 26.9%) and 20J (Gamma, 13.5%).

Table 31: All Randomised Participants – MK-4482-002 Combined IA3/IA4

	MK-4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Stratification Factor at Randomization Collected via IRT: Time from Symptom Onset to Randomization						
≤3 Days	191	(49.4)	190	(49.0)	381	(49.2)
>3 Days	196	(50.6)	198	(51.0)	394	(50.8)
SARS-CoV-2 RNA at Baseline in Nasopharyngeal Sample (Qualitative Assay)						
Detectable	332	(85.8)	331	(85.3)	663	(85.5)
Undetectable	28	(7.2)	29	(7.5)	57	(7.4)
Unknown*	27	(7.0)	28	(7.2)	55	(7.1)
SARS-CoV-2 Baseline Antibody						
Positive	71	(18.3)	70	(18.0)	141	(18.2)
Negative	299	(77.3)	288	(74.2)	587	(75.7)
Unknown*	17	(4.4)	30	(7.7)	47	(6.1)

* Missing data, invalid sample, tests not done, or results reported as "Unknown" are categorized as Unknown.

Table 32: Number of Participants Infected With Different Viral Clades Based on NextstrainClade Designation Nasopharyngeal Sample – All Randomised Participants – MK-4482-002 Combined IA3/IA4

Clade Designation	MK-4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants with evaluable sequence data available	260		267		527	
19B	1	(0.4)	1	(0.4)	2	(0.4)
20A	3	(1.2)	2	(0.7)	5	(0.9)
20B	4	(1.5)	4	(1.5)	8	(1.5)
20C	0	(0.0)	1	(0.4)	1	(0.2)
20D	2	(0.8)	1	(0.4)	3	(0.6)
20H (Beta)	5	(1.9)	6	(2.2)	11	(2.1)
20I (Alpha)	12	(4.6)	8	(3.0)	20	(3.8)
20J (Gamma)	35	(13.5)	48	(18.0)	83	(15.7)
21A (Delta)	96	(36.9)	90	(33.7)	186	(35.3)
21G (Lambda)	12	(4.6)	7	(2.6)	19	(3.6)
21H (Mu)	70	(26.9)	80	(30.0)	150	(28.5)
21I (Delta)	6	(2.3)	3	(1.1)	9	(1.7)
21J (Delta)	12	(4.6)	15	(5.6)	27	(5.1)
Unknown	2	(0.8)	1	(0.4)	3	(0.6)

Unknown: The sequence could not be classified by Nextstrain into a currently known clade.
Percentage is based on the number of participants with evaluable sequence data available.

- **Numbers analysed**

The MITT population comprised 762/775 (98.3%) of randomised subjects, with 385 in the molnupiravir 800 mg BID group and 377 in the placebo group. Ten subjects were excluded because of no treatment taken and 3 were hospitalised before the first dose.

- **Outcomes and estimation**

The percentage who was hospitalised or died through Day 29 in the molnupiravir 800 mg BID group (7.3%) was statistically significantly lower than in the placebo group (14.1%).

Molnupiravir met the protocol-defined criterion (1-sided p-value boundary <0.0092 at IA4) for demonstration of superiority to placebo for the primary efficacy endpoint.

Table 33: Incidence of Hospitalisation of Death Through Day 29 – Modified Intent-To-Treat Population – MK-4482-002 Combined IA3/IA4

Treatment	N	n (%)	Treatment vs. Placebo		
			Unadjusted Difference	Adjusted Difference in Rates % (97% CI)*	p-Value
MK-4482 800 mg	385	28 (7.3)	-6.8	-6.8 (-11.3, -2.4)	0.0012
Placebo	377	53 (14.1)			

* Adjusted difference, the corresponding confidence intervals and the one-sided p-values are based on Mantel-Haenszel method stratified by randomization strata.
Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.
The p-value boundary for early efficacy is 0.0092 using the Gamma family spending function with γ = -4, based on the final evaluable sample size at the IA3/IA4 timepoint (n = 762 in the MITT population out of a total of 1130 planned; information fraction = 40%).

All 8 participants who died through Day 29 were in the placebo group and were hospitalised prior to death. One participant in the placebo group but no subject in the molnupiravir group was imputed as a failure for the primary endpoint due to unknown mortality status at the time of database lock. Two placebo and one molnupiravir subjects had unknown hospitalisation status at Day 29 and were counted as alive and not hospitalised in the primary analysis.

Table 34: Summary of Hospitalisation or Death Through Day 29 – Modified Intent-To-Treat Population – MK-4482-002 Combined IA3/IA4

	MK-4482 800 mg		Placebo	
	n	(%)	n	(%)
Participants in population	385		377	
Hospitalization or Death	28	(7.3)	53	(14.1)
Hospitalization	28	(7.3)	52	(13.8)
Death	0	(0.0)	8	(2.1)
Unknown Day 29 Survival Status*	0	(0.0)	1	(0.3)

n= number of participants with the corresponding event.
Every participant is counted a single time for each applicable row and column. Participants who died were hospitalized prior to death; such participants are counted once each in the Hospitalization and Death rows.
* Unknown Day 29 survival status is treated as failure, i.e., counted as hospitalization or death in the primary analysis for the primary efficacy endpoint.

The percentages with *COVID-related* hospitalisation or death through Day 29 was 6.5% for molnupiravir vs. 13.3% for placebo, giving a 6.8 percentage point reduction [95% CI: -11.1, -2.6].

Table 35: Incidence of COVID-related Hospitalisation or Death Through Day 29 – Modified Intent-To-Treat Population – MK-4482-002 Combined IA3/IA4

Treatment	N	n (%)	Treatment vs. Placebo	
			Unadjusted Difference	Adjusted Difference in Rates % (95% CI)*
MK-4482 800 mg	385	25 (6.5)	-6.8	-6.8 (-11.1, -2.6)
Placebo	377	50 (13.3)		

* Adjusted differences and the corresponding confidence intervals are based on Miettinen & Nurminen method stratified by randomization strata.
N= number of participants in the modified intent-to-treat population.
n= number of participants died or hospitalized through Day 29.
Unknown survival status at Day 29 was not counted as having an outcome of COVID-related hospitalization or death.

Results of time-to-event sensitivity analyses were consistent with the results of the primary analysis.

Table 36: Analysis of Time to Hospitalisation or Death Through Day 29 - Modified Intent-To-Treat Population – MK-4482-002 Combined IA3/IA4

Treatment	N	Number of Events (%)	Person-day	Event Rate/ 100 Person-days	Median Time to Hospitalization or Death * (days)(95% CI)	Hospitalization or Death Rate at Day 29 in % * (95% CI)
MK-4482 800 mg	385	28 (7.3)	10531.0	0.3	NR (NA, NA)	7.3 (5.1, 10.4)
Placebo	377	52 (13.8)	9712.0	0.5	NR (NA, NA)	13.8 (10.7, 17.7)
Comparison					Hazard Ratio b (95% CI)*	p-Value c
MK-4482 800 mg vs. Placebo					0.51 (0.32, 0.81)	0.0017

* From product-limit (Kaplan-Meier) method for censored data.
b Based on stratified Cox regression model with Efron's method of tie handling with treatment as covariate and randomization stratum as stratification factor. Hazard ratio < 1 favors the MK-4482 800 mg group.
c One-sided p-value based on log-rank test stratified by randomization stratification stratum.
NR = Not reached; NA = Not applicable.
N= number of participants in the Modified Intent-To-Treat population.

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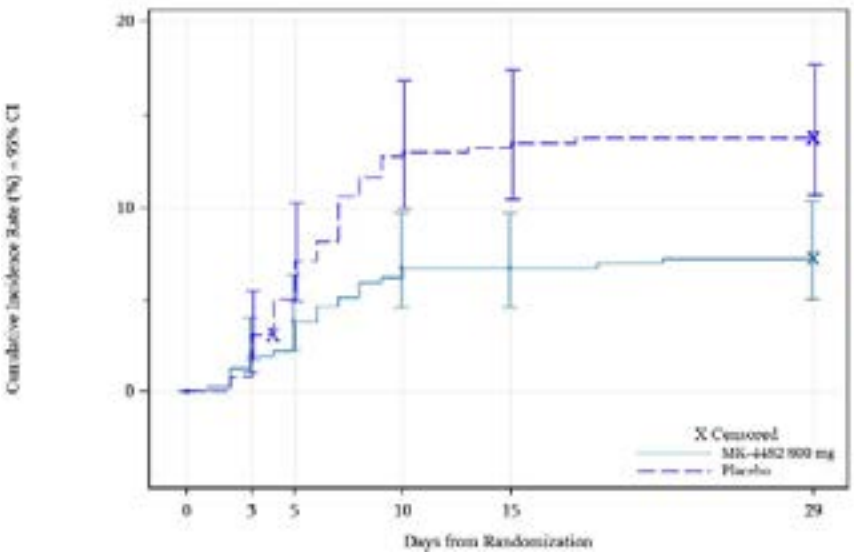

Figure 16: Kaplan-Meier Plot for Hospitalisation or Death Through Day 29 - Modified Intent-To-Treat Population – MK-4482-002 Combined IA3/IA4

Results of a sensitivity analysis which excluded participants who did not receive at least 48 h treatment (<5 doses) or who were hospitalised or died before their 5th dose were consistent with the results of the primary analysis based on the MITT population. Rates were 5.7% vs. 11.5% (-5.8 [-10.0, -1.7]).

Results of subgroup analyses were consistent with the results of the primary analysis for the following:

- TSSO to randomisation (≤3 days 8.5% vs. 12.4%; >3 [4-5] days 6.1%, 15.6%)
- Age group (≤60 years 6.9% vs. 12.7%; >60 years 10% vs. 21.8%)
- Obesity (BMI ≥30; yes 6.2% vs. 12.5%, no 11.4% vs. 18.8%)
- Diabetes mellitus (yes 18.8% vs. 23.2%, no 5.6% vs. 12.5%)
- Viral clades (20J [Gamma], 21A [Delta], 21H [Mu]); see table below
- COVID-19 severity (mild, moderate); see table below
- Region (North America, Latin America, Europe, and Africa); see table below
- Seronegative participants (based on SARS-CoV-2 nucleocapsid antibodies); see table below

Table 37: Incidence of Hospitalisation or Death Through Day 29 by Baseline Clade - Modified Intent-To-Treat Population – MK-4482-002 Combined IA3/IA4

	MK-4482 800 mg		Placebo		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)*
Baseline Clade						
20I (Gamma)	0/35	(0.0)	9/47	(19.1)	-19.1	(-32.6, -8.4)
21A, 21I, 21J (Delta)	9/114	(7.9)	16/106	(15.1)	-7.2	(-16.2, 1.3)
21H (Mu)	6/69	(8.7)	12/76	(15.8)	-7.1	(-18.2, 4.0)
Other	5/41	(12.2)	6/31	(19.4)	-7.2	(-26.0, 9.9)

* The corresponding confidence interval is based on Miettinen & Nurminen method.
m= number of participants in the modified intent-to-treat population with the corresponding baseline clade.
n= number of participants died or hospitalized through Day 29.
Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.
This table only presents baseline clade that with ≥ 25 participants in both treatment groups.

Table 38: Incidence of Hospitalisation or Death Through Day 29 by Baseline COVID Severity - Modified Intent-To-Treat Population – MK-4482-002 Combined IA3/IA4

	MK-4482 800 mg		Placebo		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)*
Participants in population	385		377			
Baseline COVID Severity						
Mild	12/222	(5.4)	21/203	(10.3)	-4.9	(-10.5, 0.2)
Moderate	16/161	(9.9)	31/173	(17.9)	-8.0	(-15.5, -0.5)
Severe	0/2	(0.0)	0/0	(0.0)		

* The corresponding confidence interval is based on Miettinen & Nurminen method.
m= number of participants in the modified intent-to-treat population with the corresponding group.
n= number of participants died or hospitalized through Day 29.
Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.

Table 39: Incidence of Hospitalisation or Death Through Day 29 by Region - Modified Intent-To-Treat Population – MK-4482-002 Combined IA3/IA4

	MK-4482 800 mg		Placebo		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)*
Participants in population	385		377			
Region						
North America	1/15	(6.7)	3/22	(13.6)	-7.0	(-28.6, 18.6)
Latin America	15/214	(7.0)	30/207	(14.5)	-7.5	(-13.7, -1.6)
Europe	8/89	(9.0)	12/87	(13.8)	-4.8	(-14.8, 4.8)
Asia Pacific	1/5	(20.0)	3/6	(50.0)	-30.0	(-71.6, 28.8)
Africa	3/62	(4.8)	5/55	(9.1)	-4.3	(-15.5, 5.6)

* The corresponding confidence interval is based on Miettinen & Nurminen method.
m= number of participants in the modified intent-to-treat population with the corresponding group.
n= number of participants died or hospitalized through Day 29.
Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.

Table 40: Incidence of Hospitalisation or Death Through Day 29 by SARS-CoV-2 Baseline Antibody - Modified Intent-To-Treat Population – MK-4482-002 Combined IA3/IA4

	MK-4482 800 mg		Placebo		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)[a]
Participants in population	385		377			
SARS-CoV-2 Baseline Antibody						
Positive	2/70	(2.9)	2/69	(2.9)	0.0	(-7.5, 7.3)
Negative	23/299	(7.7)	49/287	(17.1)	-9.4	(-14.9, -4.1)

[a] The corresponding confidence interval is based on Miettinen & Nurminen method.
n= number of participants in the modified intent-to-treat population with the corresponding group.
m= number of participants died or hospitalized through Day 29.
Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.

In the subgroup of participants positive for SARS-CoV-2 antibodies at baseline (approximately 18% in each group), there was no difference between intervention groups in the percentage of participants who were hospitalised or died (2.9% in both groups).

- **Ancillary analyses**

On request, the applicant provided an additional sensitivity analysis with the following rules applied:

- Patients in the placebo group with unknown survival status at day 29 to be treated as "alive and not hospitalised";
- Patients in the placebo group alive but with unknown hospitalisation status at day 29 to be treated as "alive and not hospitalised"
- Patients in the molnupiravir group with unknown survival status at day 29 to be treated as failures, i.e. "hospitalised or dead"
- Patients in the molnupiravir group alive but with unknown hospitalisation status at day 29 to be treated as failures, i.e. "hospitalised or dead"

The results as shown below were consistent with those from the primary analysis. In this "worst case" analysis, one participant in the placebo group with unknown survival status at Day 29 was counted as "alive and not hospitalised". Two participants in placebo group alive but with unknown hospitalisation status at Day 29 had been counted as "alive and not hospitalised" in the primary analysis so there was no change to their status. No participants in the molnupiravir group had unknown survival status at Day 29 and one who was alive but with unknown hospitalisation status at day 29 was treated as failure, i.e. "hospitalised or dead".

Table 41: Incidence of Hospitalisation or Death Through Day 29 - Modified Intent-To-Treat Population, Worst-case Analysis – MK-4482-002 Combined IA3/IA4

Treatment	N	n (%)	Treatment vs. Placebo		
			Unadjusted Difference	Adjusted Difference in Rates % (95% CI)*	p-Value
MK-4482 800 mg	385	29 (7.5)	-6.3	-6.3 (-10.8, -1.9)	0.0026
Placebo	377	52 (13.8)			

* Adjusted differences, the corresponding confidence intervals and the one-sided p-values are based on Miettinen & Nurminen method stratified by randomization strata.

Worst-case missing data sensitivity analysis of the primary endpoint at IA3/IA4, as follows:

- Participants in the placebo group with unknown survival status at day 29 to be treated as "alive and not hospitalized"
- Participants in the placebo group alive but with unknown hospitalization status at day 29 to be treated as "alive and not hospitalized"
- Participants in the molnupiravir group with unknown survival status at day 29 to be treated as failures, i.e. "hospitalized or dead"
- Participants in the molnupiravir group alive but with unknown hospitalization status at day 29 to be treated as failures, i.e. "hospitalized or dead"

The p-value boundary for early efficacy is 0.0092 using the Gamma family spending function with γ = -1 based on the final evaluable sample size at the IA3/IA4 timepoint (n = 762 in the MITT population out of a total of 1550 planned; information fraction = 49%).

Most participants (>98%) in both intervention groups had a baseline score of 2 following the WHO 11- point scale score. The majority in both intervention groups (66.3%) improved to a score of 0 (uninfected; no viral RNA detected) or 1 (asymptomatic; viral RNA detected) by Day 29. The effect of treatment on resolution of baseline signs and symptoms suggested some benefit for molnupiravir, as summarised in the figure below for study MK-4482-002 combined IA3/IA4 with regard to the secondary objectives analysis.

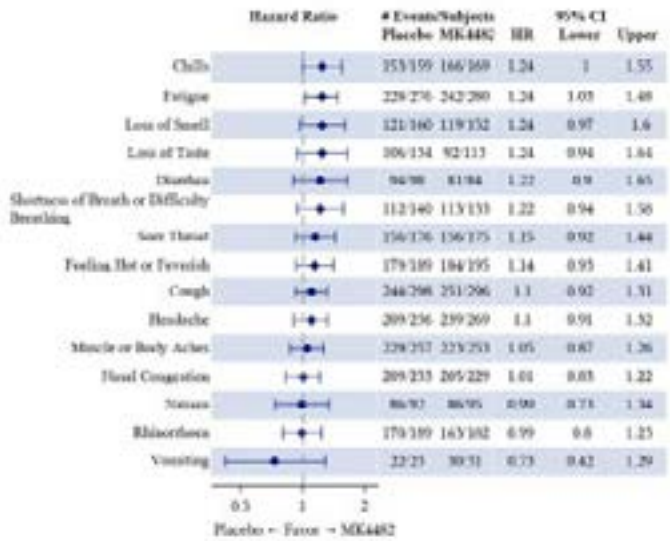

Figure 17: Hazard Ratio of Time to Sustained Improvement or Resolution of Signs and Symptoms Through Day 29 - Modified Intent-To-Treat Population – MK-4482-002 Combined IA3/IA4

At the time of the database lock for IA3/IA4, qualitative and quantitative SARS-CoV-2 RNA PCR for most participants were available through Day 10. Post-baseline SARS-CoV-2 viral sequence data were available from 92 participants (n=42 MOV; n=50 placebo).

Molnupiravir was associated with a greater reduction in SARS-CoV-2 RNA from baseline compared with the placebo group at Days 3 and 5 but not at later time points. Results stratified by baseline SARS-CoV-2 RNA

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titre (>10^6 and ≤10^6 copies/mL) were generally consistent with the overall results for the mean change from baseline in SARS-CoV-2 RNA.

After adjusting for baseline RNA titre, the adjusted mean difference in SARS-CoV-2 RNA (in $\log_{10}$ scale) was -0.24 at Day 3 and -0.44 at Day 5, which corresponds to a 42% and a 64% relative reduction in the geometric mean SARS-CoV-2 RNA titre. Among those with >10^6 copies/mL, after adjusting for baseline RNA titre, the largest difference was a 70% relative reduction observed at Day 5.

Among those participants with ≤10^6 copies/mL, the largest difference was a 70% relative reduction at Day 3. The percentages with undetectable SARS-CoV-2 RNA in NP samples by qualitative PCR was comparable between treatment groups and regardless of baseline SARS-CoV-2 RNA titre.

Molnupiravir was associated with a higher mutation rate vs. placebo (7.4 vs. 3.4) in those with paired baseline and Day 5 SARS-CoV-2 viral sequences. Mean numbers of transversion mutations were low in both groups.

Summary of main efficacy results as of IA3/4

The following table summarises the efficacy results from the main study at the time of IA3/4, supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 42: Summary of Efficacy for Study MK-4482-002

Title: A Phase 2/3, randomised, placebo-controlled, double-blind clinical study to evaluate the efficacy, safety, and pharmacokinetics of molnupiravir in non-hospitalised adults with covid-19	
Study identifiers	Protocol Number: P002 (MK-4482-002; MOVe-OUT) EudraCT: 2020-003368-24 IND: 147734 NCT: NCT04575597
Design	MK4482-002 (MOVe-OUT) is a Phase 2/3, randomised, placebo-controlled, double blind, multisite study to evaluate the efficacy, safety and PK of molnupiravir (MOV) in non-hospitalised adults with laboratory-confirmed COVID-19. Part 1 (Phase 2) evaluated dose selection for Part 2 (Phase 3). Part 2 (Phase 3) evaluated the efficacy of MOV 800 mg Q12H for 5 days.
Duration of main phase (Part 2 IA3/IA4)	First Participant First Visit: 06-MAY-2021 Last Participant Last Visit (through Day 29 visit): 10-SEP-2021
Hypothesis	• Superiority
Primary Objective and Hypothesis	• **Objective:** To evaluate the efficacy of MOV compared to placebo. **Hypothesis:** MOV is superior to placebo as assessed by the percentage of participants who are hospitalised and/or die from randomisation through Day 29.

Secondary Objective	**Objective:** To evaluate the efficacy of MOV compared to placebo as assessed by time to sustained resolution or improvement, and time to progression of each targeted self-reported sign/symptom of COVID-19 from randomisation through Day 29.		
Secondary Objective	**Objective:** To evaluate the efficacy of MOV compared to placebo as assessed by the odds of a more favourable response on the WHO 11-point ordinal scale on Day 3, end of treatment (EOT), Day 10, Day 15, and Day 29.		
Treatments groups	MOV	800 mg Q12H for 5 days 387 randomised; 386 received treatment; 371 (96.1%) completed treatment; 369 (95.6%) completed Day 29	
	Placebo	388 randomised; 379 received treatment; 355 (93.7%) completed treatment; 358 (94.5%) completed Day 29	
Endpoints and definitions	Primary endpoint	Efficacy	Percentage of participants who were hospitalised or died through Day 29
	Secondary endpoints	Efficacy	Time to sustained improvement or resolution, and time to progression of each targeted self-reported COVID-19 sign/symptom through Day 29
	Secondary endpoint	Efficacy	Odds of a more favourable response on the WHO 11-point ordinal outcome scale through Day 29.
Database lock	18-SEP-2021		

Results and Analysis	
Analysis description	**Primary Analysis (Incidence of Hospitalisation or Death Through Day 29)**
Analysis population and time point description	Population: modified intent-to-treat (MITT) population consisting of all randomised and treated, not hospitalised before the first dose

Descriptive statistics and estimate variability/ Effect estimate per comparison	**Treatment Group**	**MOV 800 mg**	**Placebo**
	N	385	377
	Number hospitalised or died through Day 29, n (%)	28 (7.3)	53 (14.1)
	Unadjusted difference	-6.8	
	Adjusted difference in rates % (95% CI)[a]	-6.8 (-11.3, -2.4)	
	p-value	0.0012	
	[a] Adjusted differences, the corresponding confidence intervals and the one-sided p-values are based on Miettinen & Nurminen method stratified by randomisation strata. Unknown survival status at Day 29 was counted as having an outcome of hospitalisation or death.		

Analysis description	**Primary Analysis (Summary of Hospitalisation or Death Through Day 29)**	
Descriptive statistics and estimate variability	**Treatment Group**	**MOV 800 mg**
	Hospitalised through Day 29	28 (7.3)
	Died through Day 29	0 (0.0)
	Unknown Day 29 survival Status[a]	0 (0.0)
	Alive with Unknown Day 29 hospitalisation status[b]	1 (0.3)
	[a]Unknown survival status at Day 29 was counted as having an outcome of hospitalisation or death in the primary efficacy analysis. [b]Alive but with unknown hospitalisation at Day 29 was counted as having an outcome of alive and not hospitalised in the primary efficacy analysis.	

Analysis description	**Primary Analysis (Incidence of COVID-related Hospitalisation or Death Through Day 29)**	
Descriptive statistics and estimate variability/ Effect estimate per comparison	**Treatment Group**	**MOV 800 mg**
	N	385
	Number with COVID-related hospitalisation or deaths through Day 29, n (%)	25 (6.5)
	Unadjusted difference	-6.8
	Adjusted difference in rates % (95% CI)[d]	-6.8 (-11.1, -2.6)
	[d] Adjusted differences and the corresponding confidence intervals are based on Miettinen & Nurminen method stratified by randomisation strata. Unknown survival status at Day 29 was not counted as having an outcome of COVID-related hospitalisation or death.	
Analysis description	**Secondary Analysis (Sustained improvement or resolution of self-reported COVID-19 signs and symptoms through Day 29)**	
Analysis population and time point description	Population: MITT	
Descriptive statistics and estimate variability	**Symptom**	**MOV 800 mg Number of events/participants (%)**

	Chills	166/169 (98.2)
	Fatigue	242/280 (86.4)
	Loss of Smell	119/152 (78.3)
	Loss of Taste	92/113 (81.4)
	Diarrhoea	81/84 (96.4)
	Shortness of Breath or Difficulty Breathing	113/133 (85.0)
	Sore Throat	156/175 (89.1)
	Feeling Hot or Feverish	184/195 (94.4)
	Cough	251/296 (84.8)
	Headache	239/269 (88.8)
	Muscle or Body Aches	223/253 (88.1)
	Nasal Congestion	205/229 (89.5)
	Nausea	86/95 (90.5)
	Rhinorrhoea	163/182 (89.6)
	Vomiting	30/31 (96.8)
Analysis description	**Secondary Analysis (Progression of self-reported COVID-19 signs and symptoms through Day 29)**	
Analysis population and time point description	Population: MITT	
Descriptive statistics and estimate variability	**Symptom**	**MOV 800 mg Number of events/participants (%)**

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Vomiting	16/379 (4.2)
Shortness of Breath or Difficulty Breathing	94/381 (24.7)
Cough	85/374 (22.7)
Chills	37/364 (10.2)
Loss of Smell	63/229 (27.5)
Feeling Hot or Feverish	57/366 (15.6)
Loss of Taste	60/268 (22.4)
Fatigue	82/364 (22.5)
Headache	71/338 (21.0)
Symptom	**MOV 800 mg** **Number of events/participants (%)**
Diarrhoea	57/375 (15.2)
Nasal Congestion	71/367 (19.3)
Nausea	60/371 (16.2)
Rhinorrhoea	59/374 (15.8)
Sore Throat	53/376 (14.1)

	Muscle or Body Aches	84/358 (23.5)
Analysis description	**Secondary Analysis (WHO 11-point ordinal outcome scale)**	
Analysis population and time point description	Population: MITT There was no appreciable difference between treatments	

Results – Part 2 (based on total randomised)

While IA3/4 included 775 subjects, there were 1239 enrolled at the time of the IA3/IA4 database lock (18 September 2021) and there were 1433 enrolled when the study was closed to further recruitment on 02 October 2021. A CSR covering all results for Part 2 up to Day 29 was made available during the procedure.

Important protocol deviations were reported for 458 (32.0%) participants (224 [31.3%] molnupiravir, 234 [32.6%] placebo). Of these, 385 (26.9%) participants had important protocol deviations that were considered to be clinically important. The most frequently reported clinically important protocol deviation was related to missing results from 1 haematology or chemistry panel at randomisation or 2 or more panels at required time points after randomisation (294 [20.5%] participants).

The PP population comprised 1344/1433 (93.8%) of randomised subjects, with 679 in the molnupiravir 800 mg BID group and 665 in the placebo group with 37 (5.2%) and 52 (7.3%) subjects in the molnupiravir and placebo groups excluded from the PP population respectively.

The most common reason for exclusion from the PP set was insufficient study medication (30 and 34 subjects respectively), which was balanced between study arms and IA3/IA4 and postIA3/IA4 populations.

For the total 1433 enrolled, baseline demographic and disease characteristics were balanced between the treatment groups. The median age was 43 years (range 18 to 90); 49% were male and 47% started molnupiravir or placebo within 3 days of COVID-19 symptom onset. The most common risk factors were obesity (74%), over 60 years of age (17%) and diabetes (16%).

Based on the total 1433 randomised, treatment with molnupiravir statistically significantly reduced the risk of hospitalisation or death through Day 29 (see next table). The actual difference vs. placebo was by 3 percentage points, which was smaller than the difference at IA3/4 (6.8 percentage points).

Table 43: Efficacy Results in Non-Hospitalised Adults with COVID-19 (Protocol 002 – Full Population)

	Molnupiravir (N=709) n (%)	Placebo (N=699) n (%)	Risk Difference* (95% CI)	p-value†
All-cause hospitalization or death through Day 29	48 (6.8)	68 (9.7)	-3.0 (-5.9, -0.1)	0.0218
Hospitalization‡	48 (6.8)	67 (9.6)		
Death	1 (0.1)	9 (1.3)		
Unknown§	0 (0.0)	1 (0.1)		

* Risk difference of molnupiravir-placebo based on Miettunen and Nurmanen method stratified by time from COVID-19 symptom onset (≤3 days vs. >3 [4-5] days).
† 1-sided nominal p-value. (Definitive hypothesis test occurred at the prospectively defined interim analysis when the efficacy boundary was crossed and efficacy was formally demonstrated.)
‡ Defined as ≥24 hours of acute care in a hospital or an acute care facility (e.g., emergency room).
§ Participants with unknown survival status at Day 29 are counted as having an outcome of all-cause hospitalization or death in the efficacy analysis.
Note: All participants who died through Day 29 were hospitalized prior to death.

Compared to the IA3/4 data, there were 2 new deaths – one in each group. In the molnupiravir group there were 20 additional instances of hospitalisation (28 vs. 48) compared to an increase by 15 events in the placebo group (52 vs. 67).

Importantly, the table above fails to reveal the difference between subjects included in IA3/4 and those not included in IA3/4, which is summarised below. This table shows that there was no detectable effect of molnupiravir in the population not included in IA3/4. Thus, the 30% difference as shown in the applicant's table above is a reflection of dilution of the 50% treatment effect at IA3/4 by no treatment effect in the non-IA3/4 population.

Table 44: Hospitalisation or Death by Day 29

	Interim Analysis Population Enrollment Dates: 5/7/2021 – 08/5/2021		**Post-Interim Analysis Population**[a] Enrollment Dates: 8/6/2021 – 10/2/2021		**Full Population** Enrollment Dates: 5/7/2021 – 10/2/2021	
	MOV	PBO	MOV	PBO	MOV	PBO
Hospitalization or death by Day 29	28/385 (7.3%)	53/377 (14.1%)	20/324 (6.2%)	15/322 (4.7%)	48/709 (6.8%)	68/699 (9.7%)
Death by Day 29	0 (0%)	8/377 (2.1%)	1/324 (<1%)	1/322 (<1%)	1/709 (<1%)	9/699 (1.3%)

[a]The Post-Interim Analysis Population includes those participants who had not reached Day 29 by the interim analysis data cutoff date of 9/18/2021.

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A further breakdown of primary endpoint events for sub-populations enrolled by date indicated that there was no discernible treatment effect for subjects beyond the first 40% enrolled, i.e. beyond those enrolled up to 21st July 2021. As shown above, the major difference between IA3/4 was not the hospitalisation/death rate in the molnupiravir group, which was little changed, but the much reduced rate in the placebo group, suggesting an important difference between the IA3/4 and post-IA3/4 populations in the background risk of progression to develop severe COVID-19.

Table 45: Incidence of Hospitalisation or Death Through Day 29 By Enrolment Timepoint Modified Intent-to-Treat Population MK-4482-002 Part 2 Day 29 DBL

	MK-4482 800 mg		Placebo		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)*
Participants in population	709		699			
Enrollment Timepoint						
0-20% (prior or equal to 6/23)	7/142	(4.9)	23/144	(16.0)	-11.0	(-18.5, -4.2)
20-40% (between 6/24 and 7/21)	13/149	(8.7)	20/143	(14.0)	-5.3	(-12.9, 2.1)
40-60% (between 7/22 and 8/11)	13/141	(9.2)	13/135	(9.6)	-0.4	(-7.7, 6.7)
60-80% (between 8/12 and 9/5)	5/137	(3.6)	7/139	(5.0)	-1.4	(-6.9, 3.9)
80-100% (after 9/5)	10/140	(7.1)	5/138	(3.6)	3.5	(-2.0, 9.5)

* The corresponding confidence interval is based on Miettinen & Nurminen method.
n= number of participants in the modified intent-to-treat population with the corresponding group.
n= number of participants died or hospitalized through Day 29.
Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.

Supportive efficacy analyses were conducted in the PP population which included 1344 participants. The incidence of hospitalisation or death through Day 29 in the Per Protocol population is comparable to that in the MITT population.

Table 46: Incidence of Hospitalisation or Death Through day 29 per Protocol Population ML-4482-002 IA3/IA4, Post-IA3/IA4, and All Participants in part 2

	MK-4482 800 mg		Placebo		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)*
Participants in population	679		665			
Time Point						
IA3/IA4	21/368	(5.7)	40/354	(11.3)	-5.6	(-9.8, -1.5)
Post-IA3/IA4	13/311	(4.2)	13/311	(4.2)	0.0	(-3.3, 3.3)
All Participants in Part 2	34/679	(5.0)	53/665	(8.0)	-3.0	(-5.7, -0.3)

* The confidence intervals are based on Miettinen & Nurminen method stratified by randomization strata.
n= number of participants in the per protocol population with the corresponding group.
n= number of participants died or hospitalized through Day 29.
Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.

Source: [P002V03MK4482: adam-adsl; adeff1]

Although the study was planned with an inferential interim analysis (IA3/4) and a final analysis (for all 1433 subjects as reported above), the marked difference between the IA3/4 and post-IA3/4 populations in the background (placebo group) rate of hospitalisations and deaths, leading to no demonstrable efficacy for molnupiravir in the post-IA3/4 population, was considered to be an unexplained anomaly of potential major concern. In particular, there was concern that the results for the post-IA3/4 population might be more relevant to the current situation in the EU. The applicant was asked to present the host and disease characteristics for the population included in IA3/4 vs. the population not included in IA3/4 to attempt to understand why the background (placebo) rate for hospitalisations and deaths was very much lower for the latter.

The next table summarises the hospitalisation/death rates by baseline characteristic for the IA3/4 and non-IA3/4 populations. Generally, reflecting the overall findings as shown above, rates for hospitalisations and deaths were lower in the post-IA3/4 placebo group subjects vs. the IA3/4 placebo group subjects regardless of the baseline characteristic. Any such differences for IA3/4 and post-IA3/4 molnupiravir subjects were generally of lesser magnitude. The rates for the "European region" showed a marked drop in both treatment groups in the post-IA3/4 population vs. the IA3/4 population.

Table 47: Incidence of Hospitalisation or Death Through Day 29 by Subgroup – Modified Intent-to-Treat Population – MK-4482-002 IA3/IA4 and Post-IA3/IA4

	IA3/IA4						Post-IA3/IA4					
	MK-4482 800 mg		Placebo		Difference		MK-4482 800 mg		Placebo		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)[a]	n/m	(%)	n/m	(%)	%	(95% CI)[a]
Time from Symptom Onset to Randomization												
≤ 3 days	16/189	(8.5)	23/185	(12.4)	-4.0	(-10.4, 2.3)	9/150	(6.0)	5/150	(3.3)	2.7	(-2.4, 8.1)
> 3 days	12/196	(6.1)	30/192	(15.6)	-9.5	(-16.0, -3.4)	11/174	(6.3)	10/172	(5.8)	0.5	(-4.8, 5.9)
Age Group												
≤ 60 years	23/335	(6.9)	41/322	(12.7)	-5.9	(-10.6, -1.4)	13/256	(5.1)	11/250	(4.4)	0.7	(-3.2, 4.6)
> 60 years	5/50	(10.0)	12/55	(21.8)	-11.8	(-26.1, 2.5)	7/68	(10.3)	4/72	(5.6)	4.7	(-4.7, 15.0)
Obesity (BMI ≥ 30)												
Yes	19/306	(6.2)	35/281	(12.5)	-6.2	(-11.2, -1.6)	10/229	(4.4)	11/226	(4.9)	-0.5	(-4.7, 3.6)
No	9/79	(11.4)	18/96	(18.8)	-7.4	(-18.0, 3.7)	10/95	(10.5)	4/96	(4.2)	6.4	(-1.2, 14.7)
Diabetes Mellitus Status												
Yes	9/49	(18.4)	13/56	(23.2)	-4.8	(-20.4, 11.2)	8/58	(13.8)	4/61	(6.6)	7.2	(-4.0, 19.4)
No	19/336	(5.7)	40/321	(12.5)	-6.8	(-11.4, -2.5)	12/266	(4.5)	11/261	(4.2)	0.3	(-3.6, 4.0)
Baseline COVID Severity												
Mild	12/223	(5.4)	21/203	(10.3)	-5.0	(-10.5, 0.1)	7/172	(4.1)	6/173	(3.5)	0.6	(-3.8, 5.1)
Moderate	16/161	(9.9)	31/173	(17.9)	-8.0	(-15.5, -0.5)	13/150	(8.7)	9/148	(6.1)	2.6	(-3.6, 9.0)
Severe	0/1	(0.0)	0/0				0/2	(0.0)	0/1	(0.0)		
Unknown	0/0		1/1	(100.0)			0/0		0/0			

	IA3/IA4						Post-IA3/IA4					
	MK-4482 800 mg		Placebo		Difference		MK-4482 800 mg		Placebo		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)[a]	n/m	(%)	n/m	(%)	%	(95% CI)[a]
SARS-CoV-2 Baseline Nucleocapsid Antibody												
Positive	2/71	(2.8)	2/70	(2.9)	-0.0	(-7.4, 7.2)	3/68	(4.4)	0/81	(0.0)	4.4	(-0.3, 12.2)
Negative	25/307	(8.1)	49/298	(16.4)	-8.3	(-13.7, -3.1)	17/250	(6.8)	15/237	(6.3)	0.5	(-4.1, 5.0)
Unknown	1/7	(14.3)	2/9	(22.2)			0/6	(0.0)	0/4	(0.0)		
Region												
North America	1/15	(6.7)	3/22	(13.6)			3/27	(11.1)	2/23	(8.7)		
Latin America	15/214	(7.0)	30/207	(14.5)	-7.5	(-13.7, -1.6)	7/115	(6.1)	4/114	(3.5)	2.6	(-3.4, 9.0)
Europe	8/89	(9.0)	12/87	(13.8)	-4.8	(-14.8, 4.8)	5/140	(3.6)	6/146	(4.1)	-0.5	(-5.6, 4.5)
Asia Pacific	1/5	(20.0)	3/6	(50.0)			4/14	(28.6)	1/10	(10.0)		
Africa	3/62	(4.8)	5/55	(9.1)	-4.3	(-15.5, 5.6)	1/28	(3.6)	2/29	(6.9)	-3.3	(-19.1, 11.9)
Sex												
Male	18/186	(9.7)	33/209	(15.8)	-6.1	(-12.8, 0.5)	14/144	(9.7)	8/146	(5.5)	4.2	(-2.0, 10.9)
Female	10/199	(5.0)	20/168	(11.9)	-6.9	(-13.2, -1.3)	6/180	(3.3)	7/176	(4.0)	-0.6	(-5.1, 3.6)
Race												
American Indian or Alaska Native	2/20	(10.0)	2/9	(22.2)			5/40	(12.5)	1/34	(2.9)	9.6	(-4.0, 23.8)
Asian	2/7	(28.6)	5/11	(45.5)			5/18	(27.8)	1/11	(9.1)		

	IA3/IA4						Post-IA3/IA4					
	MK-4482 800 mg		Placebo		Difference		MK-4482 800 mg		Placebo		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)*	n/m	(%)	n/m	(%)	%	(95% CI)*
Black or Africa American	3/27	(11.1)	1/19	(5.3)			0/12	(0.0)	0/15	(0.0)		
White	11/194	(5.7)	23/204	(11.3)	-5.6	(-11.3, -0.1)	8/203	(3.9)	9/201	(4.5)	-0.5	(-4.8, 3.7)
Multiple	10/137	(7.3)	22/134	(16.4)	-9.1	(-17.2, -1.5)	2/51	(3.9)	4/61	(6.6)	-2.6	(-12.4, 7.5)
Ethnicity												
Hispanic Or Latino	16/222	(7.2)	31/221	(14.0)	-6.8	(-12.8, -1.1)	9/129	(7.0)	4/125	(3.2)	3.8	(-1.9, 10.0)
Not Hispanic Or Latino	12/163	(7.4)	22/155	(14.2)	-6.8	(-14.0, -0.0)	11/189	(5.8)	11/195	(5.6)	0.2	(-4.7, 5.2)
Not Reported	0/0		0/1	(0.0)			0/4	(0.0)	0/0			
Unknown	0/0		0/0				0/2	(0.0)	0/2	(0.0)		
Baseline SARS-CoV-2 Quantitative Assay Viral Load Status												
undetectable [<500 copies/mL]	0/39	(0.0)	0/49	(0.0)	0.0	(-7.3, 9.1)	0/33	(0.0)	0/37	(0.0)	0.0	(-9.5, 10.6)
low VL [500 to <=10^6 copies/mL]	5/92	(5.4)	6/78	(7.7)	-2.3	(-11.1, 5.6)	5/90	(5.6)	3/102	(2.9)	2.6	(-3.6, 9.8)
high VL [>10^6 copies/mL]	23/241	(9.5)	45/243	(18.5)	-9.0	(-15.3, -2.8)	15/191	(7.9)	11/174	(6.3)	1.5	(-4.0, 7.0)
Unknown	0/13	(0.0)	2/7	(28.6)			0/10	(0.0)	1/9	(11.1)		
Baseline SARS-CoV-2 Qualitative Assay Viral Load Status												
Detectable	28/347	(8.1)	50/341	(14.7)	-6.6	(-11.5, -1.9)	20/296	(6.8)	15/293	(5.1)	1.6	(-2.3, 5.7)
Undetectable	0/29	(0.0)	0/29	(0.0)	0.0	(-11.9, 11.9)	0/26	(0.0)	0/24	(0.0)		
Unknown	0/9	(0.0)	3/7	(42.9)			0/2	(0.0)	0/5	(0.0)		
Baseline Clade												
20J (Gamma)	0/35	(0.0)	10/49	(20.4)	-20.4	(-33.7, -9.6)	0/2	(0.0)	0/1	(0.0)		
21H (Mu)	6/73	(8.2)	14/81	(17.3)	-9.1	(-20.0, 1.7)	0/10	(0.0)	2/11	(18.2)		
21A, 21I, 21J (Delta)	14/139	(10.1)	19/128	(14.8)	-4.8	(-13.1, 3.2)	17/220	(7.7)	10/215	(4.7)	3.1	(-1.6, 7.9)
21I (Delta)	3/35	(8.6)	7/29	(24.1)	-15.6	(-35.2, 2.6)	4/20	(20.0)	0/15	(0.0)		
21J (Delta)	11/99	(11.1)	12/95	(12.6)	-1.5	(-11.1, 7.9)	13/199	(6.5)	10/200	(5.0)	1.5	(-3.2, 6.5)
Other	5/50	(10.0)	6/37	(16.2)	-6.2	(-22.6, 8.2)	0/5	(0.0)	1/7	(14.3)		
Unavailable	3/88	(3.4)	4/82	(4.9)	-1.5	(-8.9, 5.4)	3/87	(3.4)	2/88	(2.3)	1.2	(-4.9, 7.7)
SARS-CoV-2 Baseline Neutralizing Antibody												
Positive	3/82	(3.7)	3/71	(4.2)	-0.6	(-8.5, 6.6)	5/108	(4.6)	0/117	(0.0)	4.6	(1.4, 10.4)
Negative	25/299	(8.4)	50/303	(16.5)	-8.1	(-13.5, -2.9)	15/214	(7.0)	15/203	(7.4)	-0.4	(-5.6, 4.8)

	IA3/IA4						Post-IA3/IA4					
	MK-4482 800 mg		Placebo		Difference		MK-4482 800 mg		Placebo		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)*	n/m	(%)	n/m	(%)	%	(95% CI)*
Unknown	0/4	(0.0)	0/3	(0.0)			0/2	(0.0)	0/2	(0.0)		

* The confidence intervals are based on the Miettinen & Nurminen method.
m= number of participants in the modified intent-to-treat population with the corresponding group.
n= number of participants died or hospitalized through Day 29.
Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.
"Other" baseline clade includes all participants with available baseline clades other than 20J (Gamma), 21A, 21I, 21J (Delta), or 21H (Mu).
"Unavailable" baseline clade: No evaluable sequence data available.
Estimated difference and 95% CI are only displayed for subgroups with sufficient sample size (≥25 in both treatment groups).

The applicant's assessment of potential contributing factors is summarised in the figure below.

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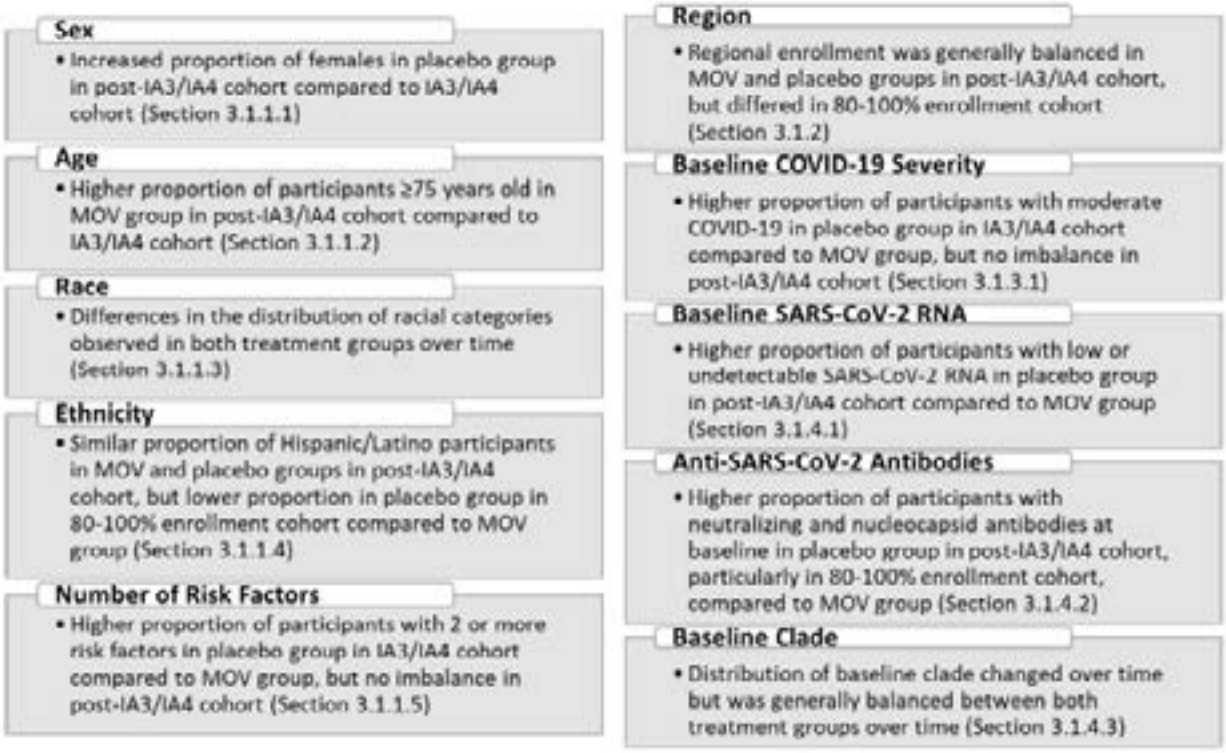

Figure 18: Summary of Baseline Characteristics Investigated for Potential Impact on the Primary Efficacy Endpoint

The proportion that was female increased from 44.1% to 54.7% for IA3/4 to post-IA3/4 populations, respectively, in the placebo group and from 51.7% to 55.9% in the molnupiravir group. See table below.

Table 48:

	IA3/IA4		Post-IA3/IA4		80-100% Enrollment Cohort		All Participants in Part 2	
	MOV (N=387)	Placebo (N=388)	MOV (N=329)	Placebo (N=329)	MOV (N=143)	Placebo (N=141)	MOV (N=716)	Placebo (N=717)
	%	%	%	%	%	%	%	%
Sex								
Male	48.3	55.9	44.1	45.3	46.9	42.6	46.4	51.0
Female	51.7	44.1	55.9	54.7	53.1	57.4	53.6	49.0
Age (years)								
18 to 49	70.8	69.8	63.8	59.0	59.4	53.9	67.6	64.9
50 to 64	21.2	20.6	23.4	27.4	23.8	29.8	22.2	23.7
65 to 74	6.2	6.2	7.6	10.6	9.1	13.5	6.8	8.2
≥75	1.8	3.4	5.2	3.0	7.7	2.8	3.4	3.2
>60	13.2	14.2	20.7	21.9	24.5	25.5	16.6	17.7
≤60	86.8	85.8	79.3	78.1	75.5	74.5	83.4	82.3
Race								
American Indian or Alaska Native	5.2	2.3	12.2	10.6	10.5	12.8	8.4	6.1
Asian	1.8	2.8	5.8	3.6	5.6	2.1	3.6	3.2
Black or African American	7.0	5.2	4.0	4.6	2.1	3.5	5.6	4.9
White	50.1	53.9	62.6	62.0	70.6	69.5	55.9	57.6
Multiple	35.9	35.8	15.5	19.1	11.2	12.1	26.5	28.2
Ethnicity								
Hispanic Or Latino	57.9	58.8	39.8	38.9	32.9	24.8	49.6	49.7
Not Hispanic Or Latino	42.1	41.0	58.4	60.5	64.3	74.5	49.6	49.9
Not Reported	0.0	0.3	1.2	0.0	2.8	0.0	0.6	0.1
Unknown*	0.0	0.0	0.6	0.6	0.0	0.7	0.3	0.3

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There was a similar shift in proportions aged >60 years in both treatment groups for IA3/4 to post-IA3/4 (13.2% molnupiravir and 14.2% placebo to 20.7% and 21.9%, respectively). For those aged 75+years there is a shift from 1.8% and 3.4% in respective groups at IA3/4 to 5.2% and 3.0% in the post-IA3/4 population.

For race or ethnicity, there were differences between the IA3/4 and post-IA3/4 populations, but these occurred in both treatment groups. It was only for small sub-populations (such as N. American natives and Asians) that some differences between treatment groups within the IA3/4 or post-IA3/4 populations were apparent but numbers here are small. There were some larger differences between the IA3/4 and post-IA3/4 populations for proportions that were white, of multiple racial descent and of Hispanic or Latino ethnicity. However, the changes observed applied similarly in both treatment groups and reflect changes in enrolment by region and/or country (see further below).

There were some changes from IA3/4 to post-IA3/4 in proportions with some individual risk factors, but these did not result in marked imbalances between the treatment groups in the post IA3/4 population. A higher proportion in the placebo group had 2 or more risk factors (21.4%) compared to the MOV group (17.6%) in the IA3/4 population. In contrast, the proportion with 2 or more risk factors in the post-IA3/4 population was not only higher but was similar in the two treatment groups (28.9% in placebo, 28.6% in MOV).

Table 49: Risk Factors for Severe Illness from COVID-19

At least one risk factor	99.5	99.0	99.4	99.7	99.3	100.0	99.4	99.3
Age >60 years	13.2	14.2	20.7	21.9	24.5	25.5	16.6	17.7
Active Cancer	1.6	2.8	2.1	1.5	2.8	0.7	1.8	2.2
Chronic Kidney Disease	3.6	5.2	7.3	7.9	9.8	9.9	5.3	6.4
Chronic Obstructive Pulmonary Disease	1.8	5.7	4.6	4.0	1.4	2.8	3.1	4.9
Obesity (BMI ≥ 30)	79.1	74.0	70.5	70.2	69.9	67.4	75.1	72.2
Serious Heart Condition	10.9	9.5	13.4	13.4	17.5	17.0	12.0	11.3
Diabetes Mellitus	12.7	14.7	17.6	19.5	14.7	16.3	14.9	16.9

*Results reported as "Unknown" are categorized as Unknown.

There were differences in region of enrolment between the IA3/4 and post-IA3/4 populations with far fewer enrolled in S. America and far more enrolled in Europe in the post-IA3/4 population vs. the IA3/4 population. However, there were no marked differences between treatment groups.

Table 50: Participants Characteristics by Population: Region All Randomised Participants

	IA3/IA4		Post-IA3/IA4		80-100% Enrollment Cohort		All Participants in Part 2	
	MOV (N=387)	Placebo (N=388)	MOV (N=329)	Placebo (N=329)	MOV (N=143)	Placebo (N=141)	MOV (N=716)	Placebo (N=717)
	%	%	%	%	%	%	%	%
Region								
North America	3.9	5.7	9.1	7.3	7.7	3.5	6.3	6.4
Latin America	55.8	55.2	35.0	35.3	26.6	23.4	46.2	46.0
Europe	23.0	23.2	42.9	45.3	58.0	65.2	32.1	33.3
Asia Pacific	1.3	1.5	4.6	3.3	4.9	2.1	2.8	2.4
Africa	16.0	14.4	8.5	8.8	2.8	5.7	12.6	11.9

Subjects from regions with higher rates of positive neutralizing antibody (Latin America: 27.5% MOV, 23.3% placebo; Europe: 29.1% MOV, 34.3% placebo; Africa: 27.8% MOV, 20.0% placebo) had a lower incidence of hospitalisation or death vs. regions with lower rates of positive neutralizing antibody status (Asia Pacific: 10.0% MOV, 11.8% placebo; North America: 13.3% MOV, 23.9% placebo).

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In the IA3/IA4 cohort, the highest enrolling countries were Colombia, the Russian Federation and South Africa. In the post-IA3/IA4 cohort, the highest enrolling countries were the Russian Federation, Guatemala, Ukraine and Mexico. The distribution of enrolment by country was generally comparable between treatment groups. The applicant claims that most country-level point estimates of the primary efficacy endpoint favoured MOV in both the IA3/IA4 and post-IA3/IA4 cohorts. In fact, this claim applies only for the IA3/4 population (first table below). The second table, which is confined to the post-IA3/4 population, does not support this claim.

Table 51: Incidence of Hospitalisation or Death Through Day 29 by Country Modified intent-to-treat population MK-4482-002 IA3/IA4

	MK-4482 800 mg		Placebo		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)*
Participants in population	385		377			
Country						
Brazil	1/31	(3.2)	8/35	(22.9)	-19.6	(-36.6, -3.6)
Canada	0/1	(0.0)	0/0	(0.0)		
Chile	1/19	(5.3)	1/17	(5.9)		
Colombia	10/115	(8.7)	17/114	(14.9)	-6.2	(-15.0, 2.3)
France	0/3	(0.0)	0/3	(0.0)		
Germany	0/2	(0.0)	0/0	(0.0)		
Guatemala	0/7	(0.0)	0/9	(0.0)		
Mexico	3/42	(7.1)	4/32	(12.5)	-5.4	(-22.1, 8.9)
Philippines	1/4	(25.0)	3/6	(50.0)		
Russian Federation	6/59	(10.2)	11/68	(16.2)	-6.0	(-18.2, 6.4)
South Africa	3/62	(4.8)	5/55	(9.1)	-4.3	(-15.5, 5.6)
Spain	2/7	(28.6)	0/4	(0.0)		
Taiwan	0/1	(0.0)	0/0	(0.0)		
Ukraine	0/18	(0.0)	1/12	(8.3)		
United States	1/14	(7.1)	3/22	(13.6)		

*The corresponding confidence interval is based on Miettinen & Nurminen method.
m= number of participants in the modified intent-to-treat population with the corresponding group.
n= number of participants died or hospitalized through Day 29.
Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.
Estimated difference and 95% CI are only displayed for countries with sufficient sample size (≥25 in both treatment groups).

Table 52: Incidence of Hospitalisation or Death Through Day 29 by Country Modified intent-to-treat population MK- 4482-002 post-IA3/IA4

	MK-4482 800 mg		Placebo		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)*
Participants in population	324		322			
Country						
Argentina	1/1	(100.0)	0/0	(0.0)		
Brazil	0/3	(0.0)	1/5	(20.0)		
Chile	0/1	(0.0)	1/1	(100.0)		
Colombia	0/21	(0.0)	1/25	(4.0)		
Egypt	1/1	(100.0)	0/1	(0.0)		
France	0/1	(0.0)	0/0	(0.0)		
Guatemala	5/48	(10.4)	0/49	(0.0)	10.4	(2.7, 22.2)
Italy	0/0	(0.0)	1/1	(100.0)		
Japan	1/5	(20.0)	0/2	(0.0)		
Mexico	1/41	(2.4)	1/34	(2.9)	-0.5	(-12.9, 10.1)
Philippines	3/9	(33.3)	0/7	(0.0)		
Russian Federation	5/96	(5.2)	4/108	(3.7)	1.5	(-4.7, 8.4)
South Africa	0/27	(0.0)	2/28	(7.1)	-7.1	(-22.8, 6.0)
Spain	0/2	(0.0)	0/0	(0.0)		
Taiwan	0/0	(0.0)	1/1	(100.0)		
Ukraine	0/41	(0.0)	1/36	(2.8)	-2.8	(-14.3, 6.0)
United Kingdom	0/0	(0.0)	0/1	(0.0)		
United States	3/27	(11.1)	2/23	(8.7)		

*The corresponding confidence interval is based on Miettinen & Nurminen method.
m= number of participants in the modified intent-to-treat population with the corresponding group.
n= number of participants died or hospitalized through Day 29.
Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.
Estimated difference and 95% CI are only displayed for countries with sufficient sample size (>25 in both treatment groups).

For Guatemala (which had 2 sites that began enrolling at the end of July 2021) there were 5 hospitalisations/deaths in the MOV group compared to 0 in the placebo group in the non-IA3/4 population. It seems that the hospitalisations occurred at non-study site facilities and information is limited. However, all five do seem to have been hospitalised due to progression to pneumonia and four had completed treatment while one was hospitalised on day 2 of treatment.

There were some differences in baseline COVID-19 severity (as defined by the applicant in the protocol) between the IA3/IA4 and post-IA3/4 cohorts but there were no differences for time from symptom onset to randomisation that were likely to have affected the treatment effect. Moreover, the distributions of the 15 individual signs and symptoms were balanced between treatment groups in the IA3/4 and non-IA3/4 populations.

Table 53: Participant Characteristics by Population: Baseline COVID-19 Disease Status All Randomised Participants

	IA3/IA4		Post-IA3/IA4		80-100% Enrollment Cohort		All Participants in Part 2	
	MOV (N=387)	Placebo (N=388)	MOV (N=329)	Placebo (N=329)	MOV (N=143)	Placebo (N=141)	MOV (N=716)	Placebo (N=717)
	%	%	%	%	%	%	%	%
Baseline COVID Severity								
Mild	57.6	54.6	52.3	54.1	54.5	55.3	55.2	54.4
Moderate	41.9	44.8	46.5	45.3	44.1	44.7	44.0	45.0
Severe	0.3	0.0	0.6	0.3	0.7	0.0	0.4	0.1
Unknown*	0.3	0.5	0.6	0.3	0.7	0.0	0.4	0.4

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Time from Symptom Onset to Randomization								
≤3 Days	48.6	47.4	46.2	46.2	53.1	51.8	47.5	46.9
>3 Days	51.2	52.3	53.5	53.5	46.9	48.2	52.2	52.9
Unknown*	0.3	0.3	0.3	0.3	0.0	0.0	0.3	0.3
Stratification Factor at Randomization Collected via IRT: Time from Symptom Onset to Randomization								
≤3 Days	49.4	49.0	45.9	46.2	53.1	52.5	47.8	47.7
>3 Days	50.6	51.0	54.1	53.8	46.9	47.5	52.2	52.3
* Missing data or results reported as "Unknown" are categorized as Unknown.								

Baseline virological characteristics for the IA3/4 and post-IA3/4 populations are summarised in the next table. In the IA3/IA4 cohort, the distribution of quantitative SARS-CoV-2 RNA titres at baseline was generally comparable between treatment groups. In the post-IA3/4 cohort, a higher proportion had a low or undetectable viral load at baseline in the placebo group.

Hospitalisation and death rates for the IA3/4 and post-IA3/4 populations by baseline serostatus defined by anti-N and by anti-spike NA showed no demonstrable benefit for molnupiravir in the baseline seropositives. Whether defined by anti-N or by NA, the baseline seronegatives included in IA3/4 derived a benefit from molnupiravir but there was no detectable benefit of treatment in the non-IA3/4 population.

During the procedure, the applicant supplemented the information on outcomes by baseline serostatus by adding results for subtype-specific IgG and IgM anti-nucleocapsid antibodies and IgG anti-spike antibodies. Subtype-specific IgG and IgM anti-nucleocapsid antibody testing was performed only for those with a positive result for baseline total serum antibodies (IgM, IgG and/or IgA) to the SARS-CoV-2 nucleocapsid protein.

The post-IA3/4 population was more likely that the IA3/4 population to have anti-nucleocapsid and/or anti-spike antibody and the rates were slightly higher for the placebo group vs. the MOV group in the post-IA3/4 population. It seems that the majority with positive results for anti-nucleocapsid had IgG rather than IgM, pointing to pre-study exposures.

Table 54: Baseline Anti-SARS-CoV-2 Antibody Characteristics Modified Intent-to-treat Population MK-4482-002 IA3/IA4 and Post-IA3/IA4

	IA3/IA4				Post-IA3/IA4			
	MK-4482 800 mg		Placebo		MK-4482 800 mg		Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)
Baseline SARS-CoV-2 Nucleocapsid IgG Antibody								
Positive	58	(15.1)	40	(10.6)	43	(13.3)	48	(14.9)
Negative	13	(3.4)	29	(7.7)	23	(7.1)	29	(9.0)
Unknown[a]	0	(0.0)	1	(0.3)	2	(0.6)	4	(1.2)
Test Not Done[b]	314	(81.6)	307	(81.4)	256	(79.0)	241	(74.8)
Baseline SARS-CoV-2 Nucleocapsid IgM Antibody								
Positive	32	(8.3)	21	(5.6)	17	(5.2)	17	(5.3)
Negative	35	(9.1)	48	(12.7)	46	(14.2)	58	(18.0)
Borderline	2	(0.5)	0	(0.0)	2	(0.6)	2	(0.6)
Unknown[a]	2	(0.5)	1	(0.3)	3	(0.9)	4	(1.2)
Test Not Done[b]	314	(81.6)	307	(81.4)	256	(79.0)	241	(74.8)
Baseline SARS-CoV-2 Spike IgG Antibody								
Positive	64	(16.6)	59	(15.6)	83	(25.6)	96	(29.8)
Negative	310	(80.5)	308	(81.7)	231	(71.3)	217	(67.4)
Borderline	7	(1.8)	6	(1.6)	5	(1.5)	6	(1.9)
Unknown[a]	4	(1.0)	4	(1.1)	5	(1.5)	3	(0.9)
Baseline SARS-CoV-2 Total Nucleocapsid Antibody								
Positive	71	(18.4)	70	(18.6)	68	(21.0)	81	(25.2)
Positive Nucleocapsid IgM[c] and Positive Nucleocapsid IgG	33	(8.6)	18	(4.8)	15	(4.6)	16	(5.0)
Positive Nucleocapsid IgM[c] and Negative Nucleocapsid IgG	1	(0.3)	2	(0.5)	4	(1.2)	2	(0.6)
Negative Nucleocapsid IgM and Positive Nucleocapsid IgG	24	(6.2)	22	(5.8)	27	(8.3)	30	(9.3)
Negative Nucleocapsid IgM and Negative Nucleocapsid IgG	11	(2.9)	26	(6.9)	19	(5.9)	27	(8.4)
Unknown Nucleocapsid IgM and/or Unknown Nucleocapsid IgG	2	(0.5)	2	(0.5)	3	(0.9)	6	(1.9)
Negative	307	(79.7)	298	(79.0)	250	(77.2)	237	(73.6)
Unknown[a]	7	(1.8)	9	(2.4)	6	(1.9)	4	(1.2)
Baseline SARS-CoV-2 Neutralizing Antibody								
Positive	82	(21.3)	71	(18.8)	108	(33.3)	117	(36.3)
Positive Spike IgG	53	(13.8)	44	(11.7)	72	(22.2)	83	(25.8)
Negative Spike IgG	24	(6.2)	27	(7.2)	31	(9.6)	32	(9.9)
Borderline Spike IgG	5	(1.3)	0	(0.0)	3	(0.9)	1	(0.3)
Unknown Spike IgG	0	(0.0)	0	(0.0)	2	(0.6)	1	(0.3)
Negative	299	(77.7)	303	(80.4)	214	(66.0)	203	(63.0)
Positive Spike IgG	11	(2.9)	15	(4.0)	11	(3.4)	13	(4.0)
Negative Spike IgG	286	(74.3)	280	(74.3)	199	(61.4)	183	(56.8)
Borderline Spike IgG	2	(0.5)	6	(1.6)	2	(0.6)	5	(1.6)
Unknown Spike IgG	0	(0.0)	2	(0.5)	2	(0.6)	2	(0.6)
Unknown[a]	4	(1.0)	3	(0.8)	2	(0.6)	2	(0.6)
Any Positive Baseline Spike Antibody (Spike IgG and/or Neutralizing Antibody)[e]								
Yes	95	(24.7)	92	(24.4)	121	(37.3)	135	(41.9)
No	290	(75.3)	285	(75.6)	203	(62.7)	187	(58.1)
Any Positive Baseline Antibody (Total Nucleocapsid, Nucleocapsid IgG, Nucleocapsid IgM, Spike IgG, and/or Neutralizing Antibody)[f]								
Yes	108	(28.1)	112	(29.7)	131	(40.4)	147	(45.7)
No	277	(71.9)	265	(70.3)	193	(59.6)	175	(54.3)

Table 55: Baseline Anti-SARS-CoV-2 Antibody Characteristics Modified Intent-to-treat Population MK-4482-002 IA3/IA4 and Post-IA3/IA4

	IA3/IA4				Post IA3/IA4			
	MK-4482 800 mg		Placebo		MK-4482 800 mg		Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)
Any Positive Baseline Nucleocapsid Antibody (Total, IgG, and/or IgM) AND Any Positive Baseline Spike Antibody (Spike IgG and/or Neutralizing Antibody)[c]								
Yes	58	(15.1)	50	(13.3)	58	(17.9)	69	(21.4)
No	327	(84.9)	327	(86.7)	266	(82.1)	253	(78.6)
All Negative Baseline Nucleocapsid Antibody (Total, IgG, and IgM) AND Any Positive Baseline Spike Antibody (IgG Spike and/or Neutralizing Antibody)[c]								
Yes	36	(9.4)	41	(10.9)	62	(19.1)	65	(20.2)
No	349	(90.6)	336	(89.1)	262	(80.9)	257	(79.8)

Note: Total nucleocapsid antibodies were assessed using the Roche Elecsys anti-SARS-CoV-2 assay. The nucleocapsid IgG and IgM antibodies were independently assessed using the Abbott Architect anti-SARS-CoV-2 assay and Immunodiagnostik serologic assays, respectively. The Spike IgG antibodies were assessed with the Euroimmun anti-Spike S1 IgG assay and SARS-CoV-2 neutralizing antibodies were assessed using the Monogram SARS-CoV-2 PhenoSense assay.

The percentage in this table is calculated based on total number of participants in the population.

[a] Missing data, invalid sample, or results reported as "Unknown" are categorized as Unknown.

[b] Only specimens with positive total anti-SARS-CoV-2 nucleocapsid antibody results (n=290) were tested for subtype-specific nucleocapsid IgG and IgM antibodies. One specimen with a negative total anti-SARS-CoV-2 nucleocapsid antibody result was tested, but this specimen was categorized as "Test Not Done".

[c] Borderline test results are counted as positive.

The proportion who progressed to hospitalisation or death was lower in participants with anti-spike IgG antibodies at baseline than in those without anti-spike IgG antibodies at baseline (1.4% vs. 8.3% in the MOV group; 0.6% vs. 12.6% in the placebo group). Among participants with and without subtype-specific IgG or IgM nucleocapsid antibodies (n=290 with test results), the findings were not as consistent.

In the IA3/IA4 cohort, among the subgroup of participants with negative spike IgG antibody status at baseline, the proportion with hospitalisation or death was 8.7% in the MOV group and 16.6% in the placebo group, consistent with results for the overall IA3/IA4 cohort. In the post-IA3/IA4 cohort, the incidence of hospitalisation or death among those with negative spike IgG antibody status was comparable between treatment groups (7.8% MOV, 6.9% placebo). The incidence of hospitalisation or death among those with subtype-specific IgG or IgM anti-nucleocapsid antibodies was low in both treatment groups and comparable between the IA3/IA4 and post-IA3/IA4 cohorts.

The incidence of hospitalisation or death among those with all negative baseline anti-SARS-CoV-2 antibody status was lower in the MOV group compared to the placebo group in the IA3/IA4 cohort (9.0% MOV, 18.5% placebo) but was comparable between treatment groups in the post-IA3/IA4 cohort (7.8% vs. 8.6%).

The incidence of hospitalisation or death among participants with all negative baseline anti-nucleocapsid antibody results AND any positive baseline anti-spike antibody result was low and generally comparable between groups in the IA3/IA4 cohort (2.8% MOV, 4.9% placebo) and post-IA3/IA4 cohort (3.2% MOV, 0% placebo). However, the small sample size of this subgroup (77 in the IA3/IA4 cohort, 127 in the post-IA3/IA4 cohort) limits interpretation of the results.

Subjects with all negative baseline anti-nucleocapsid antibody results AND any positive baseline anti-spike antibody result have a pattern suggestive of prior undisclosed SARS-CoV-2 vaccination or a waning anti-nucleocapsid response.

The distribution of participants with this pattern was generally comparable between the MOV and placebo groups in both the IA3/IA4 cohort (MOV 9.4%, placebo 10.9%) and post-IA3/IA4 cohort (MOV 19.1%, placebo 20.2%). The incidence of hospitalisation or death for these participants was low in the IA3/IA4 cohort (MOV 2.8%, placebo 4.9%) and post-IA3/IA4 cohort (MOV 3.2%, placebo 0%). Thus, prior undisclosed SARS-CoV-2 vaccination was unlikely to have affected clinical outcomes in the IA3/IA4 and post-IA3/IA4 cohorts.

The distribution of viral clade before and after IA3/IA4 was generally comparable between the MOV and placebo groups. A lower proportion had 21H (Mu), 20J (Gamma) or 21I (Delta) and a higher proportion had 21J (Delta) after IA3/IA4. In the IA3/4 population the efficacy by clade mostly favoured MOV except for 21J (Delta). In the non-IA3/4 population, there was no consistent effect of molnupiravir. However, denominators are small.

Table 56: Participants Characteristics by Population: Virological Characteristics All Randomised Participants

	IA3/IA4		Post-IA3/IA4		80-100% Enrollment Cohort		All Participants in Part 2	
	MOV (N=387)	Placebo (N=388)	MOV (N=329)	Placebo (N=329)	MOV (N=143)	Placebo (N=141)	MOV (N=716)	Placebo (N=717)
	%	%	%	%	%	%	%	%
SARS Quant Assay Viral Load at Baseline								
High VL [>10^6 copies/mL]	62.3	62.9	58.1	52.9	56.6	46.8	60.3	58.3
Low VL [500 to ≤10^6 copies/mL]	24.0	20.4	27.4	31.0	27.3	29.8	25.6	25.2
Undetectable [<500 copies/mL]	10.1	12.6	10.0	11.2	10.5	17.0	10.1	12.0
Unknown*	3.6	4.1	4.6	4.9	5.6	6.4	4.1	4.5
SARS-CoV-2 RNA at Baseline in Nasopharyngeal Sample (Qualitative Assay)								
Detectable	89.9	88.4	90.0	89.1	89.5	85.1	89.9	88.7
Undetectable	7.5	7.5	7.9	7.3	8.4	11.3	7.7	7.4
Unknown*	2.6	4.1	2.1	3.6	2.1	3.5	2.4	3.9
SARS-CoV-2 Baseline Neutralizing Antibody								
Positive	21.4	18.6	32.8	35.6	33.6	41.1	26.7	26.4
Negative	77.3	78.4	65.0	61.7	63.6	56.0	71.6	70.7
Unknown*	1.3	3.1	2.1	2.7	2.8	2.8	1.7	2.9
SARS-CoV-2 Baseline Nucleocapsid Antibody								
Positive	18.6	18.3	20.7	24.6	21.0	29.1	19.6	21.2
Negative	79.3	77.1	76.0	72.0	76.2	67.4	77.8	74.8
Unknown*	2.1	4.6	3.3	3.3	2.8	3.5	2.7	4.0
Baseline Clade								
19B (Washington State)	0.3	0.3	0.6	0.6	0.0	0.0	0.4	0.4
20A	0.8	0.5	0.3	0.3	0.0	0.0	0.6	0.4
20B	1.0	1.0	0.0	0.0	0.0	0.0	0.6	0.6
20D	0.5	0.3	0.0	0.6	0.0	0.0	0.3	0.4
20H (Beta)	1.3	1.5	0.0	0.0	0.0	0.0	0.7	0.8
20I (Alpha)	4.4	2.6	0.0	0.0	0.0	0.0	2.4	1.4
20J (Gamma)	9.0	12.9	0.6	0.3	0.0	0.0	5.2	7.1
21A (Delta)	1.3	1.0	0.3	0.0	0.7	0.0	0.8	0.6
21G (Lambda)	3.9	2.8	0.3	0.0	0.0	0.0	2.2	1.5
21H (Mu)	19.1	21.9	3.0	3.3	2.1	0.7	11.7	13.4
21I (Delta)	9.0	7.5	6.1	4.6	7.0	3.5	7.7	6.1
21J (Delta)	25.6	25.0	60.8	61.1	59.4	61.7	41.8	41.6
Unknown	0.8	0.5	0.3	0.6	0.7	1.4	0.6	0.6
Unavailable	23.0	22.2	27.7	28.6	30.1	32.6	25.1	25.1

* Missing data, invalid sample, tests not done, or results reported as "Unknown" are categorized as Unknown.
"Unknown" baseline clade: The sequence could not be classified by Nextstrain into a currently known clade.
"Unavailable" baseline clade: No evaluable sequence data available.

The applicant applied multivariable analyses to determine if changes in the distribution of baseline factors over time sufficiently explain the decline in the event rate in the placebo group observed over the time course of the trial.

The factors most predictive of hospitalisation/death were identified via stepwise selection logistic regression models using a set of baseline characteristics that were identified to be associated with the primary efficacy endpoint in bivariate analysis ($p<0.01$). All baseline characteristics were considered for selection in the models except for clade due to the large proportion with unavailable information (25.1% in both treatment groups). Selection models were run across treatment groups and for each treatment group individually.

A stepwise selection logistic regression model on all participants randomised in Part 2 selected the following 6 variables:

• Age (continuous)

• Sex (Male versus Female)

• Asian race (Yes [participants who identified as being only of Asian race or of multiple races including Asian race] versus No)

• Diabetes mellitus (Yes versus No)

• Positive anti-SARS-CoV-2 neutralizing antibodies (Yes versus No)

• High viral load (Yes [SARS-CoV-2 RNA titre >106 copies/mL] versus No [SARS-CoV-2

RNA titre ≤106 copies/mL])

During the procedure, logistic regression was repeated adding viral clade as a factor.

Treatment group-specific multivariable logistic regression models were used to predict the event rate in the last 20% enrolled using the data from the first 80% enrolled.

For MOV, the predicted event rate (average of the participant-level predicted probabilities) for the last 20% was higher than the actual and predicted event rates for the first 80% (8.3% vs. 6.7%, respectively), suggesting that the last 20% was at higher risk of hospitalisation/death vs. the first 80%).

For placebo, the predicted event rate for the last 20% was lower than the actual and predicted event rates for the first 80% (8.7% vs. 11.2%, respectively). For both groups the actual hospitalisation/death rates in the last 20% were lower than predicted by the model (7.1% actual vs. 8.3% predicted in the MOV group, 3.6% vs. 8.7% in the placebo group). The actual placebo event rate observed in the last 20% was substantially lower than the model predicted.

Similar results were obtained when using the participants in the IA3/IA4 cohort (approximately the first 50% of the study population enrolled) to predict the hospitalisation/death rates for the MOV and placebo groups in the post-IA3/IA4 cohort.

Table 57: Treatment Group-specific Multivariable Logistic Regression Models of Hospitalisation/Death Rate Modified Intent-to-treat Population Model on IA3/IA4 Population to Predict Rate for Post-IA3/IA4

Baseline Characteristic	MK-4482 800 mg	Placebo
	Odds Ratio (95% CI)[a]	Odds Ratio (95% CI)[a]
Age (continuous)	1.04 (1.00, 1.07)	1.03 (1.01, 1.06)
Sex (Male versus Female)	2.35 (1.00, 5.50)	1.40 (0.74, 2.64)
Asian Race (Yes versus No)[b]	2.22 (0.33, 15.10)	3.45 (0.94, 12.69)
Diabetes Mellitus (Yes versus No)	3.38 (1.32, 8.71)	1.55 (0.72, 3.32)
Positive anti-SARS-CoV-2 Neutralizing Antibodies (Yes versus No)	0.51 (0.13, 1.95)	0.37 (0.10, 1.31)
High Viral Load (Yes [SARS-CoV-2 RNA titer $>10^4$ copies/mL] versus No [SARS-COV-2 RNA titer $\leq 10^4$ copies/mL])	2.64 (0.88, 7.93)	3.36 (1.37, 8.27)
Participants in IA3/IA4 Population (approximately first 50% of participants enrolled)		
Predicted Event Rate	7.3%	14.1%
Actual Event Rate	7.3%	14.1%
Participants in Post-IA3/IA4 Population (approximately last 50% of participants enrolled)		
Predicted Event Rate	8.5%	12.6%
Actual Event Rate	6.2%	4.7%
Absolute Difference in Event Rates (Predicted – Actual)	2.3%	7.9%

[a] Odds ratios and corresponding 95% CIs were determined from treatment group-specific models using the participants in the IA3/IA4 population (approximately the first 50% of participants enrolled into the trial).
[b] For the Asian Race baseline characteristic variable used in the logistic regression models, participants who identified as being only of Asian race or of multiple races including Asian race are categorized as "Yes".

The applicant concluded that the results reinforce the potential impact of small changes in the distribution of baseline factors on the event rates over the time course of the trial and subsequently on the point estimate of the treatment difference. The results also indicate that there may have been additional unknown factors that may have contributed to the lower than expected event rate in both groups (especially in the placebo group) observed over time.

Additional virologic analyses

The applicant observes that the analyses of change from baseline in SARS-CoV-2 RNA in IA3/IA4 and post-IA3/IA4 cohorts showed greater mean reductions in the molnupiravir group on Days 3, 5 and 10. In fact, the tables below show that the greatest difference between molnupiravir and placebo groups was -0.42 $\log_{10}$ copies/mL at EOT in the IA3/4 population. These trends were also generally consistent in the subgroups of participants with high and low baseline SARS-CoV-2 viral load. For the total Part 2 population, those with anti-N at baseline had a maximum difference for molnupiravir vs. placebo in viral load of -0.28 $\log_{10}$ copies/mL, which occurred on day 10. For the majority that did not have anti-N at baseline, the maximum difference was -0.36 $\log_{10}$ copies/mL on day 3. Note that there was no discernible treatment effect for

molnupiravir in the IA3/4 population that was seropositive for anti-N or NA at baseline and there was no detectable treatment effect in the post-IA3/4 population regardless of seronegative or seropositive status based on anti-N or NA at baseline.

Table 58: Longitudinal Analysis of Mean Change from Baseline (Log10 Copies/mL) in SARS-CoV-2-RNA Based on Quantitative Assay Nasopharyngeal Sample Modified Intent-to-Treat population MK-4482-002 IA3/IA4

	Baseline		Day 3		Change from Baseline at Day 3	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[a]
MK-4482 800 mg	333	6.98 (1.870)	321	5.88 (1.933)	333	-1.13 (-1.27, -0.98)
Placebo	321	7.14 (1.774)	312	6.20 (1.689)	321	-0.93 (-1.07, -0.78)
Estimated Difference			Difference in LS Means at Day 3		(95% CI)	
MK-4482 800 mg vs. Placebo			-0.20		(-0.39, 0.00)	

	Baseline		FOT (Day 5)		Change from Baseline at FOT (Day 5)	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[a]
MK-4482 800 mg	333	6.98 (1.870)	308	4.79 (1.583)	333	-2.27 (-2.44, -2.11)
Placebo	321	7.14 (1.774)	303	5.27 (1.701)	321	-1.85 (-2.01, -1.69)
Estimated Difference			Difference in LS Means at FOT (Day 5)		(95% CI)	
MK-4482 800 mg vs. Placebo			-0.42		(-0.63, -0.21)	

	Baseline		Day 10		Change from Baseline at Day 10	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[a]
MK-4482 800 mg	333	6.98 (1.870)	290	3.70 (1.208)	333	-3.35 (-3.52, -3.18)
Placebo	321	7.14 (1.774)	281	3.88 (1.299)	321	-3.21 (-3.37, -3.04)
Estimated Difference			Difference in LS Means at Day 10		(95% CI)	
MK-4482 800 mg vs. Placebo			-0.14		(-0.33, 0.04)	

Table 59: Longitudinal Analysis of Mean Change from Baseline (Log10 Copies/mL) in SARS-CoV-2-RNA Based on Quantitative Assay Nasopharyngeal Sample Modified Intent-to-Treat population MK-4482-002 IA3/IA4

	Baseline		Day 3		Change from Baseline at Day 3	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[a]
MK-4482 800 mg	281	6.77 (1.746)	249	5.59 (1.814)	281	-1.22 (-1.39, -1.05)
Placebo	276	6.64 (1.867)	258	5.68 (1.947)	276	-1.01 (-1.18, -0.84)
Estimated Difference			Difference in LS Means at Day 3		(95% CI)	
MK-4482 800 mg vs. Placebo			-0.21		(-0.45, 0.02)	

	Baseline		FOT (Day 5)		Change from Baseline at FOT (Day 5)	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[a]
MK-4482 800 mg	281	6.77 (1.746)	250	4.54 (1.641)	281	-2.25 (-2.43, -2.07)
Placebo	276	6.64 (1.867)	244	4.56 (1.635)	276	-2.11 (-2.29, -1.92)
Estimated Difference			Difference in LS Means at FOT (Day 5)		(95% CI)	
MK-4482 800 mg vs. Placebo			-0.14		(-0.38, 0.09)	

	Baseline		Day 10		Change from Baseline at Day 10	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[a]
MK-4482 800 mg	281	6.77 (1.746)	228	3.46 (1.134)	281	-3.27 (-3.45, -3.09)
Placebo	276	6.64 (1.867)	229	3.59 (1.246)	276	-3.10 (-3.28, -2.93)
Estimated Difference			Difference in LS Means at Day 10		(95% CI)	
MK-4482 800 mg vs. Placebo			-0.17		(-0.36, 0.03)	

The proportion who had detectable viral RNA at baseline and achieved undetectable SARS-CoV-2 RNA increased at each post-baseline study visit and was generally comparable between the treatment groups in the IA3/IA4 and post-IA3/IA4 cohorts. Results were also comparable between treatment groups regardless of

baseline RNA titre. A higher proportion achieved undetectable SARS-CoV-2 RNA at each visit among those with a baseline titre $\leq 10^6$ copies/mL compared to those with $>10^6$ copies/mL in the IA3/IA4 and post-IA3/IA4 cohorts.

In the IA3/IA4 cohort, infectious virus was detected at Day 3 in 3/359 [0.8%] in the molnupiravir group and 22/353 [6.2%] in the placebo group, with Day 5 rates of 0/344 [0%] and 6/340 [1.8%]. In the post-IA3/IA4 cohort, infectious virus was detected at Day 3 in 0/278 [0%] and 8/290 [2.8%] in respective groups. On Day 5, the rates were 0% vs. 3.0%.

NA titres were assessed at baseline, Day 10 and Day 29. There were increases in seropositivity rates with time in both treatment groups. The mean changes from baseline were mostly slightly smaller for the MOV group compared to the placebo group, but there was no appreciable difference by Day 29. In both treatment groups, the proportion seropositive based on NA at baseline, Day 10 and Day 29 was higher in the post-IA3/IA4 cohort than in the IA3/IA4 cohort.

Table 60: Proportion of Participants with Detectable SARS-CoV-2 Neutralizing Antibody Over time Modified Intent-to-Treat population MK-4482-002 IA3/IA4

Visit	MK-4482 800 mg		Placebo		Difference
	n/N	% (95% CI)[a]	n/N	% (95% CI)[a]	% (95% CI)[b]
Baseline	82/381	21.5 (17.5, 26.0)	71/374	19.0 (15.1, 23.3)	2.5 (-3.2, 8.3)
Day 10	257/350	73.4 (68.5, 78.0)	271/344	78.8 (74.1, 83.0)	-5.3 (-11.7, 1.0)
Day 29	269/351	76.6 (71.9, 81.0)	267/337	79.2 (74.5, 83.4)	-2.6 (-8.8, 3.6)

Table 61: Proportion of Participants with Detectable SARS-CoV-2 Neutralizing Antibody Over time Modified Intent-to-Treat population MK-4482-002 IA3/IA4

Visit	MK-4482 800 mg		Placebo		Difference
	n/N	% (95% CI)[a]	n/N	% (95% CI)[a]	% (95% CI)[b]
Baseline	108/322	33.5 (28.4, 39.0)	117/320	36.6 (31.3, 42.1)	-3.0 (-10.4, 4.3)
Day 10	242/288	84.0 (79.3, 88.1)	262/294	89.1 (85.0, 92.4)	-5.2 (-10.8, 0.4)
Day 29	246/286	86.0 (81.4, 89.8)	256/295	86.8 (82.4, 90.4)	-0.7 (-6.4, 4.9)

The proportions with detectable anti-N antibody at baseline and post-baseline visits was generally comparable between the MOV and placebo groups in both the IA3/IA4 and post-IA3/IA4 cohorts. As for seropositivity rates based on NA, the anti-N seropositivity rates increased over time.

Table 62: Proportion of Participants with Detectable SARS-CoV-2 Nucleocapsid Antibody Over time Modified Intent-to-Treat population MK-4482-002 IA3/IA4

Visit	MK-4482 800 mg		Placebo		Difference
	n/N	% (95% CI)[a]	n/N	% (95% CI)[a]	% (95% CI)[b]
Baseline	71/378	18.8 (15.0, 23.1)	70/368	19.0 (15.1, 23.4)	-0.2 (-5.9, 5.4)
EOT (Day 5)	142/361	39.3 (34.3, 44.6)	146/353	41.4 (36.2, 46.7)	-2.0 (-9.1, 5.1)
Day 10	257/354	72.6 (67.6, 77.2)	281/338	83.1 (78.7, 87.0)	-10.5 (-16.6, -4.3)
Day 29	321/348	92.2 (88.9, 94.8)	315/336	93.8 (90.6, 96.1)	-1.5 (-5.5, 2.4)

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Table 63: Proportion of Participants with Detectable SARS-CoV-2 Nucleocapsid Antibody Over Time Modified Intent-to-Treat population MK-4482-002 IA3/IA4

Visit	MK-4482 800 mg		Placebo		Difference
	n/N	% (95% CI)*	n/N	% (95% CI)*	% (95% CI)†
Baseline	68/318	21.4 (17.0, 26.3)	81/318	25.5 (20.8, 30.6)	-4.1 (-10.6, 2.5)
EOT (Day 5)	148/299	49.5 (43.7, 55.3)	170/305	55.7 (50.0, 61.4)	-6.2 (-13.9, 1.6)
Day 10	219/280	78.2 (72.9, 82.9)	247/289	85.5 (80.9, 89.3)	-7.5 (-13.8, -1.2)
Day 29	264/280	94.3 (90.9, 96.7)	282/293	96.2 (93.4, 98.1)	-2.0 (-5.8, 1.6)

NGS analysis was performed on NP swab samples at baseline and Day 5 [EOT]) with RNA titres ≥600 copies/mL (but many samples with >9000 copies/mL could not be assayed) and samples from Days 10, 15 and 29 with ≥100,000 copies/mL. In the IA3/IA4 cohort, paired NGS data from baseline and

EOT were available for 133 MOV group and 155 placebo subjects compared to 72 and 78 in the post-IA3/IA4 cohort. Limited numbers had post-treatment samples with ≥100,000 copies/mL.

MOV was associated with a higher viral mutation (error) rate across the viral genome compared with placebo. In the IA3/IA4 cohort, the mean error rate (number of nucleotide changes per 10,000

bases) was 8.3 in the MOV group at Day 5 vs. 2.6 in the placebo group. In the post-IA3/IA4 cohort, the rates were 5.5 vs. 3.4, respectively.

Higher mean numbers of transition errors (C to U, G to A, U to C, and A to G) were observed across the viral genome in samples from the MOV group compared with the placebo group at Day 5 but a similar pattern was observed for the IA3/IA4 and post-IA3/IA4 cohorts. Treatment emergent amino acid changes (differed between baseline and post-baseline samples at ≥5% in 2 or more participants) in the replicase and spike proteins were more common in the MOV group in the IA3/IA4 and post-IA3/IA4 cohorts.

Among the viral replicase complex proteins (nsp7-nsp14), TE amino acid changes were uncommon with no specific substitution observed in >3 per group within each of the IA3/IA4 and post-IA3/IA4 cohorts. Overall, the number of changes detected across all proteins was higher in the IA3/IA4 cohort.

(27 changes at 22 loci) compared with the post-IA3/IA4 cohort (13 changes at 13 loci), which may reflect the larger number of available sequencing samples in the IA3/IA4 cohort. In the post-IA3/IA4 cohort, all protein loci with amino acid substitutions in replicase proteins (with the exception of nsp10 THR49ILE and nsp12 THR739ILE), were also observed in the IA3/IA4 cohort, indicating that there was no substantial difference between cohorts in patterns of amino acid changes in the replicase proteins.

TE amino acid substitutions in the viral spike protein were also more common in the MOV group.

In the IA3/IA4 cohort, 71 different amino acid changes at 44 loci were observed, while 30 changes at 24 loci were detected in the post-IA3/IA4 cohort. Multiple changes (substitutions, insertions, and deletions) observed at positions TYR144-TYR145 were counted as a single loci change. The majority of TE amino acid changes observed in the post-IA3/IA4 cohort were also detected in the IA3/IA4 cohort. These results indicate no difference in the pattern of TE spike changes between the IA3/IA4 and post-IA3/IA4 cohorts was evident, and therefore are unlikely to account for any differences in the primary efficacy endpoint results between the cohorts. Among MOV-treated participants, no infectious virus was recovered from any sample with TE spike mutations, suggesting that it is unlikely that variants with changes in the spike protein would be further transmitted.

Other considerations explored

Prior and concomitant medication use before and after IA3/IA4 was investigated. Specifically, use of systemic corticosteroids, antivirals or monoclonal antibodies with activity against SARS-CoV-2, chloroquine, ivermectin, azithromycin and colchicine. Subjects who started such medications only after hospitalisation were excluded from the analysis. Prior use of these medicines was not common (9.2% MOV, 9.7% placebo) among all participants in Part 2. Their use was more common overall in the IA3/IA4 cohort but was balanced between treatment groups in the IA3/4 and post-IA3/4 populations.

Systemic corticosteroid use was more common in the placebo group (6.6%) compared to the MOV group (3.9%) in the IA3/IA4 cohort. In the post-IA3/IA4 cohort, systemic corticosteroid use was more common in the MOV group (8.0%) compared to the placebo group (5.3%). While corticosteroid use seems beneficial in hospitalised patients with more advanced COVID-19, early use may suppress the immune response and delay viral clearance.

At the time of public announcement of the IA3/IA4 results on 01 OCT 2021, approximately 20% had not yet completed the Day 29 visit but the double blind design was maintained. In a sensitivity analysis of all Part 2 data that censored those who had not completed the Day 29 visit on 01 OCT 2021 there were 45 (6.3%) cases of hospitalisation or death in the MOV group vs. 66 (9.4%) in the placebo group (HR=0.66, 95% CI [0.45, 0.97], p-value=0.0157). This compares to rates of 6.8% vs. 9.6% cases in the reported final analysis for all Part 2 data.

The applicant also discusses the disease epidemiology, seroprevalence and vaccination rates (noting that all subjects in the study were unvaccinated) in the various countries that contributed to the study. Regarding changes in seroprevalence over time, the differences by region/country discussed are mostly based on estimates that preceded the period of conduct of the study. Although all of the data point to an increasing level of natural exposure to virus as the pandemic continues, the protective effect of natural priming on the rate of hospitalisation and death in a population such as that enrolled into the study (i.e. with at least one pre-existing risk factor) is unclear. Interpreting the potential effect of natural priming is also complicated by the variable level of cross-protection conferred by the immune response to the infecting strain against each new variant that emerges.

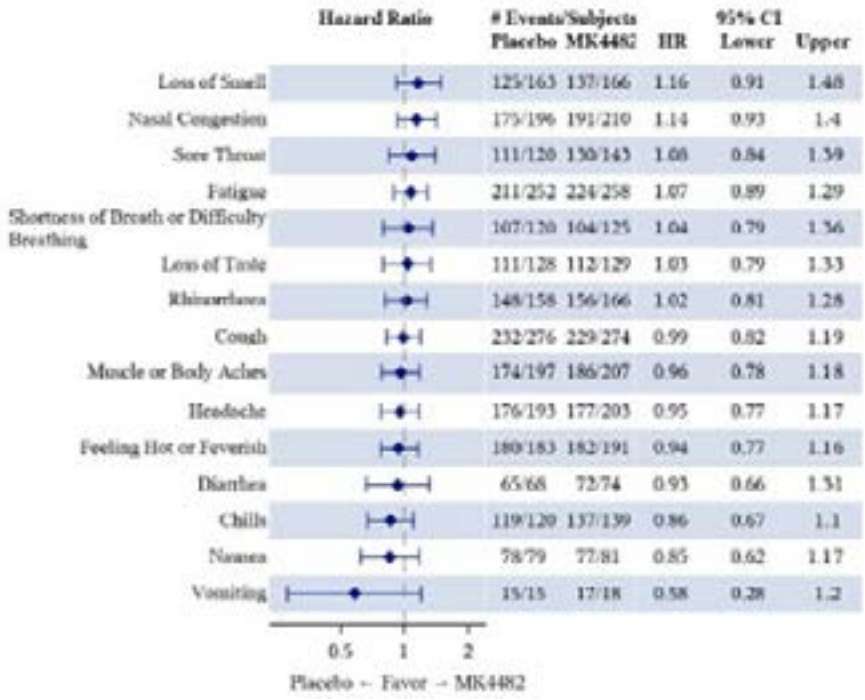
The applicant further considers that changes in the SOC during the study could have resulted in fewer cases of progression in the placebo group without necessarily having a detectable additional effect in the molnupiravir group. In this case, it is clear that guidelines and available options for treatment did change in several regions while the study was ongoing. Nevertheless, it is not possible to identify any specific changes that occurred in one or more regions during conduct of the study that could explain the IA3/3 vs. post-IA3/4 results.

Other analyses of the post-IA3/4 population

There was no consistent benefit for molnupiravir based on time to resolution of the individual signs and symptoms captured either in the IA3/4 population or in the total Part 2 population.

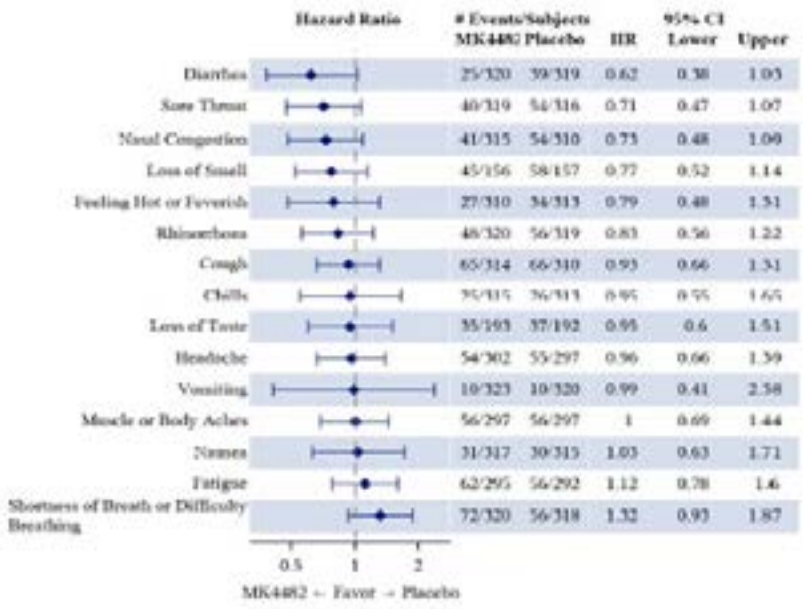
Additional analyses confined to the post-IA3/4 population showed no discernible benefit for molnupiravir for resolution of the captured signs and symptoms.

Figure 19: Hazard Ratio of Time to Sustained Improvement or Resolution of Signs and Symptoms Through day 29 Modified intent -to-treat population MK-4482-002 Post-IA3/IA4



Furthermore, the following figures in the table below shows the time to progression of signs and symptoms in the post-IA3/4 population.

Figure 20: Hazard Ratio to Progression of Signs and Symptoms Through day 29 Modified intent -to-treat population MK-4482-002 Post-IA3/IA4



Other studies

Indian studies in non-hospitalised subjects

Three studies were completed in non-hospitalised patients. These were sponsored by Indian companies that manufacture molnupiravir under licence from the applicant. They were all prospective, open label, randomised, multicentre, parallel group studies comparing molnupiravir with whatever constituted standard of care at the time of study conduct at participating sites but with some restrictions as detailed below. The primary endpoint was the rate of hospitalisation within 14 days of randomisation. Hospitalisation was defined as hospital admission for more than 24 hours with respiratory rate ≥ 24/ minute and SpO2 ≤ 93% in room air, requiring oxygen supplementation.

Aurobindo study CR216-21

This was a phase 3, prospective, open label, randomised, multicentre, parallel group study conducted between 1st July and 24th August 2021 in patients with mild COVID-19 disease. Eligible adults were aged ≤ 60 years and not hospitalised. They were to have a positive screening RT-PCR for SARS-CoV-2 and any one of fever, cough, sore throat, nasal congestion, malaise, headache or any other signs and COVID-19 symptoms without any evidence of breathlessness or hypoxia (normal

saturation) within 5 days prior to randomisation. The initial protocol required patients to have a risk factor for progressing to severe COVID-19 but this was amended to make it optional.

The major exclusions were known hypersensitivities of relevance, prior vaccination against COVID-19, respiratory rate ≥ 24/min, breathlessness, SpO2 ≤ 93% on room air, pulse rate < 50 bpm at rest, known liver disease (including HBV or HCV), platelet count <100,000/µL, ANC < 500 mm^3, AIDS-defining illness in the past 6 months, pregnancy or breastfeeding, immunosuppression and any uncontrolled co-morbid conditions.

Molnupiravir 800 mg (4 capsules of 200 mg) was administered orally every 12 hours for 5 days to the test group. Both groups received standard of care (SOC) as per guidance developed by Government of India or per the investigator's discretion. All patients were prescribed antipyretics, antitussives and multivitamins as a part of symptomatic management. Receipt of the following medications during the time periods listed below was planned to consider for exclusion of patient from study but medications were not to be withheld if required:

☐ Favipiravir, oseltamivir, remdesivir or any other anti-viral treatments

☐ Immunosuppressive treatments within 30 days of prior to randomisation

☐ Systemic corticosteroids (i.e. ≥ 20 mg/day of prednisone or equivalent) for ≥ 14 days within 30 days before enrolment and during the study

☐ Blood/ plasma products or immunoglobulins within 120 days before enrolment and during the study

The primary endpoint was the rate of hospitalisation from randomisation up to Day 14.

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The secondary efficacy endpoints were:

☐ Rate of hospitalisation up to Day 28

☐ Proportion with clinical improvement at end of treatment, Day 10 and Day 14

☐ Time to clinical improvement from randomisation to Day 14

☐ Mortality rate at Day 14 and Day 28

☐ Rate of SARS-CoV2 RT-PCR negativity in nasopharyngeal and/or oropharyngeal swab at the end of treatment, Day 10 and Day 14

☐ Change in SARS CoV-2 viral load from baseline to end of the treatment, Day 10 and Day 14

Clinical improvement was measured by using 11 point WHO clinical progression scale. A decrease of at least two points on the 11-point scale (0 to 10) compared to the baseline value (e.g. from 3 to 1) was defined as improvement.

The ITT population (all randomised) was the primary analysis population. There were 1220 patients randomised of which 1216 took the study medication as prescribed and completed the EOT visit.

All the patients assigned to molnupiravir took all 10 doses except for one.

Demographic factors and most of the COVID-19 symptoms were comparable among the treatment groups. Generally, the population was about two thirds male and persons aged 30-40 years predominated. The CSR does not provide information on the proportions with any risk factor likely predisposing to progression to severe COVID-19. Since persons aged 60+ years were anyway excluded and the BMI data suggests there were few obese subjects, it seems likely that rates for any predisposing factor were low.

Table 64: Demographic and Baseline Characteristics Details-ITT population (N=1220)

Parameter	Statistics	Test (N=610) n (%)	Reference (N=610) n (%)	Total (N=1220) n (%)	P-Value
Age (years)	n	610	610	1220	<.0001*
	Mean	37.0	36.0	36.5	
	Median	36.0	35.0	36.0	
	SD	11.39	10.64	11.03	
	Min,Max	18, 60	18, 60	18, 60	
Gender n (%)	Female	239 (39.2%)	229 (37.5%)	468 (38.4%)	<.0001*
	Male	371 (60.8%)	381 (62.5%)	752 (61.6%)	
Race n (%)	Asian-Indian	610 (100%)	610 (100%)	1220 (100%)	
Ethnicity n (%)	Non-Hispanic or Non-Latino	610 (100%)	610 (100%)	1220 (100%)	
Height (m)	n	610	610	1220	<.0001*
	Mean	1.6	1.6	1.6	
	Median	1.6	1.6	1.6	
	SD	0.09	0.09	0.09	
	Min,Max	1.17, 1.9	1.4, 1.9	1.17, 1.9	
Weight (kg)	n	610	610	1220	<.0001*
	Mean	63.5	64.6	64.0	
	Median	63.0	64.4	64.0	
	SD	10.29	10.03	10.17	
	Min,Max	35, 110	37.8, 101.1	35, 110	
BMI (Kg/m^2)	n	610	610	1220	<.0001*
	Mean	24.0	24.4	24.2	
	Median	23.9	24.5	24.2	
	SD	3.64	3.64	3.64	
	Min,Max	14.84, 40.9	15.06, 40.74	14.84, 40.9	
Time from symptom onset prior to the day of randomization n(%)	<=3 Days	340 (55.7%)	321 (52.6%)	661 (54.2%)	<.0001*
	>3 Days	270 (44.3%)	289 (47.4%)	559 (45.8%)	
COVID-19 SYMPTOMS (SCREENING)	Fever or chills	406 (66.6%)	421 (69.0%)	827 (67.8%)	
	Cough	300 (49.2%)	300 (49.2%)	600 (49.2%)	
	Fatigue	223 (36.6%)	205 (33.6%)	428 (35.1%)	
	Shortness of Breath or Difficulty in breathing	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	Expectoration	24 (3.9%)	26 (4.3%)	50 (4.1%)	

Parameter	Statistics	Test (N=610) n (%)	Reference (N=610) n (%)	Total (N=1220) n (%)	P-Value
	Myalgia	213 (34.9%)	203 (33.3%)	416 (34.1%)	
	Rhinorrhea	64 (10.5%)	71 (11.6%)	135 (11.1%)	
	Sore throat	172 (28.2%)	176 (28.9%)	348 (28.5%)	
	Diarrhea	46 (7.5%)	38 (6.2%)	84 (6.9%)	
	Headache	192 (31.5%)	192 (31.5%)	384 (31.5%)	
	Nausea or Vomiting	40 (6.6%)	49 (8.0%)	89 (7.3%)	
	Loss of smell (Anosmia)	163 (26.7%)	146 (23.9%)	309 (25.3%)	
	Loss of taste (Ageusia)	167 (27.4%)	154 (25.2%)	321 (26.3%)	
	Nasal Congestion (stuffy nose)	75 (12.3%)	79 (13.0%)	154 (12.6%)	
COVID-19 SYMPTOMS (DAY 1)	Fever or chills	370 (60.7%)	392 (64.3%)	762 (62.5%)	
	Cough	279 (45.7%)	285 (46.7%)	564 (46.2%)	
	Fatigue	210 (34.4%)	193 (31.6%)	403 (33.0%)	
	Shortness of Breath or Difficulty in breathing	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	Expectoration	18 (3.0%)	27 (4.4%)	45 (3.7%)	
	Myalgia	187 (30.7%)	178 (29.2%)	365 (29.9%)	
	Rhinorrhea	52 (8.5%)	57 (9.3%)	109 (8.9%)	
	Sore throat	148 (24.3%)	153 (25.1%)	301 (24.7%)	
	Diarrhea	33 (5.4%)	22 (3.6%)	55 (4.5%)	
	Headache	179 (29.3%)	173 (28.4%)	352 (28.9%)	
	Nausea or Vomiting	25 (4.1%)	32 (5.2%)	57 (4.7%)	
	Loss of smell (Anosmia)	151 (24.8%)	140 (23.0%)	291 (23.9%)	
	Loss of taste (Ageusia)	148 (24.3%)	141 (23.1%)	289 (23.7%)	
	Nasal Congestion (stuffy nose)	70 (11.5%)	76 (12.5%)	146 (12.0%)	

N = Number of subjects in specific group; n = Number of subjects with data available; Calculation of percentages based on N. SD = Standard Deviation.
*Statistically significant at 5% significance level.
Baseline: Baseline is defined as last observed measurement prior to the first dose of the study treatment.
Test Product(T): Molnupiravir with Standard of Care
Reference Product(R): Standard of Care

The predefined primary endpoint was not analysed because there were no instances of hospitalisation meeting the required criteria in the 14-day observation period (or in the 28-day follow-up). There were no deaths.

Observations for secondary endpoints were as follows:

The numbers and percentages of patients with clinical improvement were higher in those given molnupiravir on days 5 (EOT), 10 and 14 although the difference narrowed between the last two time points due to a high proportion improving in the control group.

Table 65: Proportion of Patients with Clinical Improvement at End of Treatment, Day 10 and Day 14

Evaluation Response	Visit	Statistics	Test (N=610)	Reference (N=610)	Risk Difference (Test vs Reference) and **95% confidence intervals (CI)	p-value
ITT Population						
Clinical Improvement	End of Treatment (Day 5)	n (%)	177 (29.0)	34 (5.6)	23.4	0.0000*
		*95% CI	0.2555, 0.3274	0.0401, 0.0768	0.1941, 0.2748	
	Day 10	n (%)	411 (67.4)	193 (31.6)	35.8	0.0000*
		*95% CI	0.6355, 0.7097	0.2807, 0.3543	0.305, 0.4098	
	Day 14	n (%)	543 (89.0)	485 (79.5)	9.5	0.0000*
		*95% CI	0.8628, 0.9125	0.7612, 0.8252	0.05456, 0.1356	
*Statistically significant at 5% level of significance.						
Treated Analysis Population						
Evaluation Response	Visit	Statistics	Test (N=609)	Reference (N=607)	Risk Difference (Test vs Reference) and **95% confidence intervals (CI)	p-value
Clinical Improvement	End of Treatment (Day 5)	n (%)	177 (29.1)	34 (5.6)	23.5	0.0000*
		*95% CI	0.2559, 0.3279	0.0403, 0.0772	0.1942, 0.2751	
	Day 10	n (%)	411 (67.5)	193 (31.8)	35.7	0.0000*
		*95% CI	0.6366, 0.7108	0.2821, 0.356	0.3044, 0.4094	
	Day 14	n (%)	543 (89.2)	485 (79.9)	9.3	0.0000*
		*95% CI	0.8644, 0.9139	0.7652, 0.8289	0.05229, 0.1329	
N= Number of subjects in specified group. Calculation of percentages are based on ITT and Treated Analysis Population. n = Number of subjects with data available. *The 95%CI was calculated by using Wilson C/c method at 5% level of significance for single proportion of each						

The median time to improvement (time from randomisation to earliest day of observed improvement) was 10 days in the molnupiravir group and 14 days in the control group. The same applied in the TAP.

Table 66: Time to Clinical Improvement (Days) from randomisation to Day 14 on 11-pont WHO Progression Scale

ITT Population					
	Statistics	Test N= 610	Reference N= 610	HR (95% CI)^	p-Value**
Event	n (%)	545 (89.3)	486 (79.7)		
Censored	n (%)	65 (10.7)	124 (20.3)		
Time to clinical improvement (days)	n	545	486	0.6083 (0.5372, 0.6887)	0.0000*
	First Quartile (Q1)	5.00	10.00		
	Median	10.00	14.00		
	Third Quartile (Q3)	10.00	14.00		

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The proportion of patients achieving negative SARS-CoV-2 RNA was 81.5% vs. 17.4%, 89.8% vs. 46.4% and 93.1% vs. 83.1% at EOT (Day 5), Day 10 and Day 14 respectively, for test and control groups.

Hetero Laboratories study

It appears that this study was of generally similar design to the Aurobindo study. It was conducted at 23 sites in India from May 2021 to August 2021.

There were 1218 subjects randomised, of which 593/608 in the molnupiravir group and 581/610 in the control group completed. Of 15 non-completers in the molnupiravir group, 9 were hospitalised, 5 withdrew consent and one was LTFU. Of 29 non-completers in the control group, 26 were hospitalised and 3 withdrew consent.

The patient characteristics were apparently balanced between groups (assuming that 45.1% and not 25.1% in the control group were enrolled within 3-5 days). Very few patients had any comorbidities that may have predisposed them to develop severe COVID. There was a much higher rate of ivermectin usage in the control group.

Table 67: Patient Characteristics

Characteristics	Molnupiravir (N=608) n (%)	Standard of Care (N=610) n (%)
Gender		
Male	408 (67.11)	425 (69.67)
Female	200 (32.89)	185 (30.33)
Race		
Indian	608 (100)	610 (100)
Age (years, Mean ± SD)	35.2 ± 10.8	34.8 ± 10.8
Height (cm, Mean ± SD)	165.6 ±9.5	165.4 ±9.4
Weight (kg, (Mean ± SD)	65.0 ±9.1	64.2 ±7.9
BMI (kg/m2, (Mean ± SD)	23.5 ±2.6	23.4 ±2.6
Comorbidities		
Obesity (BMI > 30)	19 (3.12)	17 (2.78)
Diabetes Mellitus	2 (0.32)	2 (0.32)
Hypertension	3 (0.49)	7 (1.14)
Time Since Symptom Onset		
<3 days	327 (53.7)	335 (54.9)
3 – 5 days	281 (46.3)	275 (25.1)
SARS CoV-2 RT-PCR Test		
Positive <48 hours	608 (100)	610 (100)
Cycle Threshold Value (Mean ± SD)	25.9 (3.8)	25.9 (3.8)
Standard of Care Provided		
Multivitamins, antipyretics and Antihistamines	478 (78.6)	472 (77.4)
Ivermectin	296 (48.68)	472 (77.38)
Inhalation Budesonide	10 (1.6)	10 (1.6)

The analysis of the primary endpoint showed a significant reduction in hospitalisation rate with molnupiravir but the actual difference was by less than 3 percentage points.

Parameter	Molnupiravir N=608 n (%)	Standard of Care N=610 n (%)	Proportion Difference	95% Confidence Interval	Molnupiravir Vs Standard of Care (p-values**)
Patients Hospitalized	9 (1.48)	26 (4.26)	-2.78	[-4.65, -0.9]	0.0053

**p-values were obtained using Fisher test

There were no deaths.

The clinical improvement was defined as in the Aurobindo study (≥ 2 point decrease on the 11- point WHO clinical progression scale compared with the baseline value). Molnupiravir gave higher rates of improvement and a shorter median time to improvement vs. the control group (6 days vs. 10 days).

Dr Reddy's study (DRL-MOL-002)

The study design was similar to that for the two prior studies. The primary efficacy endpoint was evaluated in subjects who received at least one dose and had an evaluable assessment of the primary endpoint.

There were 1,218 subjects randomised (1:1) from 04-JUN-2021, with LPLV on 07-FEB-2022 and 1,216 received at least 1 dose of study treatment. The majority was male (58.4%) and all subjects were of Asian ethnicity with a mean age of approximately 39 years. Most subjects (>98%) were unvaccinated.

Only two subjects were hospitalised (1 through Day 14 and 1 between Days 15 and 28). Both patients received SOC only. No deaths were reported. The MOV+SOC group was associated with faster improvement and more rapid achievement of viral negativity compared with SOC.

Table 68: Time to Achieve Clinical Improvement Full Analysis Set (DRL-MOL-002)

	Parameter, n(%)[a]	MOV+SOC (N=603)	SOC (N=609)
Clinical Improvement (at least 1-point improvement)	n	598	599
	NI	5	10
	Median time[a]	5	6
	95% CI for Median	(NE, NE)	(5, 9)
	Q1:Q3	5:10	5:14
	p-value[b]	<0.0001	
Clinical Improvement (at least 2-point improvement)	n	582	581
	NI	21	28
	Median time[a]	5	10
	95% CI for Median	(5:6)	(9:10)
	Q1:Q3	5:10	5:14
	p-value[b]	<0.0001	

Other molnupiravir studies published or otherwise publicly reported

During the procedure, the applicant reviewed the literature for recent studies in which molnupiravir was compared to no specific anti-COVID-19 treatment, with sotrovimab or with nimatrelvir/ritonavir (NMR/RTV). Few were prospective and most were retrospective reviews of data collected by healthcare organisations and/or government databases. Those studies of most relevance to the target EU population for molnupiravir may be summarised as follows.

The PANORAMIC study

Conducted only in the UK, this was a prospective and randomised open-label study that compared molnupiravir to SOC. The study population was enrolled from Dec 8 2021 onwards, just as the country transitioned from the delta to the omicron period. BA.1 was more or less replaced by BA.2 by end of March 2022 and has since been replaced by BA.4 and BA.5. The vaccination history and natural exposure status of UK residents is broadly in line with that of the majority of EU MS, leading to findings that are likely applicable across Europe.

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The population enrolled into PANORAMIC broadly resembled that of MK-4482-002 in that adults were outpatients aged 50+ years and/or were to have at least one of the listed risk factors for progression. However, in great contrast to MK-4482-002, 98.9% had received at least one dose of a SARS-CoV-2 vaccine and 94.4% had received at least three doses. Randomisation was stratified by age <50/50+ and vaccination (yes/no). In fact, the mean age (range) was 56.6 (range 18 to 99) years and 68.9% had co-morbidities. Just over half (51%) were age 18-<65 years with at least one risk factor for progression to severe COVID-19.

The molnupiravir regimen was the same as in MK-4482-002 (800 mg BID for 5 days) and 87% of subjects started within 5 days of symptom onset with a median time elapsed of 3 days. Adherence to a 5-day course was ~95% and <1% received other specific treatments for COVID-19.

In the primary analysis, the actual hospitalisation and death rate was very low (0.8%) in the MOV+SOC and SOC groups, such that no benefit for MOV could be demonstrated based on the pre-defined primary endpoint in a population likely typical for Europe in 2022. The same conclusion applied in the subgroup analyses of the primary endpoint.

Subjects completed online symptom diaries for 28 days and rated a range of symptoms. They also self-reported recovery. The observed median (IQR) time-to-first-recovery from randomisation was 9 (5–23) days for MOV and 15 (7–not reached) for SOC. There was an estimated benefit of 4.2 (95% BCI: 3.8 – 4.6) days in time-to-first-recovery (TTR) giving a posterior probability of superiority of >0.999. The estimated median TTR for molnupiravir was 10.3 days vs. 14.5 days for SOC, giving a hazard ratio [95% BCI] of 1.36 days, which met the pre-specified superiority threshold. Subgroup analysis demonstrated that this benefit for molnupiravir was consistent across all studied groups.

Other studies of molnupiravir vs. SOC

A study from Poland suggested lower mortality if MOV was given within 5 days of onset to Polish subjects aged >60 or >80 years but there was no effect of MOV on rates of IMV. A study in Israel from Najjar-Debbiny was conducted in a population at considerable risk for disease progression and outcomes were defined as severe COVID-19 or COVID-19-related mortality and the composite. It may be presumed that the majority was highly vaccinated. Results for the composite outcome and its components were comparable between treatment groups for the overall population. MOV was associated with reduced risk of the composite outcome in older (>75 years of age) subjects, in females and in those inadequately vaccinated for COVID-19 and it reduced both severe COVID-19 and COVID-19-related mortality in these subgroups. The possibility that MOV could reduce hospitalisation rates at least in some specific high risk groups is further supported by some studies as summarised below.

Title (Country) / First Author / Journal / Date Published	Study Design / Population Enrollment Time Period/ SARS-CoV-2 Variant(s) (if known)	Treatment Groups, N (%)	Main Outcome / Endpoint Results
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 (Hong Kong) • Wan et al, 2022 [Ref. 5.4: 086OJR] • *The Lancet Regional Health – Western Pacific* ahead of print (https://doi.org/10.1016/j.lanwpc.2022.100602) • Published 05-OCT-2022	Retrospective cohort study • Nonhospitalized patients ≥60 years of age with mild-to-moderate COVID-19 with ≥1 chronic disease • 22-FEB-2022 to 31-MAR-2022 • Omicron	After IPTW Adjustment Outpatient: • Control: 23,430 • MOV: 18,637.1 • NMV+r: 14,120.9 Inpatient: • Control: 20,057 • MOV: *Not reported in manuscript* • NMV+r: *Not reported in manuscript*	After IPTW Adjustment *Values are HR (95% CI).* Control=Reference **Inpatient** / **MOV** / **NMV+r** 28-day All-cause mortality: 0.31 (0.24, 0.40) p<0.0001 / 0.10 (0.05, 0.21) p<0.0001 28-day hospital re-admission: 0.71 (0.52, 0.97) p=0.031 / 0.47 (0.24, 0.93) p=0.030 **Outpatient** / **MOV** / **NMV+r** 28-day all-cause mortality: Not analyzed due to small number of deaths 28-day clinic re-attendance: 1.80 (1.60, 2.01) <0.0001 / 1.45 (1.11, 1.91) p=0.0069 28-day hospital re-admission: 0.72 (0.52, 0.98) p=0.039 / 0.37 (0.23, 0.60) p<0.0001
Demographics and Outcomes of Initial Phase of COVID-19 Medicines Delivery Units Across 4 UK Centers During Peak B1.1.529 Omicron Epidemic: A Service Evaluation (England) • Brown et al, 2022 [Ref. 5.4: 086OD0] • *Open Forum Infectious Diseases* (https://doi.org/10.1093/ofid/ofac527) • Published 06-OCT-2022	Retrospective review performed as part of a service evaluation of 4 COVID-19 medicines delivery units in England • Symptomatic nonhospitalized patients with SARS-CoV-2 at risk for severe disease • 20-DEC-2021 to 09-JAN-2022 • Omicron B1.1.529	Total N=4788 • Eligible for treatment: 850 ○ MOV: 442 (52.0%) ○ Sotrovimab: 186 (21.9%) ○ Declined treatment: 222 (26.1%) • Ineligible for treatment: 3139 • Unable to contact: 799	Hospitalized due to COVID-19 within 14 days of referral, n (%) • MOV: 8 (1.8%) • Sotrovimab: 6 (3.2%)

Title (Country) / First Author / Journal / Date Published	Study Design / Population Enrollment Time Period/ SARS-CoV-2 Variant(s) (if known)	Treatment Groups, N (%)	Main Outcome / Endpoint Results
Characteristics and Outcomes of Patients With COVID-19 at High-risk of Disease Progression Receiving Sotrovimab, Oral Antivirals or No Treatment in England (England) • Patel et al, 2022 [Ref. 5.4: 086MY0] • https://doi.org/10.1101/2022.11.28.22282808 • Pre-print posted 29-NOV-2022	Retrospective cohort study using data from England's Discover dataset. • Nonhospitalized patients ≥12 years of age • 01-DEC-2021 to 31-MAY-2022 • Omicron BA.1, BA.2, and BA.5 predominance during the study	Total N=5547 • MOV: 470 (8.5%) • NMVr+: 337 (6.1%) • Sotrovimab: 696 (12.5%) • Untreated: 4044 (72.9%)	Values are n (%) [95% CI] **Treatment** / **COVID-19 Hosp** / **All Cause Hosp** / **Death** Sotrovimab (n=666): 5 (0.7%) [0.1, 1.3] / 35 (5.0%) [3.4, 6.6] / 8 (1.3%) [0.3, 1.9] NMV+r (n=337): <5 (0.3-1.2%) / 5 (1.5%) [0.2, 2.8] / <5 (0.3-1.2%) MOV (n=470): 10 (2.1%) [0.8, 3.4] / 19 (4.0%) [2.2, 5.8] / 7 (1.5%) [0.4, 2.6] Untreated (n=4044): 114 (2.8%) [2.3, 3.3] / 251 (6.2%) [5.5, 6.9] / 75 (1.9%) [1.5, 2.3] *Due to n<5, the number was suppressed; range of 1-4 events used to calculate range Hosp=hospitalization
Real-world Clinical Outcomes of Treatment With Molnupiravir for Patients With Mild-to-Moderate Coronavirus Disease 2019 During the Omicron Variant Pandemic (Japan) • Suzuki et al, 2022 [Ref. 5.4: 086SDN] • *Clinical and Experimental Medicine* (https://doi.org/10.1007/s10238-022-00949-3) • Published 05-DEC-2022	Retrospective cohort study of 23 hospitals in Fukushima Prefecture • Hospitalized patients ≥18 years of age with mild-to-moderate COVID-19 with ≥1 risk factor for severe disease January 2022 to April 2022 • Omicron (B.1.1.529 presumed)	Total N after PSW: 920 • MOV: 230 (25%) • No MOV: 690 (75%)	After PSW: **Outcome** / **MOV** / **No MOV** / **p-value** Any deterioration: 9 (3.9) / 58 (8.4) / 0.034 Mechanical ventilation: 0 / 1 (0.10) / 1.000 Death: 2 (0.90) / 3 (0.41) / 0.596 Values are n (%)
Oral Antiviral Treatment for COVID-19 in Patients With Systemic Autoimmune Rheumatic Diseases (Greece) • Gerolymatou et al, 2022 [Ref. 5.4: 086VQH] • *Journal of Rheumatology* (https://doi.org/10.3899/jrheum.221014) • Published 15-DEC-2022	Retrospective study at 2 tertiary rheumatology centers using the national electronic database for social security services in Greece • Outpatients with systemic autoimmune rheumatic diseases receiving intense immunosuppressive immunomodulatory therapy at risk for severe disease • February 2022 to August 2022 • Variant not reported	Total N=74 • MOV: 26 (35.1%) • NMV+r: 48 (64.9%)	Adverse events, n (%) • MOV: 0 • NMV+r: 4 (8.3%) Severe disease/hospitalization • MOV: 1 • NMV+r: 1

Title (Country) / First Author / Journal / Date Published	Study Design / Population Enrollment Time Period/ SARS-CoV-2 Variant(s) (if known)	Treatment Groups, N (%)	Main Outcome / Endpoint Results
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 (United States) • Bajema et al, 2022 [Ref. 5.4: 0868WG] • https://doi.org/10.1101/2022.12.05.22283134 • Pre-print posted 16-DEC-2022	Retrospective target trial matched cohort emulation studies (n=3) • At-risk adult patients in VHA care • January 2022 to February 2022 • Omicron B.1.1.529, BA1.1	Trial 1 Total N=3174 • NMV+r: 1587 (50%) • No treatment:1587 (50%) Trial 2 Total N=1794 • MOV: 897 (50%) • No treatment: 897 (50%) Trial 3 Total N=1538 • MOV: 769 (50%) • NMV+r: 769 (50%)	30-day Outcomes Trial 1: NMV+r vs no treatment; Trial 2: MOV vs no treatment; Trial 3: NMV+r vs MOV Hosp or death: 0.53 (0.39-0.72); 0.77 (0.55-1.08); 0.63 (0.36-1.10) Hosp: 0.66 (0.48-0.91); 0.91 (0.64-1.31); 0.70 (0.37-1.34) Death: 0.23 (0.09-0.52); 0.51 (0.23-1.13); 0.14 (0.02-1.16) Values are Risk Ratio (95% CI)

aOR=adjusted odds ratioAVT=antiviral therapy; CI=confidence interval; COVID-19=coronavirus disease 2019; Hosp=hospitalization; HR=hazard ratio; IBD=inflammatory bowel disease; MOV=molnupiravir; NMV+r=nirmatrelvir+ritonavir; PCR=polymerase chain reaction; PSM=propensity score matching; PSW=propensity score weighting; RDV=remdesivir; RWE=real world evidence; SARS-CoV-2=severe acute respiratory syndrome coronavirus type 2; SO=symptom onset; UK=United Kingdom; US=United States; VHA=Veterans Hospital Administration; vs=versus

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The two studies MK4482-006 and 002 were double blind and placebo-controlled in design.

In MK4482-002 Part 2, in contrast to MK4482-006 and MK4482-002 Part 1, eligible subjects were to be enrolled within 5 days of symptom onset and were to have at least one underlying condition listed in the protocol as potentially predisposing them to develop severe COVID-19. The change in selection criteria reflected Part 1 data suggesting that the maximum benefit of molnupiravir would occur if treatment starts within 5 days of symptom onset in a population that could be regarded as being at some risk of progression up the WHO scale. The study populations were unvaccinated with respect to SARS-CoV-2.

The protocol for MK4482-002 attempted to subdivide subjects into those with mild or moderate disease at baseline, mainly based on presence of one of shortness of breath on exertion, tachypnoea or tachycardia. Very importantly, although the study allowed subjects to receive supplemental oxygen to treat COVID-19 at up to 4L/min, it was clarified that none was actually receiving supplemental oxygen at the time of enrolment into Part 1 or 2.

All subjects enrolled into Part 2 were to have at least one of the protocol-listed risk factors for progression to severe COVID-19 and >99% met this criterion. Therefore, the population in which efficacy was shown was not on supplemental oxygen at study entry and had at least one protocol-listed risk factor for progression.

The study allowed use of corticosteroids, such that any benefit of molnupiravir in preventing progression was in addition to steroids. Other standard of care modalities were also allowed. Other antiviral agents against SARS-CoV-2 (including monoclonal antibodies) were not allowed.

Part 2 involved stratification at randomisation according to time from symptom onset (TSSO) prior to the day of randomisation (≤3 days, >3 days), having reduced the maximum allowed for eligibility to 5 days based on Part 1. This stratification seems appropriate since Part 1 had already pointed to the importance of TSSO (≤5 days, >5 days) on outcomes.

A primary analysis in the MITT (all-treated) population in which unknown survival was counted as failure is acceptable.

In the selected population, the primary endpoint of all-cause hospitalisation (as defined by the applicant) or death up to Day 29 was appropriate. There was no pre-planned hypothesis testing in the dose-finding Part 1 and subjects enrolled into Part 1 were not included in analyses of Part 2, which stands alone. Part 2 was

planned to have overall power of 97% to demonstrate superiority of molnupiravir 800 mg BID over placebo at an overall one-sided, 2.5% alpha level, if the underlying treatment difference (MOV minus placebo) in the percentage hospitalised and/or dying through Day 29 was -6 percentage points. The assumptions made were based on emerging evidence from various clinical trials and were reasonable.

The four planned interim analyses were generally appropriate given the lack of any prior evidence of efficacy based on a clinically relevant endpoint. In the final event, IA3 was not required since enrolment into Part 2 progressed quickly and 775 subjects (about 50% of the original projected total) were included in IA4. Enrolment into Part 2 continued while the database was cleaned and while IA3/4 was conducted. Enrolment was finally halted on October 2 2021, by which time 1433 subjects had been randomised.

Efficacy data and additional analyses

Selection of 800 mg BID for 5 days in MK4482-002 Part 2

MK4482-006 provided some preliminary evidence that molnupiravir had an antiviral effect in a population similar to that enrolled into MK4482-002 Part 1.

There was no effect of active treatment at any dose tested for the pre-defined primary endpoint of median time to viral clearance. The proportion with undetectable SARS-CoV-2 RNA was statistically significantly greater in the molnupiravir 800 mg group (but not in the 200 mg and 400 mg groups) compared with the placebo group on some days (p=0.0373 on Day 5 and p=0.0343 on Day 28).

With 35.3% in the 800 mg group vs. 18.2% in the placebo group seropositive at baseline, and with a very clear effect of baseline seropositivity on positive cultures (e.g. 56% of seronegative and 11% of seropositive subjects in the placebo group), the results based on positive cultures over time are difficult to interpret.

At the same time, there did not seem to be rate-limiting safety issues, such that progression to MK4482-001 Part 1 and MK4482-002 Part 1 with doses up to 800 mg BID was a reasonable choice.

The selection of a 5-day course (10 doses) is not substantiated by data with molnupiravir but it is in line with durations of treatment that have been effective in outpatients with influenza.

MK4482-002 Part 1 enrolled a population in which ~75% had at least one of the protocol-listed risk factors for severe COVID-19 (mostly obesity, diabetes and age >60 years) and ~66% had a TSSO within 5 days. Just over half met the applicant's criteria for moderate disease while none was receiving supplemental oxygen at study entry.

A low percentage (<15%) was already seropositive for SARS-CoV-2 (based on anti-N antibody) and most (>80%) had RT-PCR confirmation of the virus as opposed to a positive antigen test at study entry. Since a central laboratory was used to determine viral loads, the applicant was requested to report the percentage that did not have a positive RT-PCR result from a local or central laboratory.

Among 299 included in the MITT population, there were only 11 events and no statistically significant differences between the four treatment groups with rates from 1.4% to 5.4%. However, among those who started treatment within 5 days of symptom onset and were at increased risk of severe COVID-19, there were 4/107 (3.7%) hospitalised in the combined molnupiravir groups vs. 4/34 (11.8%) in the placebo group.

While Part 1 was not intended to address specific hypotheses, it did suggest that a benefit of molnupiravir might be more evident when it was started within 5 days of symptom onset and in those at increased risk of severe COVID-19. The results led the DSMB to recommend continuation to Part 2, which seems appropriate.

Part 1 did not provide good support for progressing to Part 2 with 800 mg BID. As described previously, the applicant conducted some exposure-response analyses to support dose selection, which are found unconvincing. Nevertheless, with no rate-limiting safety concerns, selection of the highest tested dose could be considered reasonable.

Efficacy of 800 mg BID for 5 days in MK4482-002 Part 2

Results from IA3/4

With slightly different selection criteria, >99% of the population enrolled into Part 2 had at least one of the protocol-listed risk factors for developing severe COVID-19, the most common factor by far being obesity. Just under 15% were aged >60 years. Using the applicant's definitions, ~44% had moderate and 56% had mild disease. As in Part 1, no subject was receiving supplemental oxygen at study entry. About half of subjects had TSSO within 3 days at the time of randomisation.

Overall, 18.6% and 18.3% per treatment group were seropositive for SARS-CoV-2 at baseline based on anti-N antibody, 21.4% and 18.6% were seropositive based on anti-spike neutralising antibody (NA) and 85.5% had a positive RT-PCR result.

Two randomised subjects had no local test result for SARS-CoV-2 but they were not treated. Another 26 (3.4%) did not have a positive RT-PCR either from the local or the central laboratory, i.e. they had only a positive antigen detection test for SARS-CoV-2. The most common genotype clades at baseline were Delta, Mu and Gamma. Due to the timing of the study, no subject was infected with an Omicron variant.

In the MITT population, which comprised 98.3% of those enrolled, IA3/4 reported a statistically significantly lower rate of all-cause hospitalisation and death through Day 29 in the molnupiravir group, with a reduction from 14.1% to 7.3% (a difference of 6.8 percentage points). The 95% confidence intervals around the difference did not span zero and the p-value was 0.0012.

In the PP population, the results are in line with those of the MITT population, although the magnitude of the difference between both arms is smaller (i.e. a difference of 5.6 percentage points favouring molnupiravir).

There were 8 documented deaths in the placebo group and none in the molnupiravir group. One additional placebo group subject had an unknown outcome (alive/not alive) at day 29. Unsurprisingly, the rates show that those who are known to have died did so after being hospitalised. There were only three subjects (1 molnupiravir and 2 placebo) with unknown hospitalisation status at Day 29.

In the planned sensitivity analysis in which only hospitalisations and deaths considered to be COVID-related were counted, the totals in each group were reduced by 3 subjects, giving rates of 6.5% vs. 13.3% and 95% CI around the difference that did not span zero. Results of a sensitivity analysis which excluded those who received <5 doses or who were hospitalised or died before their 5th dose were consistent with the results of the primary analysis. The Kaplan-Meier curve showed separation between groups from Day 3 onwards.

The subgroup analyses were generally in keeping with the primary analysis.

In the seronegative majority (based on SARS-CoV-2 nucleocapsid antibodies) of the study population the analysis of the primary endpoint gave rates of 7.7% for molnupiravir and 17.1% for placebo (95% CI -14.9, -4.1). In contrast, in the subgroup seropositive for SARS-CoV-2 antibodies at baseline, there was no difference between intervention groups in the percentage of participants who were hospitalised or died (2.8% and 2.9% per group). A similar pattern applied in those seronegative and seropositive based on NA antibody at baseline, with hospitalisation/death rates of 8.4% for molnupiravir vs. 16.5% for placebo in the former group but 3.7% vs. 4.2% in the latter group. In this unvaccinated study population, the presence of anti-N

and/or NA at baseline in persons who presented within 5 days of symptom onset, with ~half within 3 days, is more likely to reflect priming by prior natural infection rather than an early primary immune response to the presenting episode. Therefore, the result in the baseline seropositives at IA3/4 is as expected, with low and similar progression rates in the molnupiravir and placebo groups.

There was a relationship between serostatus of subjects and baseline viral load. Baseline seropositives predominated in the subset with low baseline loads and seronegatives predominated in those with high baseline loads.

In the subjects that started treatment within 3 days of symptom onset, the difference between molnupiravir and placebo for hospitalisation/death rates was -4.0% (based on 16 and 23 events), whereas the difference was -9.5% in the group that started treatment on days 4 or 5 from symptom onset. The applicant explored the host and disease factors for the subsets divided by TSSO.

There were some imbalances in host and disease factors between TSSO subgroups that could have contributed to the overall treatment effect but it is not possible to draw firm conclusions.

For those who received corticosteroids before hospitalisation, the hospitalisation/death rates were 11.7% (7/60) in the molnupiravir group and 22.5% (16/71) in the placebo group. For the majority that did not receive corticosteroids, the rates were 6.5% and 12.1%, respectively.

Given that subjects entering this study had a baseline score of 2 (>98%), this study was not powered to detect a difference in reduction in scores by Day 29.

Continuation of MK4482-002 Part 2 after IA3/4

In the case of a positive efficacy outcome at IA3/4, there were no plans per protocol to discontinue enrolment prior to reaching the planned final sample size (300 in Part 1 and 1550 in Part 2).

However, after review of IA3/IA4, the study was closed to further enrolment on 02 October 2021 at the recommendation of the eDMC and in consultation with the FDA. While IA3/4 included 775 subjects, there were actually 1239 enrolled at the time of the IA3/IA4 database lock (18 September 2021) and there were 1433 enrolled when the study was closed to further recruitment on 02 October 2021.

The MITT population (primary efficacy analysis) included 1408 (98.3%) of all randomised subjects, 709 (99.0%) in the molnupiravir group and 699 (97.5%) on placebo.

The PP population consisted of 1344 (93.8%) of all randomised subjects, 679 (94.8%) in the molnupiravir group and 665 (92.7%) on placebo. The number and causes for protocol deviations were equally distributed in both intervention groups and at the IA3/IA4 and All Participants in Part 2 populations.

For the total population enrolled into Part 2, there were 2 additional deaths – one in each group – compared to the IA3/4 analysis. In the molnupiravir group there were 20 additional instances of hospitalisation (28 at IA3/4 vs. 48 total) compared to an increase by 15 events in the placebo group (52 vs. 67). The rates for hospitalisations and deaths for the total population in Part 2 were 48/709 (6.8%) for molnupiravir and 68/699 (9.7%) for placebo, giving a difference of 3 percentage points, which was statistically significant (p=0.0218). Results of primary analysis in the PP population were consistent with the findings in the MITT population, i.e., the treatment difference between groups was of 3 percentage points (p=0.0138) in favour of molnupiravir.

Although the final analysis for all 1433 subjects yielded a statistically significant difference between molnupiravir and placebo, the magnitude of effect was very much less than that of IA3/4. Most importantly,

the final estimate of a 30% reduction in the primary endpoint rate was derived from a 50% reduction in the IA3/4 population and no demonstrable efficacy in the post-IA3/4 population. Moreover, in the first 40% enrolled the rates for hospitalisation and death were 20/291 (6.9%) for molnupiravir vs. 43/287 (15.0%) for placebo. However, for the latter 60% enrolled, the rates were 28/418 (6.7%) vs. 25/412 (6.1%).

The small difference between IA3/4 and post-IA3/4 populations for hospitalisation/death rates in the molnupiravir group but reduction in the placebo group pointed to a change during the study in the way that the background population responded to natural infection with SARS-CoV-2. It seems that the background progression rate (as estimated in the placebo group) was reduced to such an extent that intervention with molnupiravir was not able to achieve a significant improvement over placebo for the primary endpoint.

The findings for the primary endpoint in the IA3/4 vs. post-IA3/4 populations raised concern that, leaving aside the fact that P002 enrolled only unvaccinated persons, it may be that molnupiravir would not be clinically beneficial in a population with a high rate of natural priming and/or boosting by contact with SARS-CoV-2, with or without clinical illness.

It is therefore relevant to note that there was no demonstrable efficacy for molnupiravir in IA3/4 or post-IA3/4 populations in subgroups seropositive at baseline for anti-N or anti-spike NA. However, it is also notable that there was efficacy for molnupiravir among baseline seronegative subjects at IA3/4 but there was no demonstrable efficacy in baseline seronegatives in the post-IA3/4 population. However, persons who have been primed may have a milder course of disease even if they no longer have detectable antibody against nucleocapsid or spike protein when infected because they would have a rapid immune memory response that may involve activation of both humoral and cellular immunity. Therefore, it cannot be ruled out that one contributing factor to the reduction in background progression rates between IA3/4 and post-IA3/4 populations was an increasing natural infection rate with time.

The applicant was asked to investigate the possible reasons for the difference in the IA3/4 vs. post-IA3/4 treatment effect as recorded below.

Efficacy in the IA3/4 vs. post-IA3/4 population by subgroup

Reflecting the marked drop in rate of hospitalisations/deaths in the placebo group in the non-IA3/4 vs. the IA3/4 population, with no appreciable change in the molnupiravir group, the rates broken down by subgroups mostly reflect the overall finding. Nevertheless, the magnitude of the difference between IA3/4 and post-IA3/4 rates is variable. Some observations of note include:

- In subjects aged 60+ years, the hospitalisation/death rate did not change in the molnupiravir group (10% IA3/4 and 10.3% post-IA3/4) but fell from 21.8% to 5.6% in the placebo group.
- In non-obese subjects, the hospitalisation/death rate hardly changed in the molnupiravir group (11.4% IA3/4 and 10.5% post-IA3/4) but fell from 18.8% to 4.2% in the placebo group.
- In patients with diabetes mellitus, the hospitalisation/death rate changed in the molnupiravir group (18.4% IA3/4 and 13.8% post-IA3/4) but fell from 23.2% to 6.6% in the placebo group.

These data suggest that there was a marked drop in the background (placebo) rate of COVID-19 progression in subjects with and without a risk factor.

- In Latin America, the hospitalisation/death rate hardly changed in the molnupiravir group (7% IA3/4 and 6.1% post-IA3/4) but fell from 14.5% to 3.5% in the placebo group. A reflective pattern occurred in those of Hispanic/Latino ethnicity.

- In contrast, in Europe there were falls in the hospitalisation/death rate in the molnupiravir group (9% IA3/4 and 3.6% post-IA3/4) and in the placebo group (13.8% to 4.1%).

These data suggest that there was a marked drop in the background (placebo) rate of COVID-19 progression in several regions where there was substantial enrolment. The fact that the rate in the molnupiravir group also seemed to drop in Europe is interesting. However, it seems that the majority of subjects in "Europe" were actually enrolled in the Russian Federation since the denominators for FR, DE, ES, IT and UK are very small.

- For those with no detectable anti-N antibody at baseline, the hospitalisation/death rate changed from 8.1% to 6.8% in the molnupiravir group but fell from 16.4% to 6.3% in the placebo group. For those seropositive for anti-N at baseline, there continued to be no discernible benefit for molnupiravir (2.8% vs. 2.9% for placebo at IA3/4 and 4.4% vs. 0% post-IA3/4).
- For those with no detectable anti-spike NA at baseline, the hospitalisation/death rate changed from 8.4% to 7.0% in the molnupiravir group but fell from 16.5% to 7.4% in the placebo group. For those seropositive for anti-spike NA at baseline, there was no discernible benefit for molnupiravir (3.7% molnupiravir vs. 4.2% placebo at IA3/4 and 4.6% vs. 0% post-IA3/4).

In those seronegative based on anti-N or anti-spike NA, the pattern for hospitalisation rates followed that overall, with marked drops only in the placebo group from IA3/4 to post-IA3/4. For those seropositive based on either assay the risk of progression was very low even at IA3/4 and there was no detectable benefit for molnupiravir in the IA3/4 or post-IA3/4 populations.

In the post-IA3/4 population, there is no subgroup found within which the results demonstrate a benefit of molnupiravir treatment vs. placebo. Furthermore, for some of the subgroups such as the participants with diabetes mellitus and those seropositive at baseline there were no differences for the primary endpoint between the study groups. Therefore, even if it were to be considered that some sort of restricted indication based on *post hoc* analyses in subgroups might be justifiable in the context of the ongoing pandemic, the results of the investigation do not allow identification of a sub-population in which there is clear efficacy for molnupiravir during the entire study.

Investigation of the possible reasons for the findings

The applicant's general conclusion was that there is no single factor or group of factors identified that explains the change in pattern of hospitalisation/death rates between the IA3/4 and the post-IA3/4 populations. Nevertheless, this leaves open the question of the relevance of the treatment effect observed only in the first ~40% of subjects enrolled to the current EU population.

While there were differences between the IA3/4 and post-IA3/4 populations, most of these occurred in both the molnupiravir and placebo groups to a similar extent. Even these changes could have contributed to the overall finding since any shift towards a population less at risk of hospitalisation/death could have led to the lower rate in the placebo group. With no additive effect on the rate already achieved by molnupiravir, the overall result would be no demonstrable treatment benefit for molnupiravir over placebo.

There were a few imbalances in the IA3/4 population that may have augmented the treatment difference that was seen in the IA3/4 analysis (e.g. higher proportion of males and higher proportion with 2+ risk factors in the placebo group). Any imbalances between treatment groups within the post-IA3/4 population leading to a lower rate in the placebo group and/or a higher rate in the molnupiravir group for any factor predisposing to progression of COVID-19 could contribute to reducing the overall difference between treatments. The

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applicant's investigation has pointed to several such imbalances that, taken together, may have contributed to the overall result.

There were differences in regional or country-specific enrolment between IA3/4 and post-IA3/4 populations. The IA3/4 population included 66 in Brazil with a marked difference in progression rate favouring molnupiravir. Other countries with fairly substantial enrolment and rates favouring molnupiravir in the IA3/4 analysis were Colombia, Mexico, Russia and S. Africa. The post-IA3/4 population included very few in Brazil, far fewer in Colombia and fewer in S. Africa. At the same time, numbers in Mexico were not reduced and numbers in Russia increased but both showed a loss of difference in rates between molnupiravir and placebo. Meanwhile numbers enrolled in Guatemala were higher in the post-IA3/4 population with 5 cases of progression in the molnupiravir group and none in the placebo group. There are no obvious explanations for these changing patterns of rates.

Shifts in proportions with mild or moderate COVID-19 at baseline or proportions treated within 3 days do not seem likely to have contributed to the findings.

By region of enrolment, the non-IA3/4 population included >40% Europeans vs. 23% in the IA3/4 population. Since very few EU countries are listed in the appendix tables 14 and 15, it seems that the majority of these "Europeans" were enrolled in the Russian Federation because otherwise the total numbers reported could not be explained. The applicant reported that Europe (including Russia) had the highest rate for positive baseline anti-spike NA (29.1% molnupiravir and 34.3% placebo). As already noted above, there was no benefit of treatment detected in baseline seropositives, whether based on anti-N or anti-spike NA levels.

The applicant has provided much detail about the virological data. In the subjects with anti-N at baseline, the change from baseline (log_{10} copies/mL) was comparable between molnupiravir and placebo groups on days 3 and 5 as well as at the post-treatment visits. In this regard, note that there was no efficacy demonstrated at IA3/4 or post-IA3/4 in baseline seropositives. In the baseline seronegatives, the magnitude of change from baseline was somewhat greater on days 3 and 5 compared to baseline seropositives but this observation applied in molnupiravir and placebo groups and the difference between treatments was very small.

When comparing the IA3/4 and post-IA3/4 populations, there was a slightly higher proportion in the molnupiravir group with low baseline load at IA3/4 and high baseline load at post-IA3/4 vs. the placebo group. However, the hospitalisation/death rates in those with low or high baseline loads were not substantially different between IA3/4 and post-IA3/4 populations in the molnupiravir group (5.4 and 5.6 low; 9.5 and 7.9 high) whereas there were falls in the placebo group (7.7 to 2.9 low; 18.5 to 6.3 high). Furthermore, with a maximum difference between molnupiravir and placebo for change in viral load from baseline of negative 0.42 log_{10} copies/mL, observed in the IA3/4 population on day 5, none of the differences are notable. Also, the difference between treatments on day 3 was -0.20 in the IA3/4 population and -0.21 in the post-IA3/4 population although the respective differences on day 5 were -0.42 compared to -0.14. Effectively, even the largest difference between molnupiravir vs. placebo in change from viral load from baseline was small in magnitude.

The distribution of clades did change between IA3/4 and post-IA3/4 populations, but the changes were similar in the molnupiravir and placebo groups. Also, up to 30% had missing data. These changes may partly reflect changes in recruitment rates by region and partly shifts in clades over time. At IA3/4 the hospitalisation/death rates were lower with molnupiravir vs. placebo except for delta 21J (11/99 [11.1%] molnupiravir and 12/95 [12.6%] placebo). In the post-IA3/4 population there were too few with gamma or mu variants to comment. For delta 21I a benefit of molnupiravir (8.6 vs. 24.1% at IA3/4) was no longer

apparent based on somewhat lower denominators. For delta 21J, with substantial denominators also in the post-IA3/4 population, there continued to be no benefit for molnupiravir although rates were lower in both treatment groups (6.5% and 5%). Due to the timing of the study, there were no infections with omicron treated.

There is no known biologically plausible reason to explain why there seemed to be little treatment effect even in the IA3/4 population in the subgroup infected with 21J (Delta). The proportion with 21J increased from ~9% per group in the first 20% enrolled, to ~27% in the second 20% enrolled and ~50% in the third 20% enrolled but with no difference between treatment groups in proportions with this variant. The difference vs. placebo in change in viral load from baseline was maximal on day 5 in IA3/4 for 21J (negative 0.58 $\log_{10}$ c/mL) but the maximum difference was reduced to negative 0.21 $\log_{10}$ c/mL on day 5 for this clade in the post-IA3/4 population. For all delta cases, more in the molnupiravir group had detectable NA at baseline at IA3/4 (18 vs. 13%) but it was 23% in each group in the post IA3/4 population. For anti-N at baseline, rates were ~10% per group at IA3/4 and ~13-16% per group post-IA3/4.

Published data for clades May-Oct 2021 suggest that 21J cases would have come mainly from Russia (98% of cases 21J) and from S. Africa (69% of cases 21J). The sequencing data from the study indicate that 21J rates did increase in these countries from the early to later parts of the study.

Treatment with molnupiravir did not interfere with the development of anti-spike NA or anti-N antibody to any marked extent based on day 10 and day 29 proportions with detectable antibody with either assay. The proportion with detectable antibody at baseline was higher in the post-IA3/4 population but this observation applied to a broadly similar extent in both molnupiravir and placebo groups.

The applicant has considered other factors that could have influenced the changes in the molnupiravir or placebo group hospitalisation/death rates over time. Since the population enrolled was non-hospitalised and not requiring oxygen at baseline, there were no major changes in approved medications during the course of the study given that monoclonal antibodies and investigational agents other than molnupiravir were prohibited. There was some use of corticosteroids in these outpatients (in low percentages) but the pattern of usage does not explain the findings.

Other management modalities could have changed during the period of subject participations in IA3/4 and post-IA3/4 populations but, in a double blind setting, it is not likely that these would have been applied at different rates in the two treatment groups. Although a major change in management that reduced the background (placebo) rate of hospitalisations/deaths could have contributed to the overall results, there does not seem to have been such a change that can be pinpointed during the course of the study.

In light of the fact that the investigations failed to pinpoint the reason(s) for the lack of demonstrable treatment effect in the post-IA3/4 population, and given the major concern that the efficacy shown at IA3/4 may not be representative of what could be expected in the current EU population, the applicant was requested to provide additional efficacy data that could be regarded as more relevant to the EU in 2022.

Additional data from other studies that included molnupiravir

Of the studies identified by the applicant as being of relevance, the UK PANORAMIC study included a population enrolled from Dec 8 2021 onwards, when BA.1 and BA.2 were the most common variants in circulation. The vaccination history and natural exposure status of UK residents is broadly in line with that of the majority of EU MS, leading to findings that would most likely also apply across Europe.

Although this was an open label study, the decision to hospitalise a subject would have followed general NHS as well as any operative local admission policies and would not likely be affected by knowledge of whether

the subject was taking/had taken molnupiravir. With high vaccination rates and prior exposure rates leading to some degree of cross-protection at least against developing severe forms of COVID-19, accompanied by the abovementioned change in predominant circulating variants, the actual hospitalisation and death rate was <1% in the MOV+SOC and SOC groups, such that no benefit for MOV could be demonstrated based on the primary endpoint in a population likely typical for Europe in 2022. The same conclusion applied in the subgroup analysis of the primary endpoint.

In this open-label study, subjects completed online symptom diaries for 28 days and rated a range of symptoms. There was a benefit for MOV of 4.2 (95% BCI: 3.8 – 4.6) days in time-to-first-recovery (TTR) giving a posterior probability of superiority of >0.999. The estimated median TTR for molnupiravir was 10.3 days vs. 14.5 days for SOC, giving a hazard ratio [95% BCI] of 1.36 days, which met the pre-specified superiority threshold. Subgroup analysis demonstrated that this benefit for molnupiravir was consistent across all studied groups.

The results suggest that addition of MOV to SOC is not at all likely to have any important effect on hospitalisation or death rates in a typical current EU population. The study suggests that MOV may be able to shorten the duration of symptomatic disease by several days even in a heavily vaccinated/exposed population infected with omicron variants. However, the study was entirely open-label and the symptom-related endpoints all depend on subjective perceptions recorded by subjects themselves in an online diary. The study is not considered adequate to serve as sole evidence of a potential benefit for MOV in terms of shortening the duration of the illness.

It was therefore potentially relevant to examine the results for symptom resolution in MK-4482-002 since this had a double-blind design. The study had a secondary objective to evaluate the efficacy of MOV compared to placebo as assessed by time to sustained resolution or improvement and time to progression of each targeted self-reported sign/symptom of COVID-19 from randomisation through Day 29. The study did not seek to determine time to resolution of all baseline signs and symptoms or time to self-reported recovery.

For the IA3/4 population, despite a benefit for MOV in terms of the hospitalisation/death rate, there was no consistent benefit for MOV over placebo for improvement or resolution of the individual signs and symptoms captured. In the post-IA3/4 population, there was no apparent benefit for MOV over placebo for improvement or resolution of the individual signs and symptoms captured. Therefore, the findings in the open-label study PANORAMIC are not supported by the data on improvement or resolution of signs and symptoms in the double-blind study MK-4482-002.

The majority of the other studies identified by the applicant was retrospective and concerned outpatients or inpatients not requiring supplemental oxygen due to COVID at time of admission. Not all had necessarily been admitted primarily due to COVID-19. Some were conducted in special populations. Many were conducted during or using data from the omicron wave although the predominant sub-variant varied. None was double-blind and placebo controlled. Several used matched controls using different methods (commonly propensity score matching) and varying ratios for the matching process. Adherence to MOV dosing is not always known or even reported and it is not always known if MOV was started within 5 days of symptom onset. Moreover, different algorithms were in place across the studies regarding selection of patients for treatment.

There was no consistent finding of a benefit for MOV in the populations studied. Some studies did suggest a benefit for MOV in preventing disease progression in some of the higher risk subgroups, such as the older (>75 years of age) patients and those inadequately vaccinated for COVID-19. In those studies that compared MOV with sotrovimab, the OpenSAFELY platform study, conducted in England when BA.1 was dominant,

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suggested that MOV might not be as good as sotrovimab for preventing hospitalisation. In studies that compared MOV with NMR/RTV, the Hong Kong study from Wong was conducted in mainly older subjects but they had low vaccination rates. The results broadly support a benefit for MOV for preventing progression in older patients who had not been vaccinated or were inadequately vaccinated. However, the mortality rates suggested that MOV may not be as good as NMR/RTV. The second Hong Kong Astudy from Yip concerned outpatients mostly 70+ years with a somewhat higher vaccination rate. However, MOV was not associated with a reduced risk of hospital admission, progression to IMV or death when compared with the no oral AVT group. NMV/RTV was associated with a reduced risk of hospitalisation compared with the MOV and the no oral AVT groups.

During the procedure, additional published studies were identified as being of interest. For example, Wai et al. reported on a retrospective cohort study in inpatients (21138) or outpatients (33217) in Hong Kong who received MOV or NMV+r in early 2022. Patients were aged ≥60 years or had at least 1 chronic disease and mild or moderate COVID-19. In the outpatient cohort, death within the 28-day observation period was reported for 65 (0.2%) patients in the control group, 8 patients (0.15%) in the MOV group and no patients in the NMV+r group. In the inpatient cohort, death within 28 days was reported for 5211 (26.0%) patients in the control group, 68 (8.5%) in the MOV group and 12 (4.3%) in the NMV+r group. Vaccination information was not available.

Patel et al. reported a retrospective cohort study of non-hospitalised patients aged ≥12 years with confirmed SARS-CoV-2 infection (positive PCR or lateral flow test) who received no treatment or treatment with sotrovimab, NMV+r or MOV and who met ≥1 of the NHS highest-risk criteria for early treatment. The primary outcomes were COVID-19-related and all-cause hospitalisations. Results suggested that molnupiravir reduced the COVID-19 hospitalisation rate in the subgroup aged from 65 years but not in younger patients.

Suzuki et al. reported a retrospective cohort study of MOV compared with no use of MOV in patients with SARS-CoV-2 infection (PCR confirmed) admitted to hospitals in Japan. Eligible patients had 1 or more risk factor for severe disease.

The primary outcomes were any clinical deterioration, need for mechanical ventilation and all-cause death. Compared with the no-MOV group, MOV was associated with a statistically significantly lower incidence of clinical deterioration both before and after propensity score weighting. The results of regression analyses identified not receiving MOV as a risk factor related to clinical deterioration of COVID-19 (OR 0.448; 95% CI 0.206, 0.973; p=0.042).

Bajema et al. reported a retrospective study with matched cohorts of non-hospitalised adults with a positive SARS-CoV-2 PCR or antigen test result in early 2022. They had at least 1 risk factor for progression to severe disease and had received treatment with either NMV+r or MOV. The 30-day rates for hospitalisation or death, hospitalisation and ICU admission were similar for MOV compared with no treatment. The 30-day risk difference for death, but not the relative risk, was lower for MOV (95% CI [-14.89, -0.16]). Notably, among patients aged ≥65 years, the rate for hospitalisation or death was significantly lower for MOV compared with no treatment.

The overall submission also refers to in-vitro data suggesting that molnupiravir remains active against the most recent VOCs. For example, in the NEJM report from Imai et al. the in-vitro susceptibilities of BQ.1.1 and XBB to remdesivir, molnupiravir and nirmatrelvir were similar to those of the ancestral strain (SARS-CoV-2/UT-NC002-1T/Human/2020/Tokyo). For BQ.1.1, the IC_{50} value was lower by a factor of 0.6 with remdesivir and higher by factors of 1.1 and 1.2 with molnupiravir and nirmatrelvir, respectively. For the XBB subvariant,

the IC_{50} value was lower by a factor of 0.8 with remdesivir, lower by a factor of 0.5 with molnupiravir and higher by a factor of 1.3 with nirmatrelvir.

Studies from India

The applicant reported three studies randomised, prospective and open-label studies conducted by licensees in India. The populations enrolled were not relevant to the current EU population, not only in terms of age restriction but also in terms of negligible vaccination rates and no requirement for risk factors for progression. In all three studies, the primary endpoint was hospitalisation rate within 14 days, with a different definition of hospitalisation vs. that used in MK-4482-002.

Two of the three studies did not show a benefit for MOV vs. SOC for the primary endpoint due to the low number of events. In the Hetero Labs study there was a significant reduction in hospitalisation rate with molnupiravir with an actual difference of <3 percentage points (1.5% vs. 4.3%). The three studies suggested that MOV can shorten the time to recovery, but they were all open-label.

Conclusion

After several rounds of questions and responses, it remains the case that the clinical benefit of MOV in patients with COVID-19 who are not receiving supplemental oxygen and who are at increased risk for progression to severe COVID-19 cannot be determined with sufficient confidence from the available data to conclude on the benefit-risk relationship. Molnupiravir exerts some anti-viral activity against SARS-CoV-2 and accumulating data suggest that it retains activity against the most recent VOCs. The applicant points to the need for IV administration of remdesivir and to the contraindications, warnings and precautions associated with use of nirmatrelvir plus ritonavir. These issues are acknowledged but they cannot *per se* assist in determining the benefit-risk relationship for molnupiravir.

From the additional data provided by the applicant, including post hoc analyses from study 002 and additional publications, it is not ruled out that molnupiravir could have some benefit and there are suggestions from several RWD (Real World Data) studies that any clinical benefit is more likely to be apparent in subgroups at highest risk of progressing to develop severe COVID-19, despite prior vaccinations and variable natural exposure histories. For example, some studies suggest that even within 2022 molnupiravir might reduce the death rate and/or hospitalisation rate in subgroups at highest risk of progression. Nevertheless, the presented RWD presented as supportive evidence were not prospective randomised and controlled studies and their observational nature raises the potential for bias (e.g. related to measurement of drug exposure, timing and outcomes, selection of comparator and methods of adjustment) as well as various confounding factors. Moreover, the method applied by the applicant to identify, select and appraise the strengths and limitations of each study based on RWD was not clear or consistent. The approaches taken within the studies to mitigate the risk and potential effect of biases on results should have been described in detail to support the selection of studies and the strength of the evidence. Moreover, the relevance of some of the studies to the EU population was not sufficiently justified. In conclusion, the RWD presented were not considered sufficient to address the concerns raised by the inconsistent results of MK4482-002 Part 2.

The open-label PANORAMIC study pointed to a benefit for molnupiravir in terms of time to recovery that was consistent across the subgroups. However, the applicant's double-blind study P002 did not seek to determine time to resolution of all baseline signs and symptoms or time to self-reported recovery. Data were reported from P002 on resolution of individual signs and symptoms. However, as described with figures in the prior reports, there was not a consistent effect of molnupiravir on time to sustained improvement or resolution of

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individual signs and symptoms in the IA3/4 or total study population and no effect of molnupiravir on these endpoints in the post-IA3/4 population.

In summary, there remains concern that the benefit seen for rates of hospitalisation and/or death in the IA3/4 analysis in an unvaccinated population enrolled relatively early on in the pandemic cannot be extrapolated to the current EU population. Moreover, in this double-blind study there was no consistent benefit for molnupiravir for the secondary endpoint of time to resolution of individual signs and symptoms. Thus, it is not possible to derive a well-substantiated indication for use from this study.

The applicant maintains that P002 showed a convincing benefit for molnupiravir and also draws from the RWD studies to derive a revised indication as follows:

Lagevrio is indicated for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are:

- *aged 65 years and older or*
- *aged 18 to <65 years who are at increased risk of progressing to severe COVID-19 and for whom alternative COVID-19 treatment options are not available or clinically appropriate.*

Healthcare providers should consider local treatment guidelines in assessing whether an individual is at increased risk for progressing to severe COVID-19.

It is agreed that any use of molnupiravir should be confined to those not requiring supplemental oxygen when starting treatment. The claimed indications for use in persons older than 65 years and for younger persons with risk for progression are not substantiated by the applicant's study or by RWD. While some studies suggest that there could be a benefit either in terms of preventing hospitalisation and/or death or facilitating faster recovery, the data do not suffice to support these specific statements.

Specifically with regard to the indication for use in persons aged from 65 years, additional subgroup analyses of study P002 were provided from which the applicant reports that the treatment benefit was -3.7% (95% CI -14.2, 7.2) based on the primary endpoint. However, previously presented disaggregated data showed that in subjects aged > 60 years the primary endpoint exhibited the same trend as in the general population, i.e. there were favourable results in the IA3/4 analysis (treatment difference -11.8 [-26.1, 2.5]) but not in the post-IA3/4 population (treatment difference 4.7 [-4.7, 15.0]). Therefore, the prior conclusion on benefit-risk in this sub-population remains unchanged.

Specifically with regard to the indication for persons aged <65 years of age for whom alternative COVID-19 treatment options are not available or clinically appropriate, it would have been expected that, at least, molnupiravir had shown the same level of efficacy as the available alternatives. As this is not the case, this proposal is not acceptable.

The problem remains that the basis for approval would be a single pivotal trial for which there are well-discussed conflicting results for different portions of the trial. It is not considered that the RWD, with all the limitations pointed out above and during the evaluations, are sufficient to override the concerns raised by the sponsored single pivotal trial.

At the same time, it is acknowledged that conducting a prospective placebo controlled RCT in such populations is not now possible and it does not seem that it would be feasible to conduct a relative efficacy study with a well-justified non-inferiority margin with a primary endpoint of hospitalisation and/or death.

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Moreover, it is not envisaged that a non-inferiority margin could be justified for an endpoint based on time to recovery.

The applicant attended an oral explanation (OE) held on 21 February 2023 where they made a presentation to address the concerns. However, after this OE the Committee concluded that the above issues and therefore the uncertainties and concerns expressed above regarding the efficacy of molnupiravir still remained.

2.5.7. Conclusions on the clinical efficacy

The major concerns on insufficient demonstration of efficacy and unfavourable benefit-risk remain as:

While the pivotal study MK4482-002 Part 2 was statistically positive in a pre-planned interim analysis, the concluding part of the trial, of almost a similar size as the pre-interim analysis part, did not show any effect at all on the primary endpoint. Due to this inconsistency of outcomes, MK4482-002 Part 2 did not confirm the efficacy of Lagevrio.

The open label PANORAMIC study did not show an impact on its primary endpoint, hospitalisation or death. Although the study pointed to a benefit for molnupiravir in terms of time to recovery, this study is not blinded and therefore not adequate to support this claim. Notably, the applicant's double-blind study P002 did not seek to determine time to resolution of all baseline signs and symptoms or time to self-reported recovery. Data were reported from P002 on resolution of individual signs and symptoms. There was not a consistent effect of molnupiravir on time to sustained improvement or resolution of individual signs and symptoms in the IA3/4 or total study population and no effect of molnupiravir on these endpoints in the post-IA3/4 population.

Data from three randomised, open-label studies conducted by licensees in India were submitted as supportive data. However, these were not considered sufficient to confirm the efficacy of Lagevrio, given the nature of endpoints and questionable external validity for the EU setting.

RWD were presented to further support efficacy. However, in the absence of randomisation, it cannot be ascertained that potential bias is controlled. Moreover, the methodology to select and appraise the quality of the studies presented was not clear. The studies presented are considered not sufficient to override the concerns raised by the inconsistent results of MK4482-002 Part 2.

Therefore, it is not possible to conclude from these data that the benefit-risk relationship for molnupiravir is favourable. In addition, this is not possible either in the targeted populations in the revised indication proposed by the applicant during the procedure. Finally, it is also not possible to identify a sub-population in which a consistent benefit for molnupiravir has been demonstrated.

In summary, there was no consistent finding of a benefit for molnupiravir to support the B/R of this product.

2.5.8. Clinical safety

2.5.8.1. Patient exposure

Patient exposure

At the time of filing the MAA, the applicant reported 1069 individuals exposed to any dose of molnupiravir, of which 593 were allocated to 800 mg BID for 5 days and received at least one 800 mg dose.

Table 69: Participants Who Received Molnupiravir (P002, P006, P001, and P004)

	Number of Participants	
Study	**Any Dose of MOV**	**MOV 800 mg Q12H[a]**
P002 (Phase 2/3)	Part 2: 386	Part 2: 386
	Part 1: 225	Part 1: 74
P006 (Phase 2a)	140	55
P001 (Phase 2)	218	72
P004 (Phase 1)	100	6
Total	**1069**	**593**
MOV=molnupiravir, Q12H=once every 12 hours [a] participants received at least 1 dose of MOV 800 mg in a dosing regimen of Q12H for 5 days		

Studies 005 and 007 are ongoing and subjects remain blinded to treatment allocation so no useful data were available. During the procedure, top line safety data become available from the total 1433 subjects randomised into study 002 Part 2, of which 710 were assigned to 800 mg BID for 5 days.

2.5.8.2. Adverse events

MK4482-004

Overall, fewer subjects had TEAEs following administration of molnupiravir than following placebo. There were no apparent treatment- or dose-related trends for AEs. The AEs reported were typical of those usually observed in Phase 1 studies. With the exception of one subject with Grade 2 AEs of pain in extremity, oropharyngeal pain and influenza-like illness after 200 mg BID, all were Grade 1 in severity. Treatment-related AEs were reported for 16.7% across the molnupiravir dose groups and 21.4% for those who received placebo.

There were no indications of bone marrow suppression by molnupiravir in any cohort and none of the decreases in platelets was clinically significant. One subject who received 600 mg in Part 1 had a decrease in platelets to $<150 \times 10^9$/L on Days -1 and 9 (188×10^9/L, 150×10^9/L and 147×10^9/L at screening, Day -1 and 9, respectively) with 178×10^9/L by the end of study visit. One subject who received 300 mg BID had

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decreases in platelets from 171 × 10^9 at screening to 130 × 10^9/L by Day 9. Platelets increased to 144 × 10^9/L by the EOS visit.

There were no trends in mean or individual subject 12-lead ECG parameters and no clinically significant findings.

MK4482-006

The table summarises the safety profile.

Table 70: Overall Summary of Treatment Emergent Adverse Events (Full Safety Population)

Category	Molnupiravir 200 mg (N=23) n (%) E	Molnupiravir 400 mg (N=62) n (%) E	Molnupiravir 800 mg (N=66) n (%) E	All Molnupiravir (N=140) n (%) E	Placebo (N=62) n (%) E
Any Adverse Event	11 (47.8) 16	20 (32.3) 42	11 (20.0) 21	42 (30.0) 79	18 (29.0) 31
Any Adverse Event Related to Study Drug	4 (17.4) 4	13 (21.0) 21	1 (1.8) 4	18 (12.9) 29	8 (12.9) 10
Any Adverse Event Grade 2 or Higher	5 (21.7) 6	7 (11.3) 9	6 (10.9) 8	18 (12.9) 23	9 (14.5) 12
Any Adverse Event Grade 3 or Higher	1 (4.3) 1	2 (3.2) 2	4 (7.3) 4	7 (5.0) 7	5 (8.1) 5
Any Adverse Event Grade 3 or Higher Related to Study Drug	0	0	0	0	0
Any Adverse Event Leading to Discontinuation from Study Drug	0	1 (1.6) 1	1 (1.8) 1	2 (1.4) 2	1 (1.6) 1
Any Related Adverse Event Leading to Discontinuation from Study Drug	0	0	0	0	0
Any Serious Adverse Event	0	2 (3.2) 2	1 (1.8) 1	3 (2.1) 3	1 (1.6) 1
Any Serious Adverse Event Related to Study Drug	0	0	0	0	0
Any Adverse Event Leading to Death	0	0	0	0	0

Abbreviations: E = number of events; n = number of participants with an event; N = number of participants.

The only AE reported in more than 5% in any group was insomnia (2.9% combined molnupiravir group vs. 6.5% placebo). AEs reported by >3% in any group were headache (4.3% vs. 4.8%), ALT increased (2.9% vs. 3.2%) and abdominal pain (0.7% vs. 3.2%). Nine subjects had an AE with onset from Day 14 onwards but none of these occurred in the 800 mg BID group.

There were 12 severe AEs reported as shown in the table. None was considered treatment-related.

Table 71: Brief Listing of Severe Treatment-Emergent Adverse Events by Treatment Group (Safety population)

Molnupiravir 200-mg	Molnupiravir 400-mg	Molnupiravir 800-mg	Placebo
N=23	N=62	N=55	N=62
n=1 (4.3%)	n=2 (3.2%)	n=4 (7.3%)	n = 5 (8.1%)
Creatinine renal clearance decreased	Cerebrovascular accident Oxygen saturation decreased	Headache Acute respiratory failure Supraventricular tachycardia Anaemia	Blood glucose decreased Blood pressure increased Migraine Hypoxia Musculoskeletal chest pain

The majority of AEs was not considered related to treatment. There was no relationship between treatment-related AE rates and molnupiravir dose and rates were mostly similar between the combined molnupiravir and placebo groups. None of the treatment-related AEs was graded as severe and none was serious.

Overall, 13 participants reported 23 TEAEs related to an abnormal clinical laboratory value (6 placebo, 3 200 mg, 8 400 mg and 6 800 mg). There were no dose- or treatment-related trends in the incidence or types of laboratory TEAEs. No participant in a molnupiravir group had a platelet value <120,000/µL at any time after baseline.

MK4482-002 Part 1

The observed safety profile is summarised in the table.

Table 72: Adverse Event Summary During Treatment 14-Day Follow-up Period All Participants as T Population MK-4482-002 IA2

	MK-4482 200mg		MK-4482 400 mg		MK-4482 800 mg		MK-4482 Combined		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	74		77		74		225		74		299	
with one or more adverse events	23	(33.8)	19	(24.7)	29	(39.2)	73	(32.4)	28	(37.8)	101	(33.8)
with no adverse event	49	(66.2)	58	(75.3)	45	(60.8)	152	(67.6)	46	(62.2)	198	(66.2)
with drug-related* adverse events	4	(5.4)	6	(7.8)	4	(5.4)	14	(6.2)	5	(6.8)	19	(6.4)
with serious adverse events	1	(1.4)	3	(3.9)	4	(5.4)	8	(3.6)	4	(5.4)	12	(4.0)
with serious drug related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.3)
discontinued drug due to an adverse event	0	(0.0)	0	(0.0)	3	(4.1)	3	(1.3)	1	(1.4)	4	(1.3)
discontinued drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.3)
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)	2	(2.7)	2	(0.9)	0	(0.0)	2	(0.7)
discontinued drug due to a serious drug related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

* Determined by the investigator to be related to the drug.

The incidence and type of AEs were comparable across the intervention groups. The most frequently reported (≥5% in any group) AEs during the treatment period through the 14-day follow-up were COVID-19 pneumonia (5.4%) in the 800 mg group and diarrhoea (5.4%) and COVID-19 (6.8%) in the placebo group. There were no clear trends in AEs by molnupiravir dose.

The most commonly (>2%) reported drug-related AE was diarrhoea, reported by 5 (2.2%) in the combined molnupiravir groups (none led to discontinuation) and 2 (2.7%) in the placebo group (one of which led to discontinuation). All drug-related AEs were Grade 1 or Grade 2. There were no AEs that met the criteria for

an event of clinical interest (ECI), which included liver transaminase increases suggestive of liver injury, platelets <50,000/µL and amylase or lipase >3xULN.

Table 73: Participants with Drug-Related Adverse Events During Treatment and 14-day follow-up Period (Incidence >0% in one or More Treatment Groups) All Participants As treated Population MK-4482-002 IA2

	MK-4482 200 mg		MK-4482 400 mg		MK-4482 800 mg		MK-4482 Combined		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	74		77		74		225		74		299	
with one or more drug-related adverse events	4	(5.4)	6	(7.8)	4	(5.4)	14	(6.2)	5	(6.8)	19	(6.4)
with no drug-related adverse events	70	(94.6)	71	(92.2)	70	(94.6)	211	(93.8)	69	(93.2)	280	(93.6)
Blood and lymphatic system disorders	**0**	**(0.0)**	**2**	**(2.6)**	**0**	**(0.0)**	**2**	**(0.9)**	**0**	**(0.0)**	**2**	**(0.7)**
Leukocytosis	0	(0.0)	1	(1.3)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.3)
Lymphopenia	0	(0.0)	1	(1.3)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.3)
Neutrophilia	0	(0.0)	1	(1.3)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.3)
Cardiac disorders	**0**	**(0.0)**	**1**	**(1.3)**	**0**	**(0.0)**	**1**	**(0.4)**	**0**	**(0.0)**	**1**	**(0.3)**
Tachycardia	0	(0.0)	1	(1.3)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.3)
Gastrointestinal disorders	**3**	**(4.1)**	**2**	**(2.6)**	**3**	**(4.1)**	**8**	**(3.6)**	**4**	**(5.4)**	**12**	**(4.0)**
Abdominal pain	1	(1.4)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.3)
Abdominal pain upper	0	(0.0)	1	(1.3)	1	(1.4)	2	(0.9)	1	(1.4)	3	(1.0)
Diarrhoea	2	(2.7)	2	(2.6)	1	(1.4)	5	(2.2)	2	(2.7)	7	(2.3)
Epigastric discomfort	1	(1.4)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.3)
Gastrointestinal disorders	**3**	**(4.1)**	**2**	**(2.6)**	**3**	**(4.1)**	**8**	**(3.6)**	**4**	**(5.4)**	**12**	**(4.0)**
Nausea	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.4)	1	(1.4)	2	(0.7)
General disorders and administration site conditions	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.4)**	**1**	**(0.4)**	**0**	**(0.0)**	**1**	**(0.3)**
Chest pain	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.4)	0	(0.0)	1	(0.3)
Investigations	**0**	**(0.0)**	**1**	**(1.3)**	**0**	**(0.0)**	**1**	**(0.4)**	**0**	**(0.0)**	**1**	**(0.3)**
Alanine aminotransferase increased	0	(0.0)	1	(1.3)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.3)
Musculoskeletal and connective tissue disorders	**1**	**(1.4)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.4)**	**0**	**(0.0)**	**1**	**(0.3)**
Back pain	1	(1.4)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.3)
Nervous system disorders	**0**	**(0.0)**	**1**	**(1.3)**	**0**	**(0.0)**	**1**	**(0.4)**	**0**	**(0.0)**	**1**	**(0.3)**
Headache	0	(0.0)	1	(1.3)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.3)
Renal and urinary disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.4)**	**1**	**(0.3)**
Renal and urinary disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.4)**	**1**	**(0.3)**
Pollakiuria	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.3)

Every participant is counted a single time for each applicable row and column.
Adverse event terms are from MedDRA Version 23.1.

MK4482-002 Part 2; data at the time of IA3/4

The table summarises the safety profile as reported at the time of the cut-off date applied to IA4.

Table 74: Analysis of Adverse Event Summary During Treatment and 14-Day Follow-Up Period All Participants As treated Population MK-4482-002 Combined IA3/IA4

	MK-4482 800 mg		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[a]
Participants in population	386		379		
with one or more adverse events	135	(35.0)	150	(39.6)	-4.6 (-11.4, 2.3)
with no adverse event	251	(65.0)	229	(60.4)	4.6 (-2.3, 11.4)
with drug-related[b] adverse events	48	(12.4)	42	(11.1)	1.4 (-3.3, 6.0)
with serious adverse events	28	(7.3)	53	(14.0)	-6.7 (-11.2, -2.4)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0.0 (-1.0, 1.0)
who died	0	(0.0)	10	(2.6)	-2.6 (-4.8, -1.4)
discontinued drug due to an adverse event	5	(1.3)	13	(3.4)	-2.1 (-4.6, 0.0)
discontinued drug due to a drug-related adverse event	3	(0.8)	3	(0.8)	-0.0 (-1.6, 1.6)
discontinued drug due to a serious adverse event	1	(0.3)	9	(2.4)	-2.1 (-4.2, -0.6)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0.0 (-1.0, 1.0)

[a] Based on Miettinen & Nurminen method.
[b] Determined by the investigator to be related to the drug.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

The most frequently reported AEs (≥5% in either group) were COVID-19 (molnupiravir 8.0%, placebo 14.8%) and COVID-19 pneumonia (4.9% vs. 9.0%). The percentages with at least 1 AE were generally comparable in the age subgroups of ≥65 years and <65 years. See the first plot below.

The majority was Grade 1 or Grade 2, with Grade 3 AEs reported in 6.7% and 7.4% and Grade 4 AEs in 1.0% and 5.3%, respectively.

The percentages with drug-related AEs were comparable (12.4% vs. 11.1%). The most frequently reported drug-related AEs (≥2%) were diarrhoea (3.1%) and nausea (2.3%) in the molnupiravir group and diarrhoea (3.2%) in the placebo group. See the second plot below.

Most drug-related AEs were Grade 1 or Grade 2, with Grade 3 AEs in one subject (0.3%) per group.

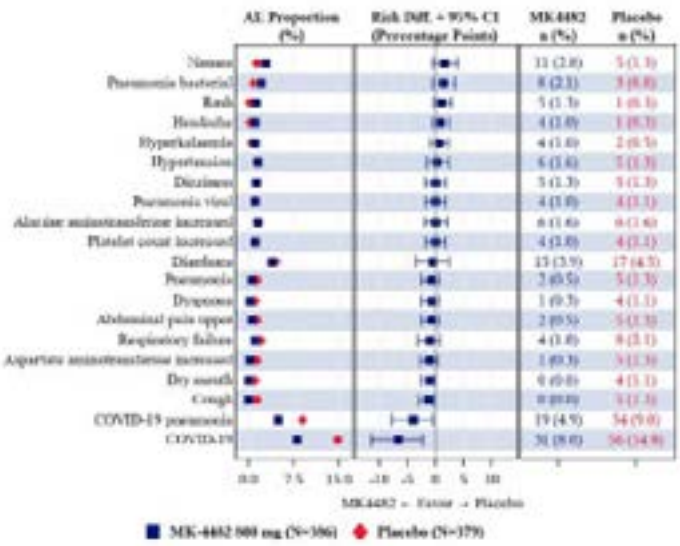

Figure 21: Rainfall Plot of Participants with Adverse Events During Treatment and 14-Day Follow-Up Period (Incidence ≥ 4 Participants in One or More Treatment Groups) All Participants as Treated Population MK-4482-002 Combined IA3/IA4

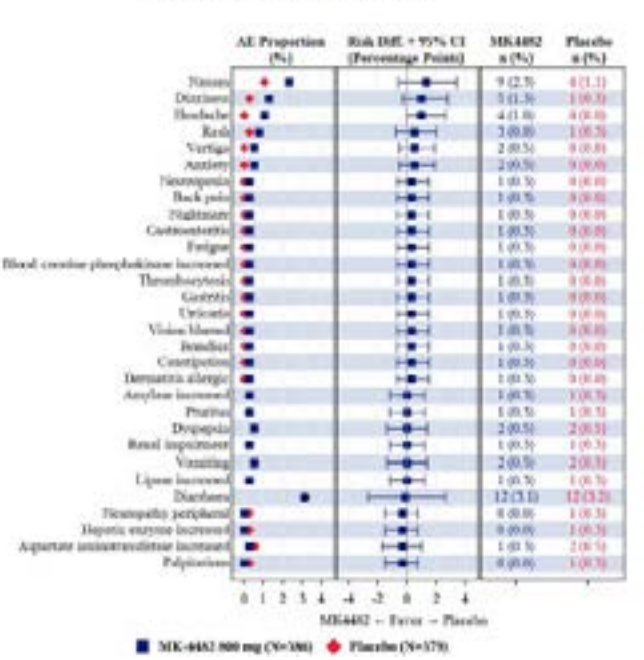

Figure 22: Rainfall Plot of Participants with Drug-related Adverse Events During Treatment and 14-Day Follow-Up Period (Incidence ≥ 0% in One or More Treatment Groups) All Participants as Treated Population MK-4482-002 Combined IA3/IA4

MK4482-002 Part 2; data at the time of stopping enrolment.

The table below summarises the safety profile based on the total 1433 subjects.

Table 75: Adverse Events Summary (Protocol 002 – Full Population)

	Molnupiravir		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[a]
Participants in population	710		701		
with one or more adverse events	216	(30.4)	231	(33.0)	-2.5 (-7.4, 2.3)
with no adverse event	494	(69.6)	470	(67.0)	2.5 (-2.3, 7.4)
with drug-related[b] adverse events	57	(8.0)	59	(8.4)	-0.4 (-3.3, 2.5)
with serious adverse events	49	(6.9)	67	(9.6)	-2.7 (-5.6, 0.2)
with serious drug-related adverse events	0	(0.0)	1	(0.1)	-0.1 (-0.8, 0.4)
who died	2	(0.3)	12	(1.7)	-1.4 (-2.7, -0.5)
discontinued drug due to an adverse event	10	(1.4)	20	(2.9)	-1.4 (-3.1, 0.1)
discontinued drug due to a drug-related adverse event	4	(0.6)	3	(0.4)	0.1 (-0.8, 1.1)
discontinued drug due to a serious adverse event	5	(0.7)	13	(1.9)	-1.2 (-2.5, 0.0)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0.0 (-0.5, 0.5)

[a] Based on Miettinen & Nurminen method.
[b] Determined by the investigator to be related to the drug.

The most common adverse reactions in the molnupiravir treatment group are shown below, all of which were Grade 1 (mild) or Grade 2 (moderate).

Table 76: Adverse Reactions Occurring in Greater Than or Equal to 1% of Participants Receiving Molnupiravir (Protocol 002)*

	Molnupiravir N=710 %	Placebo N=701 %
Diarrhea	2%	2%
Nausea	1%	1%
Dizziness	1%	1%

*Frequencies of adverse reactions are based on all adverse events attributed to study intervention by the investigator.

MK4482-001 Part 1

The table summarises the safety profile observed over 29 days in this study in hospitalised subjects.

Table 77: Adverse Events Summary During Treatment and 14-Day Follow-up Period All Participants as Treated Population MK-4482-001 IA2

	MK-4482 200 mg		MK-4482 400 mg		MK-4482 800 mg		MK-4482 Combined		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	73		73		72		218		75		293	
with one or more adverse events	40	(54.8)	36	(49.3)	45	(62.5)	121	(55.5)	46	(61.3)	167	(57.0)
with no adverse event	33	(45.2)	37	(50.7)	27	(37.5)	97	(44.5)	29	(38.7)	126	(43.0)
with drug-related* adverse events	8	(11.0)	6	(8.2)	10	(13.9)	24	(11.0)	16	(21.3)	40	(13.7)
with serious adverse events	11	(15.1)	9	(12.3)	13	(18.1)	33	(15.1)	12	(16.0)	45	(15.4)
with serious drug-related adverse events	1	(1.4)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.3)
who died	6	(8.2)	4	(5.5)	4	(5.6)	14	(6.4)	2	(2.7)	16	(5.5)
discontinued drug due to an adverse event	0	(0.0)	1	(1.4)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.3)
discontinued drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)	1	(1.4)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.3)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

* Determined by the investigator to be related to the drug.

The most frequently reported AEs (>5%) in the molnupiravir groups were COVID-19, AST/ALT elevation, constipation, bacterial pneumonia, hyperglycaemia and respiratory failure. The most frequently reported AEs (>5%) in the placebo group were constipation, COVID-19, COVID-19 pneumonia, ALT increased and respiratory failure.

AEs considered treatment-related by investigators were reported less often with molnupiravir (8.2% to 13.9%) compared with placebo (21.3%). The most common (>2%) treatment-related AE in the combined molnupiravir groups was ALT increased (2.3%) but this was also reported for 4% in the placebo group. Urticaria considered treatment-related was reported for 2 subjects who received molnupiravir and no placebo subjects. Treatment was not discontinued due to these AEs.

Two participants had laboratory values that met the predefined criteria for an ECI. One received molnupiravir 800 mg BID and had post-baseline elevated AST or ALT ≥3x ULN and elevated total bilirubin ≥2x ULN and alkaline phosphatase <2x ULN (thus satisfying the criteria for potential DILI) on Day 14. These criteria were no longer satisfied on Day 15 when alkaline phosphatase became >2x ULN, secondary to fatal septic shock and cholestasis; thus, the event was not considered DILI. The other received placebo and had platelets <50,000 µL on Day 10 with fatal septic shock due to bacterial pneumonia on Day 11.

2.5.8.3. Serious adverse event/deaths/other significant events

MK4482-006

There were no deaths in the combined molnupiravir groups. One participant in the placebo group died 31 days after discontinuation from the study after a SAE of hypoxia.

Four subjects had SAEs (including the fatal SAE in the placebo subject who died), of which 3 received molnupiravir as summarised in the table below. Two SAEs in participants randomised to 400 mg and 800 mg resulted in discontinuation from the study. None of the four SAEs was considered treatment-related.

Table 78: Brief Tabular Summary of Serious Adverse Events

Event Preferred Term	Treatment	No. of Doses Taken	Baseline Antibody Status*	Baseline Viral Load (Log_{10} copies/mL)	TSSO to First Dose (Days)	Risk factors for Severe COVID-19 Disease	Seriousness Criteria	Severity	Causality	Outcome
Oxygen saturation decreased	MOL 400 mg	8	Negative	8.71	5.0	No. of risk factors = 2 BMI ≥30 Diabetes	Hospitalization	Severe	Not related	Recovered
Acute respiratory failure	MOL 800 mg	2	Positive	7.14	4.6	No. of risk factors = 3 BMI ≥35 Diabetes Age ≥55 and hypertension	Hospitalization	Severe	Not related	Recovered
Hypoxia	Placebo	2	Negative	7.64	4.5	No. of risk factors = 3 BMI ≥30 Age ≥65 History of smoking	Hospitalization, death	Severe	Not related	Died after dis-continuation from the study
Cerebrovascular accident	MOL 400 mg	9	Negative	4.87	4.8	No. of risk factors = 2 Diabetes Age ≥55 and hypertension	Hospitalization	Severe	Not related	Recovered

MK4482-002 Part 1

There was one death in a placebo subject at Day 36 due to COVID-19 pneumonia and mesenteric thrombosis. SAEs were reported by 4% of subjects, with COVID-19 pneumonia in 2.7% combined molnupiravir subjects and 2.7% placebo subjects. No SAE was considered treatment-related.

Table 79: Participants With Serious Adverse Events During Treatment and 14-Day Follow-Up Period (Incidence >0% in One or More Treatment Groups) All Participants as Treated Population – MK-4482-002 IA2

	MK-4482 200 mg		MK-4482 400 mg		MK-4482 800 mg		MK-4482 Combined		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	74		77		74		225		74		299	
with one or more serious adverse events	1	(1.4)	3	(3.9)	4	(5.4)	8	(3.6)	4	(5.4)	12	(4.0)
with no serious adverse events	73	(98.6)	74	(96.1)	70	(94.6)	217	(96.4)	70	(94.6)	287	(96.0)
Infections and infestations	**1**	**(1.4)**	**2**	**(2.6)**	**4**	**(5.4)**	**7**	**(3.1)**	**2**	**(2.7)**	**9**	**(3.0)**
COVID-19	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.3)
COVID-19 pneumonia	1	(1.4)	2	(2.6)	3	(4.1)	6	(2.7)	2	(2.7)	8	(2.7)
Pneumonia	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.4)	0	(0.0)	1	(0.3)
Metabolism and nutrition disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.4)**	**1**	**(0.3)**
Diabetic metabolic decompensation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.3)
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**1**	**(1.3)**	**0**	**(0.0)**	**1**	**(0.4)**	**0**	**(0.0)**	**1**	**(0.3)**
Pulmonary embolism	0	(0.0)	1	(1.3)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.3)
Vascular disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.4)**	**1**	**(0.3)**

MK4482-002 Part 2

At the time of IA3/4, AEs leading to death were reported for 0 (0.0%) participants in the molnupiravir group and 10 (2.6%) in the placebo group. For the total 1433 enrolled, AEs leading to death occurred in 2 (<1%) of the participants receiving molnupiravir and 12 (2%) of participants receiving placebo.

Table 80: Participants With Adverse Events Resulting in Death During Treatment and 14-Day Follow-Up Period (Incidence >0% in One or More Treatment Groups) All Participants as Treated Population – MK-4482-002 IA3/IA4

	MK-4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	386		379		765	
with one or more adverse events resulting in death	0	(0.0)	10	(2.6)	10	(1.3)
with no adverse events resulting in death	386	(100.0)	369	(97.4)	755	(98.7)
Infections and infestations	**0**	**(0.0)**	**8**	**(2.1)**	**8**	**(1.0)**
COVID-19	0	(0.0)	7	(1.8)	7	(0.9)
COVID-19 pneumonia	0	(0.0)	3	(0.8)	3	(0.4)
Septic shock	0	(0.0)	1	(0.3)	1	(0.1)
Staphylococcal bacteraemia	0	(0.0)	1	(0.3)	1	(0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**(0.0)**	**1**	**(0.3)**	**1**	**(0.1)**
Metastases to lung	0	(0.0)	1	(0.3)	1	(0.1)
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**3**	**(0.8)**	**3**	**(0.4)**
Acute respiratory failure	0	(0.0)	1	(0.3)	1	(0.1)
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**3**	**(0.8)**	**3**	**(0.4)**
Respiratory failure	0	(0.0)	2	(0.5)	2	(0.3)

Every participant is counted a single time for each applicable row and column.
Adverse event terms are from MedDRA Version 24.0.

At the time of IA3/4, the percentage with SAEs was 7.3% in the molnupiravir group compared with 14% in the placebo group.

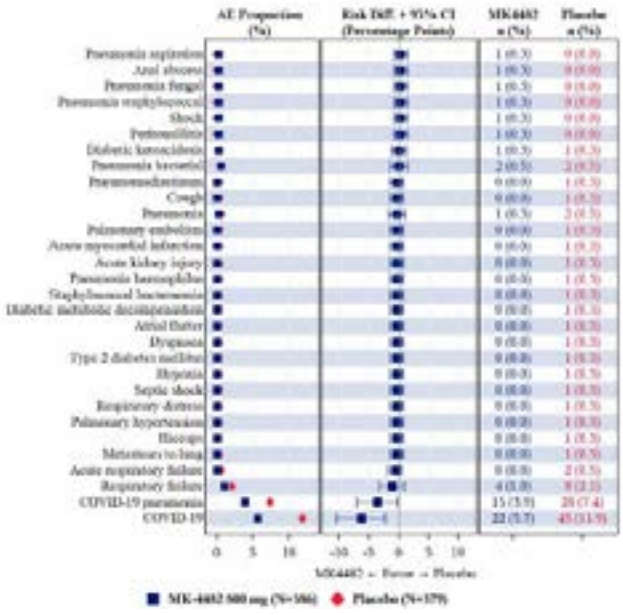

Figure 23: Rainfall Plot of Participants with Serious Adverse Events During Treatment and 14-Day Follow-Up Period (Incidence ≥ 0% in One or More Treatment Groups) All Participants as Treated Population MK-4482-002 Combined IA3/IA4

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None of the SAEs was considered drug-related by the investigators. One SAE of pulmonary embolism (molnupiravir group; unrelated) was reported after database lock so it is not included in the safety summary tables. The most frequently reported SAEs (≥5% in either group) were COVID-19 (5.7% molnupiravir vs. 11.9% placebo) and COVID-19 pneumonia (3.9% vs. 7.4%) and discontinuations due to SAEs occurred in 0.3% vs. 2.4%.

For the total 1433 enrolled, SAEs occurred in 7% receiving molnupiravir and 10% receiving placebo. One SAE in the placebo arm was considered drug-related by the investigator (pancreatitis) and most SAEs were COVID-19 related. Fewer participants in the MOV group discontinued study intervention due to an SAE than in the placebo group (0.7% vs 1.9%); none was related to study intervention per investigator assessment.

MK4484-001 Part 1

The safety analysis counted AEs that led to death with onset during treatment and the 14-day follow up period regardless of the timing of the death. There were 16 subjects who had AEs resulting in death (6 in the 200 mg group, 4 in the 400 mg group, 4 in the 800 mg group and 2 placebo). Most deaths occurred in subjects with severe COVID-19 at baseline (12/16), who were >60 years of age (13/16), who had underlying comorbidities (14/16) and/or had duration of COVID-19 symptoms >5 days before randomisation (12/16). None of the deaths was considered treatment-related by investigators.

The proportions with SAEs were comparable across groups. COVID-19 (7.5%) and respiratory failure (4.4%) were the most frequently reported SAEs. One participant in the 200 mg had an SAE of Grade 3 urticaria considered treatment-related. The subject withdrew consent after the first dose of molnupiravir and the urticaria had onset the following day. It lasted for 2 days and resolved. One subject in the 400 mg group discontinued treatment due to an SAE of respiratory failure, which resolved after 2 months.

2.5.8.4. Laboratory findings

MK4482-006

Mean change from Baseline values for platelet count showed increases for all groups at all post-baseline time points. The incidence of shifts in platelets from Grade 0 at Baseline to ≥1 post-Baseline was higher in the placebo group than in the molnupiravir groups.

There were no important treatment- or dose-related trends in mean clinical chemistry data. Mean ALT decreased from baseline to Day 28 in all groups and AST was lower at many post-baseline time points and on Day 28 was lower in all groups. Mean creatinine clearance was slightly lower post-baseline in the placebo group and slightly higher in the molnupiravir 800 mg group. Few participants experienced treatment-emergent laboratory abnormalities.

No subject met the criteria for Hy's law. One subject in the 400 mg group had a Grade 3 ALT value by Day 5 and a Grade 2 AST value on Days 3 and 5 (see table below). The subject had no relevant medical history or concomitant medications during the study. Subject's Baseline viral load was 31,595 copies/mL and the subject had antibodies to SARS-CoV-2. By Day 7, no SARS-CoV-2 RNA was detectable. The subject took all 10 doses of study drug and completed the study. The Grade 3 ALT value was not reported as an AE.

Table 81: Selected Laboratory Values for Participants

Analyte (Unit:) (Normal Range:)	Screening	Day 1	Day 3	Day 5	Day 7	Day 14	Day 28
ALT (IU/L) (Screening: 5 – 45) Days 0-28: 0-44)	64*	43	163**	241***	194**	52	28
AST (IU/L) (Screening: 1 – 40) (Days 0-28: 0-40)	72*	29	128**	117**	48	19	20
Bilirubin (mmol/L (Screening: 0.00171 -0.02394) Days 0-28: 0-0.02052)	0.0171	0.01197	0.00855	0.01026	0.00855	0.01026	0.01197

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase.
*Grade 1
**Grade 2
***Grade 3

MK4482-002 Part 1

The proportions with laboratory values that met predefined limits of change (worsening Grade 3 or 4) were comparable between the molnupiravir and placebo groups. There was no evidence of haematologic, pancreatic or hepatic toxicity as a function of either dose or treatment. No subject had a change in platelets that met the predefined ECI criteria.

Table 82: Analysis of Participants with Laboratory Findings that Met Predetermined Criteria Worsening Grade 3 or 4 – All Participants as Treated Population MK-4482-002 IA2

Test Name (Unit)	Criterion	Treatment	N	n/m (%)	Difference in % vs Placebo Estimate (95% CI)[a]
Chemistry					
Alanine Aminotransferase (IU/L)	Grade 3: 5.0 - <10.0 x ULN or Grade 4: >=10.0 x ULN	MK-4482 200 mg	74	1/54 (1.9)	0.1
		MK-4482 400 mg	77	1/60 (1.7)	-0.1
		MK-4482 800 mg	74	0/58 (0.0)	-1.7
		Placebo	74	1/58 (1.7)	
Aspartate Aminotransferase (IU/L)	Grade 3: 5.0 - <10.0 x ULN or Grade 4: >=10.0 x ULN	MK-4482 200 mg	74	1/66 (1.5)	-0.0
		MK-4482 400 mg	77	0/68 (0.0)	-1.6
		MK-4482 800 mg	74	0/64 (0.0)	-1.6
		Placebo	74	1/64 (1.6)	
Creatinine (mg/dL)	Grade 3: >1.8 - <3.5 x ULN or Increase to 1.5 to <2.0 x above baseline	MK-4482 200 mg	74	2/64 (3.1)	3.1
		MK-4482 400 mg	77	1/65 (1.5)	1.5
		MK-4482 800 mg	74	1/65 (1.5)	1.5
		Placebo	74	0/66 (0.0)	
GFR from Creatinine Adjusted for BSA (mL/min/1.73m2)	Grade 3: 30 - <60 or 30% - <50% decrease from participant's baseline or Grade 4: <30 or >=50% decrease from participant's baseline	MK-4482 200 mg	74	8/64 (12.5)	4.9 (-5.9, 16.3)
		MK-4482 400 mg	77	4/65 (6.2)	-1.4 (-11.3, 8.3)
		MK-4482 800 mg	74	4/65 (6.2)	-1.4 (-11.3, 8.3)
		Placebo	74	5/66 (7.6)	

MK4482-002 Part 2 IA3/4

No molnupiravir subject had laboratory values that met the predefined ECI criteria for potential DILI, for platelet count of <50,000 cells/µL or had a >50% drop in platelets. Percentages with any Grade 1 laboratory

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findings were 1.9% for molnupiravir and 3.4% for placebo with Grade 2 in 0.6% and 0.9%. Grade 1 absolute neutrophil counts occurred in 1.2% and 3.2% and Grade 2 in 1.2% and 0.4% with no Grade 3 or 4 results. Grade 3 or Grade 4 ALT increases occurred in 1.6% and 2.5% and abnormal lipase (>3× ULN) occurred in 0.0% and 1.7%, respectively.

Table 83: Participants with Laboratory Findings that Met Predetermined Criteria – All Participants as Treated Population MK-4482-002 IA3/IA4

Criteria	MK-4482 800 mg		Placebo		Total	
	n/m	(%)	n/m	(%)	n/m	(%)
Participants in population	386		379		765	
CHEMISTRY						
Albumin (g/dL)						
Grade 1: 3.0 - <LLN	12/359	(3.3)	15/354	(4.2)	27/713	(3.8)
Grade 2: ≥2.0 - <3.0	7/359	(1.9)	6/354	(1.7)	13/713	(1.8)
Grade 3: <2.0	0/359	(0.0)	0/354	(0.0)	0/713	(0.0)
Alkaline Phosphatase (IU/L)						
Grade 1: 1.25 - <2.5 x ULN	12/356	(3.4)	9/353	(2.5)	21/709	(3.0)
Grade 2: 2.5 - <5.0 x ULN	0/356	(0.0)	1/353	(0.3)	1/709	(0.1)
Grade 3: 5.0 - <10.0 x ULN	0/356	(0.0)	0/353	(0.0)	0/709	(0.0)
Grade 4: ≥10.0 x ULN	0/356	(0.0)	0/353	(0.0)	0/709	(0.0)
Alanine Aminotransferase (IU/L)						
Grade 1: 1.25 - <2.5 x ULN	56/316	(17.7)	58/323	(18.0)	114/639	(17.8)
Grade 2: 2.5 - <5.0 x ULN	9/316	(2.8)	31/323	(9.6)	40/639	(6.3)
Grade 3: 5.0 - <10.0 x ULN	4/316	(1.3)	8/323	(2.5)	12/639	(1.9)
Grade 4: ≥10.0 x ULN	1/316	(0.3)	0/323	(0.0)	1/639	(0.2)
Amylase (IU/L)						
Grade 1: 1.1 - <1.5 x ULN	19/357	(5.3)	31/353	(8.8)	50/710	(7.0)
Grade 2: 1.5 - <3.0 x ULN	6/357	(1.7)	16/353	(4.5)	22/710	(3.1)
Grade 3: 3.0 - <5.0 x ULN	1/357	(0.3)	1/353	(0.3)	2/710	(0.3)
Grade 4: ≥ 5.0 x ULN	0/357	(0.0)	1/353	(0.3)	1/710	(0.1)
Aspartate Aminotransferase (IU/L)						
Grade 1: 1.25 - <2.5 x ULN	33/359	(9.2)	55/350	(15.7)	88/709	(12.4)
Grade 2: 2.5 - <5.0 x ULN	6/359	(1.7)	17/350	(4.9)	23/709	(3.2)
Grade 3: 5.0 - <10.0 x ULN	4/359	(1.1)	2/350	(0.6)	6/709	(0.8)
Grade 4: ≥10.0 x ULN	0/359	(0.0)	0/350	(0.0)	0/709	(0.0)
Bicarbonate (mEq/L)						
Grade 1: 16.0 - <LLN	55/302	(18.2)	52/299	(17.4)	107/601	(17.8)
Grade 2: 11.0 - <16.0	2/302	(0.7)	6/299	(2.0)	8/601	(1.3)
Grade 3: 8.0 - <11.0	0/302	(0.0)	0/299	(0.0)	0/601	(0.0)
Grade 4: <8.0	0/302	(0.0)	0/299	(0.0)	0/601	(0.0)
Bilirubin (mg/dL)						

Grade 1: 1.1 - <1.6 x ULN	10/359	(2.8)	9/354	(2.5)	19/713	(2.7)
Grade 2: 1.6 - <2.6 x ULN	2/359	(0.6)	0/354	(0.0)	2/713	(0.3)
Grade 3: 2.6 - <5.0 x ULN	0/359	(0.0)	0/354	(0.0)	0/713	(0.0)
Grade 4: ≥5.0 x ULN	0/359	(0.0)	0/354	(0.0)	0/713	(0.0)
Calcium, High (mg/dL)						
Grade 1: 10.6 - <11.5	2/358	(0.6)	2/354	(0.6)	4/712	(0.6)
Grade 2: 11.5 - <12.5	0/358	(0.0)	0/354	(0.0)	0/712	(0.0)
Grade 3: 12.5 - <13.5	0/358	(0.0)	0/354	(0.0)	0/712	(0.0)
Grade 4: ≥13.5	0/358	(0.0)	0/354	(0.0)	0/712	(0.0)
Calcium, Low (mg/dL)						
Grade 1: 7.8 - <8.4	21/358	(5.9)	33/354	(9.3)	54/712	(7.6)
Grade 2: 7.0 - <7.8	8/358	(2.2)	9/354	(2.5)	17/712	(2.4)
Grade 3: 6.1 - <7.0	4/358	(1.1)	8/354	(2.3)	12/712	(1.7)
Grade 4: <6.1	4/358	(1.1)	3/354	(0.8)	7/712	(1.0)
Creatine Kinase (IU/L)						
Grade 1: 3.0 - <6.0 x ULN	7/354	(2.0)	2/345	(0.6)	9/699	(1.3)
Grade 2: 6.0 - <10.0 x ULN	3/354	(0.8)	4/345	(1.2)	7/699	(1.0)
Grade 3: 10.0 - <20.0 x ULN	1/354	(0.3)	2/345	(0.6)	3/699	(0.4)
Grade 4: ≥ 20.0 x ULN	0/354	(0.0)	1/345	(0.3)	1/699	(0.1)
Creatinine (mg/dL)						
Grade 1: 1.1 - 1.5 x ULN	1/359	(0.3)	3/356	(0.8)	4/715	(0.6)
Grade 2: >1.5 - 1.8 x ULN or Increase to 1.5 to < 1.5 x baseline	23/359	(6.4)	17/356	(4.8)	40/715	(5.6)
Grade 3: >1.8 - <3.5 x ULN or Increase to 1.5 to <2.0 x above baseline	6/359	(1.7)	7/356	(2.0)	13/715	(1.8)
Grade 4: ≥3.5 x ULN or Increase of ≥2.0 x above baseline	1/359	(0.3)	2/356	(0.6)	3/715	(0.4)
GFR from Creatinine Adjusted for BSA (mL/min/1.73m2)						
Grade 2: 60 - <90 or 10% - <30% decrease from participant's baseline	62/295	(21.0)	77/288	(26.7)	139/583	(23.8)
Grade 3: 30 - <60 or 30% - <50% decrease from participant's baseline	16/295	(5.4)	20/288	(6.9)	36/583	(6.2)

Lipase (IU/L)						
Grade 1: 1.1 - <3.0 x ULN	19/357	(5.3)	12/353	(3.4)	31/710	(4.4)
Grade 2: 3.0 - <5.0 x ULN	6/357	(1.7)	19/353	(5.4)	25/710	(3.5)
Grade 3: 5.0 - <5.0 x ULN	0/357	(0.0)	3/353	(0.8)	3/710	(0.4)
Grade 4: ≥5.0 x ULN	0/357	(0.0)	3/353	(0.8)	3/710	(0.4)

MK4482-002 Part 2 total enrolled

Grade 3 and 4 decreases in haemoglobin were uncommon. Grade 1 and 2 decreases in haemoglobin (i.e., 8.5 – 10.4 g/dL in females and 9.0 – 10.9 g/dL in males) were reported in 4% of participants receiving molnupiravir and 2% of participants receiving placebo.

Table 84: Selected Grade 3 and Grade 4 Laboratory Abnormalities (Protocol 002 – Full Population)

Criterion*	Molnupiravir N = 710 %	Placebo N = 701 %
Chemistry		
Alanine Aminotransferase (IU/L)		
Grade 3: 5.0 - <10.0 x ULN	1%	2%
Grade 4: ≥10.0 x ULN	<1%	0%
Aspartate Aminotransferase (IU/L)		
Grade 3: 5.0 - <10.0 x ULN	1%	<1%
Grade 4: ≥10.0 x ULN	0%	0%
Creatinine (mg/dL)		
Grade 3: >1.8 - <3.5 x ULN or Increase to 1.5 to <2.0 x above baseline	2%	2%
Grade 4: ≥3.5 x ULN or Increase of ≥2.0 x above baseline	<1%	1%
Lipase (IU/L)		
Grade 3: 3.0-<5.0 x ULN	<1%	<1%
Grade 4: ≥5.0 x ULN	0%	1%
Hematology		
Hemoglobin (g/dL)		
Grade 3: Male: 7.0 - <9.0 Female: 6.5 - <8.5	<1%	1%
Grade 4: Male: <7.0 Female: <6.5	0%	0%
Platelets (10^9/L)		
Grade 3: 25 - <50	0%	0%
Grade 4: <25	0%	<1%
Leukocytes (10^9/L)		
Grade 3: 1.000 – 1.499	<1%	<1%
Grade 4: <1.000	0%	0%

*For graded criteria: Participants are counted once per test in the highest grade reported.
For inclusion in this analysis, both a baseline and at least 1 post-baseline laboratory value had to be present.
Only participants with a worsened grade from baseline were included.
Grades are based on the NIH DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 or predefined limit of change (PDLC).
ULN = Upper limit of normal range.

No participants had laboratory values that met the predefined ECI criteria for potential DILI; a single participant in each group had laboratory values that met the predefined ECI criteria for post-baseline platelet value <50,000/µL, but none of them was considered by the investigator to be related to study intervention.

MK4482-001 Part 1

While the CSR states that there were no clinically meaningful findings in the laboratory values that met

pre-determined criteria, section 4.3 reports the ECI resulting from a subject who received molnupiravir 800 mg BID and had post-baseline elevated AST or ALT ≥3x ULN and elevated total bilirubin ≥2x ULN and alkaline phosphatase <2x ULN (thus satisfying the criteria for potential DILI) on Day 14. These criteria were

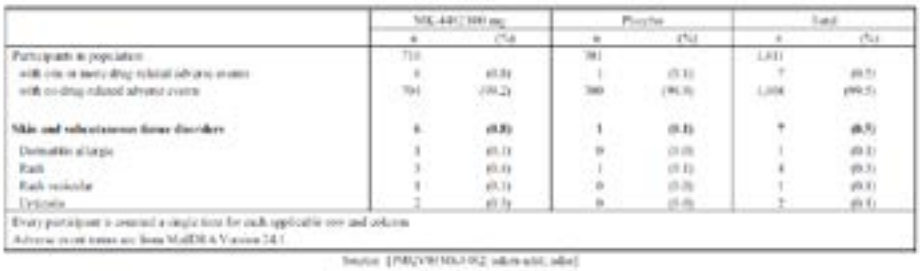
no longer satisfied on Day 15 when alkaline phosphatase became >2x ULN, secondary to fatal septic shock and cholestasis; thus, the event was not considered DILI. See also under AEs above.

2.5.8.5. Immunological events

Although no SAEs likely to represent hypersensitivity were reported, there have been reports of urticaria, rash and pruritus although not necessarily considered treatment-related.

In MK4482-002 Part 2 total enrolled, AEs related to hypersensitivity and allergic reactions were reported for 14 (2.0%) participants in the molnupiravir group and 6 (0.9%) participants in the placebo group. The percentage of participants with AEs of rash considered by the investigator to be related to study drugs is shown in the table below.

Table 85: Participants With Drug-Related Adverse Events of Rash During Treatment and 14-Day Follow-Up Period (Incidence>0% in One or More Treatment Groups) All Participants as Treated Population MK-4482-002 Part 2 Day 29 DBL



2.5.8.6. Discontinuation due to adverse events

Discontinuations due to AEs

In MK-4482-004, one subject had pruritus and rash with 800 mg BID that was considered treatment-related and discontinued drug on Day 4.

In MK4482-006, three of the four SAEs (see above) led to study drug discontinuation and all of these subjects also discontinued from the study but none of the SAEs was considered treatment-related.

MK4482-002 Part 1

AEs leading to treatment discontinuation were reported for 4 (1.3%) subjects. In the molnupiravir groups, 3/225 discontinued due to an AE (2 due to COVID-19 pneumonia, 1 due to hypoaesthesia and insomnia) but none was considered treatment-related. One placebo subject discontinued due to drug-related diarrhoea.

MK4482-002 Part 2

At the time of IA3/4, AEs leading to discontinuation of study drug occurred in 1.3% in the molnupiravir group and 3.4% in the placebo group. Drug-related AEs leading to discontinuation of study drug were reported for 0.8% in each group.

Table 86: Participants with Adverse Events Leading to Discontinuation of Treatment (Incidence >0% in One or More Treatment Groups) All Participants as Treated Population MK-4482-002 Combined IA3/IA4

	MK-4482 800mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	386		379		765	
with one or more adverse events leading to discontinuation	5	(1.3)	13	(3.4)	18	(2.4)
with no adverse events leading to discontinuation	381	(98.7)	366	(96.6)	747	(97.6)
Eye disorders	**1**	**(0.3)**	**0**	**(0.0)**	**1**	**(0.1)**
Vision blurred	1	(0.3)	0	(0.0)	1	(0.1)
Gastrointestinal disorders	**2**	**(0.5)**	**2**	**(0.5)**	**4**	**(0.5)**
Abdominal pain upper	0	(0.0)	2	(0.5)	2	(0.3)
Diarrhoea	0	(0.0)	2	(0.5)	2	(0.3)
Nausea	2	(0.5)	0	(0.0)	2	(0.3)
Vomiting	2	(0.5)	0	(0.0)	2	(0.3)
General disorders and administration site conditions	**1**	**(0.3)**	**1**	**(0.3)**	**2**	**(0.3)**
Chest discomfort	0	(0.0)	1	(0.3)	1	(0.1)
Fatigue	1	(0.3)	0	(0.0)	1	(0.1)
Infections and infestations	**1**	**(0.3)**	**8**	**(2.1)**	**9**	**(1.2)**
COVID-19	0	(0.0)	7	(1.8)	7	(0.9)
Infections and infestations	**1**	**(0.3)**	**8**	**(2.1)**	**9**	**(1.2)**
COVID-19 pneumonia	0	(0.0)	3	(0.8)	3	(0.4)
Peritonsillitis	1	(0.3)	0	(0.0)	1	(0.1)
Tonsillitis	1	(0.3)	0	(0.0)	1	(0.1)
Metabolism and nutrition disorders	**0**	**(0.0)**	**1**	**(0.3)**	**1**	**(0.1)**
Diabetic metabolic decompensation	0	(0.0)	1	(0.3)	1	(0.1)
Musculoskeletal and connective tissue disorders	**0**	**(0.0)**	**1**	**(0.3)**	**1**	**(0.1)**
Myalgia	0	(0.0)	1	(0.3)	1	(0.1)
Nervous system disorders	**2**	**(0.5)**	**0**	**(0.0)**	**2**	**(0.3)**
Dizziness	1	(0.3)	0	(0.0)	1	(0.1)
Headache	1	(0.3)	0	(0.0)	1	(0.1)
Psychiatric disorders	**0**	**(0.0)**	**1**	**(0.3)**	**1**	**(0.1)**
Insomnia	0	(0.0)	1	(0.3)	1	(0.1)
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**1**	**(0.3)**	**1**	**(0.1)**
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**1**	**(0.3)**	**1**	**(0.1)**
Hiccups	0	(0.0)	1	(0.3)	1	(0.1)

Every participant is counted a single time for each applicable row and column.
Adverse event terms are from MedDRA Version 24.0.

For the total enrolled into Part 2, discontinuations due to AEs were reported for 10 molnupiravir and 20 placebo patients, of which 4 and 3 in respective groups were thought to be treatment-related and 5 and 13 were SAEs. The proportion with AEs leading to study intervention discontinuation was comparable (1.4% molnupiravir, 2.9% placebo). AEs leading to discontinuation that were related to study drugs per investigator assessment occurred in 0.6% in the molnupiravir group (vision blurred, nausea, vomiting, fatigue, dizziness, headache, and urticaria) and in 0.4% in the placebo group (abdominal pain upper, diarrhoea, chest discomfort, and insomnia).

Table 87: Participants with Adverse Events Leading to Discontinuation of Treatment (Incidence >0% in One or More Treatment Groups) All Participants as Treated Population MK-4482-002 Part 2 Day 29 DBL

	MK-4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Infections and infestations	**4**	**(0.6)**	**12**	**(1.7)**	**16**	**(1.1)**
COVID-19	3	(0.4)	10	(1.4)	13	(0.9)
COVID-19 pneumonia	1	(0.1)	2	(0.3)	3	(0.2)
Pyelonephritis	1	(0.1)	0	(0.0)	1	(0.1)
Tonsillitis	1	(0.1)	0	(0.0)	1	(0.1)
Investigations	**0**	**(0.0)**	**1**	**(0.1)**	**1**	**(0.1)**
Alanine aminotransferase increased	0	(0.0)	1	(0.1)	1	(0.1)
Aspartate aminotransferase increased	0	(0.0)	1	(0.1)	1	(0.1)
Metabolism and nutrition disorders	**0**	**(0.0)**	**1**	**(0.1)**	**1**	**(0.1)**
Diabetic metabolic decompensation	0	(0.0)	1	(0.1)	1	(0.1)
Musculoskeletal and connective tissue disorders	**0**	**(0.0)**	**1**	**(0.1)**	**1**	**(0.1)**
Myalgia	0	(0.0)	1	(0.1)	1	(0.1)
Nervous system disorders	**2**	**(0.3)**	**0**	**(0.0)**	**2**	**(0.1)**
Dizziness	1	(0.1)	0	(0.0)	1	(0.1)
Headache	1	(0.1)	0	(0.0)	1	(0.1)

	MK-4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Psychiatric disorders	**0**	**(0.0)**	**1**	**(0.1)**	**1**	**(0.1)**
Insomnia	0	(0.0)	1	(0.1)	1	(0.1)
Respiratory, thoracic and mediastinal disorders	**1**	**(0.1)**	**1**	**(0.1)**	**2**	**(0.1)**
Hiccups	0	(0.0)	1	(0.1)	1	(0.1)
Hypoxia	1	(0.1)	0	(0.0)	1	(0.1)
Skin and subcutaneous tissue disorders	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**
Urticaria	1	(0.1)	0	(0.0)	1	(0.1)

Every participant is counted a single time for each applicable row and column.
Adverse event terms are from MedDRA Version 24.1.

Source: [P002V05MK4482 tables-ad6; adae]

MK4482-001 Part 1

One participant in the 400 mg group discontinued treatment due to an SAE of respiratory failure, which resolved after 2 months. This was not considered treatment-related.

2.5.8.7. Post marketing experience

As of 30-Nov-2022, the safety database included 12 reports of bradycardia among 7067 reports containing 11,939 events from valid spontaneous and non-interventional study sources. During the clinical trials, there were two reports of bradycardia, both in patients hospitalised with COVID-19 and both considered unrelated to molnupiravir.

Of the 12 cases, 7 occurred in male subjects and 5 in females. Age was reported in 10 cases and ranged between 45-96 years, with one additional case indicating age as "9 decades". Time to onset was reported in 11 cases and ranged between Day 2 to 4 in 8 cases and 1 day, 2 days and 3 weeks after the last molnupiravir dose in 3 cases. Action taken with molnupiravir in the 8 cases where the event occurred before the last dose was discontinuation in 6 cases, continuation in 2 cases and not reported in 1 case.

In four cases, the causal relationship to molnupiravir was considered probable due to the temporal relationship, missing alternative explanations and positive de-challenge/resolution/regression after discontinuation. In two cases, there was an at least possible causal relationship. In four cases relationship was considered unlikely and in two unclassifiable. Most, but not all, of the cases where a causal relationship could not be ruled out were elderly patients.

Based on these reports, bradycardia should be added as an ADR with an appropriate estimated frequency in the table in section 4.8 of the SmPC and reflected in section 4 of the PIL.

2.5.9. Discussion on clinical safety

Of the 1069 subjects, mostly infected with COVID-19, exposed to molnupiravir and included in the initial filing, 593 received 800 mg BID for up to 5 days and 587 of this number had COVID-19. The vast majority of these 587 were enrolled into MK4482-002 so they provide safety data for the target population. This total is considered appropriate in light of the intended usage of molnupiravir. During the MAA, the total exposed to up to 800 mg BID was increased due to limited safety data made available from the total 1433 subjects enrolled into study Part 2. Generally, the safety profile reported thus far from the total enrolled seems to be in line with that reported from IA3/4. However, details on safety in the additional subjects vs. IA3/4 are very limited at present.

For all AEs and for drug-related AEs there was no clear trend to a major effect of molnupiravir dose on the safety profile. For the most part the overall rates and rates for individual PTs have overlapped between molnupiravir and placebo groups. Relatively few AEs have been Grade 3 or 4 and there has been no excess of these in molnupiravir-treated subjects.

There was a subject in MK4482-004 with pruritus and rash who discontinued. In MK4482-002, 5 (1.3%) in the molnupiravir 800 mg BID group and 1 in the placebo group had a rash, regardless of relatedness. There have also been several reports of urticaria although no SAEs likely to represent hypersensitivity were reported. Rash and urticaria have been included in the table of ADRs in section 4.8 of the SmPC.

The applicant did not conduct a TQT study (see the nonclinical report) but did collect ECGs in MK4482-004, which did not suggest any clinically important effect on cardiac conduction.

The applicant has paid close attention to any possible effects of molnupiravir on bone marrow, including any events of low haemoglobin and thrombocytopenia. Thus far, the clinical data do not point to an issue of concern arising from a 5-day treatment course.

There have been instances of on-treatment elevations in transaminases but so far there does not seem to have been an excess of instances in molnupiravir-treated subjects.

In MK4482-001 Part 1, one subject who received molnupiravir 800 mg BID had post-baseline elevated AST or ALT ≥3x ULN and elevated total bilirubin ≥2x ULN and alkaline phosphatase <2x ULN (thus satisfying the criteria for potential DILI) on Day 14. However, on Day 15 the ALP became >2x ULN, secondary to fatal septic shock and cholestasis. The applicant considers that this was not a case of DILI but it is difficult to determine if this subject had DILI before progressing to septic shock.

With the exception of MK4482-001 Part 1, in which molnupiravir failed to show a clinical benefit, there were no deaths in molnupiravir-treated subjects.

In MK4482-001 Part 1, counting AEs that led to death with onset during treatment and the 14-day follow up period regardless of the timing of the death, 16 had AEs resulting in death (6 in the 200 mg group, 4 in the 400 mg group, 4 in the 800 mg group and 2 placebo). Most deaths occurred in subjects who had severe COVID-19 at baseline (12/16), were >60 years of age (13/16), had underlying comorbidities (14/16) and/or had duration of COVID-19 symptoms >5 days before randomisation (12/16). None of the deaths was considered treatment-related by investigators. With small groups and with no dose-related trend, it seems unlikely that molnupiravir contributed to death and the distribution may have arisen by chance.

Rates for SAEs have not been higher with molnupiravir and much of the difference vs. placebo in MK4482-002 was driven by the rate of worsening of COVID-19 in the placebo group.

Translating the safety data into Section 4.8, the applicant provided on request a discussion to support the derivation of ADRs and frequencies listed in the table in section 4.8 of the SmPC. This was later updated in response to a request for a further detailed analysis of neurological events that took into account all available safety data from P002 Part 2.

There is an additional potential safety concern arising from the nonclinical data. In a preliminary embryo-fetal development (EFD) study in rats, significant maternal and developmental toxicity was noted at 1000 mg/kg (margin of exposure of 7.5 fold at RHD). Increases in post-implantation loss as well as reduced fetal body weights were seen. In addition, malformations occurred including abnormal and/or small eye/eye socket, absent kidney, rib malformations and thoracic and lumbar vertebra malformations. The definitive EFD study used a maximum of 500 mg/kg with no molnupiravir-related malformations observed. The only developmental toxicity was decreased fetal weights at 500 mg/kg (margin of exposure of 2.9 fold at RHD). The NOAEL for maternal and developmental toxicity in rats was 250 mg/kg, which represents a margin of exposure of 0.8 fold the NHC exposure measured at the RHD.

In rabbits, the preliminary EFD study identified maternal toxicity at 1000 mg/kg with effects on body weight and food consumption similar to those in rats. No developmental toxicity was reported at any dose level. For the definitive study, the maximum dose used was 750 mg/kg. At doses ≥ 400 mg/kg maternal toxicity was noted and the proposed NOAEL for maternal toxicity was 125 mg/kg (margin of exposure of 1.5 fold).

Developmental toxicity effects in the definitive study in rabbits and attributed to molnupiravir were limited to decreased live fetal weights at 750 mg/kg (margin of exposure of 18-fold at RHD). However, the study report has an increased number of visceral malformations seen in the 400 and 750 mg/kg groups with 6 foetuses from 6 different litters affected in the top dose group compared to 2 in the control group. Although the incidence is low, 2/6 of these malformations were absent kidney, which was also seen in the study in rats. Furthermore, there are effects seen on the gallbladder, which are not evident in control animals. At the applicant's NOAEL for developmental toxicity of 400 mg/kg a margin of exposure of 6.5 fold.

While an absolute contraindication for use in pregnancy and breastfeeding is not thought to be necessary, the draft SmPC recommendation to avoid molnupiravir during pregnancy and lactation is appropriate. The advice that WOCP should use contraception during treatment and for at least 4 days after the last dose is appropriate, along with the advice not to resume breastfeeding for 4 days after the last dose. This 4-day window is based not only on the plasma half-life of NHC but also on recognition that NHC-TP persists in host cells beyond the plasma half-life. Thus, the 4-day window is considered conservative but supportable.

A further issue arose from company's safety database reports, including 12 cases of bradycardia. Review of these cases suggested that four could be considered to have a probable relationship to molnupiravir while two had at least a possible causal relationship.

Based on these reports, the Committee recommended to add bradycardia as an ADR with an appropriate estimated frequency in the table in section 4.8 of the SmPC and reflected in section 4 of the PIL. However, in light of the negative outcome this was not further pursued.

2.5.10. Conclusions on the clinical safety

In light of the nonclinical findings, noting that the target population is confined to adults at this time, it is appropriate that Section 4.6 of the SmPC advises that use of molnupiravir is not recommended during pregnancy or breastfeeding with a 4-day post-treatment window for use of contraception and avoidance of breastfeeding. It does not seem necessary to impose a contraindication to such usage.

The potential concerns regarding effects of molnupiravir on bone marrow do not appear to be clinical concerns when treatment is restricted to 800 mg BID for up to 5 days. Further information on effects on transaminases is needed from wider usage before a firm conclusion can be drawn on any appreciable risk associated with molnupiravir. Meanwhile, data suggest no undue risk of pancreatitis.

An excess of deaths with molnupiravir vs. placebo was seen only in MK4482-001 Part 1 and there is no evidence of a relationship to dose. With relatively small denominators, the differences in numbers may have arisen by chance. The data from treated outpatients does not show any deaths in the molnupiravir groups.

There are no outstanding issues for safety except for bradycardia as an ADR in the SmPC and PL; however, in light of the negative outcome this is not further pursued as this stage of the procedure.

2.6. Risk Management Plan

2.6.1. Safety concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	Risk of embryofoetal toxicity
Missing information	Safety during breastfeeding

2.6.2. Pharmacovigilance plan

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
N/A	N/A	N/A	N/A	N/A
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
N/A	N/A	N/A	N/A	N/A
Category 3 - Required additional pharmacovigilance activities				
N/A	N/A	N/A	N/A	N/A

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2.6.3. Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Risk of embryofoetal toxicity	Routine risk minimisation measures: Pregnancy and Preclinical Safety section of the prescribing information (Sections 4.6 and 5.3 of the SmPC) "What you need to know before you take Lagevrio"-section of the Package Leaflet: Information for the patient	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Pregnancy questionnaire (attached in Annex 4)
Safety during breastfeeding	Routine risk minimisation measures: Lactation section of the prescribing information (Section 4.6 of the SmPC) "What you need to know before you take Lagevrio"-section of the Package Leaflet: Information for the patient	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Molnupiravir Lactation and Breastfeeding Questionnaire to collect information regarding safety during breastfeeding (attached in Annex 4)

2.6.4. Conclusion

The CHMP, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan version 0.2 cannot be agreed at this stage.

2.7. Pharmacovigilance

2.7.1. 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.

2.7.2. Periodic Safety Update Reports submission requirements

N/A

2.8. Product information

2.8.1. 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 reason:

The applicant conducted pilot user testing with 6 subjects to support a draft a package leaflet. The testing was conducted through individual telephone interviews and participants received all the materials via mail.

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The package leaflet was a 4-language leaflet (worst-case scenario) from the Patheon, Whitby-packaging site, where English is placed as the third language, and the remaining languages are represented by Lorem Ipsum text. The package leaflet used for testing was a life-size mock-up in alignment with the final version intended for marketing. The results of the pilot user consultation were made available and gave 6/6 positive responses to all questions.

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Isentress. The bridging report submitted by the applicant has been found acceptable.

However, in light of the negative opinion, a satisfactory package leaflet cannot be agreed at this stage.

2.8.2. Labelling exemptions

On the basis of article 63.3 of Directive 2001/83/EC, the following 3-step exemptions from labelling requirements have been granted temporarily:

- Step 1: UK packs (non-serialised) supplied for a period as short as possible, i.e. no longer than 2 months after EC decision
    - English-only outer carton, bottle label and package leaflet;
    - omission of the EU marketing authorisation number (UK product license number instead);
    - inclusion of the UK MAH name and address;
    - omission of country-specific blue box information;
    - no serialisation features (anti-tampering device only);
    - alternative access to the package leaflet and country-specific blue box information in the national languages of the Member States where the medicinal product is marketed will be provided via a QR code included in the outer packaging and the printed package leaflet (see section 2.8.3).

  However, considering that this product is to be self-administered at home, a printed package leaflet in the national language(s) must be distributed locally alongside the supply of each pack for safety reasons.
- Step 2: trilingual packs supplied no later than 2 months after EC decision with a transition to country-specific mock-ups in a staggered approach (4 to 9 months after EC decision)
    - Translation exemption to supply the medicinal product as a trilingual pack, i.e. outer carton, bottle label and package leaflet will be printed in English, French, German only;
    - omission of country-specific blue box information;
    - alternative access to the package leaflet and country-specific blue box information in the national languages of the Member States where the medicinal product is marketed will be provided via a QR code included in the outer packaging and the printed package leaflet (see section 2.8.3).
- Step 3: country-specific packs (multilingual packs as per country clusters) supplied 4 to 9 months after

EC decision.

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.

The derogations above should be seen in the context of the flexibilities described in the Labelling flexibilities for COVID-19 therapeutics (EMA/35618/2021, 12 March 2021) 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.

2.8.3. Quick Response (QR) code

A request to include a QR code in the labelling (i.e. outer carton) and the package leaflet for the purpose of providing statutory information has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code: package leaflet, blue box information and details of national reporting systems to communicate adverse reactions in all EU official languages.

2.8.4. Additional monitoring

N/A

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

COVID-19 is the clinical disease resulting from SARS-CoV-2 infection. The WHO declared a global pandemic due to SARS-CoV-2 on 11-MAR-2020. As of early October 2021, over 235 million confirmed cases of COVID-19 and 4.8 million COVID-19-related deaths had been reported globally with over 70 million cases and 1.3 million deaths in the European region.

SARS-CoV-2 infection may result in a range of clinical manifestations. There is a higher risk of more severe COVID-19 disease in adults compared with children, especially in those aged 60+ years. Data indicate that between 5-20% of adults with COVID-19 due to alpha or delta variants progress to severe disease, characterised primarily by acute respiratory failure. The mortality rate for hospitalised patients with severe COVID-19 is approximately 28% [95% CI: 24% to 33%], with a higher rate in those who are admitted to an ICU. The majority of COVID-19 fatalities occur in persons aged 60+ years who also have at least one underlying medical condition recognised or thought to predispose to disease progression.

3.1.2. Available therapies and unmet medical need

In the European Union, two antiviral agents other than molnupiravir and several monoclonal antibodies have been approved or given a positive opinion under Article 5(3) for treatment of COVID-19. With emergence of the omicron variant, not all monoclonal antibodies directed at the spike protein retain potentially useful activity. Therefore, there remains a degree of unmet medical need for safe and effective treatments for COVID-19 due to currently circulating variants.

Molnupiravir is an orally administered, direct-acting antiviral agent that has been developed for treatment of COVID-19. After oral administration of molnupiravir as multiples of 200 mg hard capsules taken without regard to food, the parent drug is converted to NHC.

NHC is taken up by host cells and is converted to the active moiety NHC-TP by host cell phosphorylases. NHC-TP interferes with SARS-CoV-2 viral replication by incorporating into the viral RNA, causing mutations throughout the genome that lead to viral error catastrophe. *In vitro*, NHC retains activity against SARS-CoV-2 harbouring RdRp mutations associated with remdesivir resistance as well as variants that have changes in the viral spike protein (e.g. the Delta variant). Preliminary in-vitro data indicate that it retains antiviral activity against the omicron variant.

3.1.3. Main clinical studies

The application is supported by four clinical studies as summarised below. The pivotal efficacy data come from MK4482-002 Part 2, which compared molnupiravir 800 mg BID for 5 days with placebo. The initial MAA was filed with the results of interim analysis 3/4 (IA3/4) of Part 2. At the time of this analysis, data were available for 775 subjects.

Results for the primary efficacy endpoint for all 1433 enrolled when recruitment stopped on 2 October 2021 were provided during the procedure.

Study	Phase/ Population	Study Results Included in Application
MK4482-002 (P002)	Phase 2 (Part 1) Phase 3 (Part 2) non-hospitalised	Phase 2 (Part 1): IA results (all Part 1 participants who completed Day 29) for safety, efficacy, virology, and PK Phase 3 (Part 2): IA[a] results (50% of randomised participants who completed Day 29) for safety, efficacy, and virology Top line results for total 1433 randomised when recruitment stopped on 2 October 2021*
MK4482-006 (P006)	Phase 2a non-hospitalised	Final results for safety, efficacy, virology, and PK
MK4482-001 (P001)	Phase 2 hospitalised	Phase 2: IA results for safety (through Day 29), efficacy (through Day 29; primary endpoint), virology, and PK*
MK4482-004 (P004)	Phase 1/ Healthy subjects	Final results for safety and PK
[a] The IA for P002 (Phase 3) includes both IA3 and IA4. IA4 was planned with the primary purpose of assessing for futility/early efficacy when 50% of the total planned for enrolment completed the Day 29 follow-up visit. Recruitment rates were such that the timing of IA3 allowed for the simultaneous conduct of IA3 and IA4 at 50% of Phase 3 enrollment (775 participants of 1550 planned).		

* Full final results for safety, efficacy, virology, and PK were provided.

3.2. Favourable effects

MK4482-002 was a double blind and placebo-controlled study. There was a dose-finding part (Part 1) and a confirmatory part (Part 2) with the selected 800 mg BID dose regimen. MK4482-002 Part 1 followed on from a preliminary dose-finding study that had a virologic primary endpoint (MK4482-006). MK4482-006 and -002 were conducted in a population of adults who were not hospitalised and not on supplemental oxygen at baseline.

In MK4482-002 Part 2, in contrast to MK4482-006 and MK4482-002 Part 1, eligible subjects were to be enrolled within 5 days of symptom onset and were to have at least one underlying condition listed in the protocol as potentially predisposing them to develop severe COVID-19. The selection criteria reflected the results of Part 1, which suggested that the maximum benefit of molnupiravir likely occurs when treatment starts within 5 days of symptom onset and in a population with some risk of progression up the WHO COVID-19 11-point severity scale. Part 2 involved stratification at randomisation according to time from symptom onset (TSSO) to randomisation (≤3 days, >3 days).

The protocol for MK4482-002 laid down criteria to subdivide subjects into those with mild or moderate disease at baseline, mainly based on presence of one of shortness of breath on exertion, tachypnoea or tachycardia. Very importantly, although the study allowed subjects to receive supplemental oxygen to treat COVID-19 at up to 4L/min, none was actually receiving supplemental oxygen at the time of enrolment into Part 1 or 2. Therefore, the population in which efficacy was shown was not on supplemental oxygen, had at least one risk factor for progression and started treatment within 5 days of symptom onset.

In the selected population, the primary endpoint of all-cause hospitalisation (as defined by the applicant) or death up to Day 29 was appropriate. The primary analysis was conducted in the MITT (all-treated) population in which unknown survival was counted as failure. There was no pre-planned hypothesis testing in Part 1 and subjects enrolled into Part 1 were not included in analyses of Part 2, which stands alone. Part 2 was planned

to have overall power of 97% to demonstrate superiority of molnupiravir 800 mg BID over placebo at an overall one-sided, 2.5% alpha level, if the underlying treatment difference (MOV minus placebo) in the percentage hospitalised and/or dying through Day 29 was -6 percentage points. The assumptions made were based on emerging evidence from various clinical trials and were reasonable.

The four planned interim analyses were generally appropriate given the lack of any prior evidence of efficacy based on a clinically relevant endpoint. In the final event, IA3 was not required since enrolment into Part 2 progressed quickly so IA3 and IA4 were combined.

At the time of IA3/4 with 755 subjects included, just under 15% were aged >60 years. Using the applicant's definitions, ~44% had moderate and 56% had mild disease. About half of subjects had TSSO within 3 days at the time of randomisation. Overall, 18.2% were already seropositive for SARS-CoV-2 at baseline and 85.5% had a positive RT-PCR result at a local laboratory. Only 26 (3.4%) treated subjects did not have a positive RT-PCR either from the local or the central laboratory, i.e. they had only a positive antigen detection test for SARS-CoV-2.

- In the MITT population, which comprised 98.3% of those enrolled, IA3/4 gave a statistically significantly lower rate of all-cause hospitalisations and deaths through Day 29 in the molnupiravir group, with a reduction from 14.1% to 7.3%. The 95% confidence intervals around the difference did not span zero and the p-value was 0.0012. There were 8 documented deaths in the placebo group and none in the molnupiravir group. One additional placebo group subject had an unknown outcome at day 29. The Kaplan-Meier curve for hospitalisations and deaths showed separation between groups from Day 3 onwards. Results of a sensitivity analysis which excluded those who received <5 doses or who were hospitalised or died before their 5th dose were consistent with the results of the primary analysis.

- In the planned sensitivity analysis in which only hospitalisations and deaths considered to be COVID-related were counted, the totals in each group were reduced by 3 subjects, giving rates of 6.5% vs. 13.3% and 95% CI around the difference that did not span zero.

The applicant clarified that 75 (19.4%) in the molnupiravir group and 100 (26.4%) in the placebo group received concomitant (Day 1 through Day 29) systemic corticosteroids in MK-4482-002 Part 2. Other than systemic corticosteroids, ≤3% used other medications for COVID-19. For those who received corticosteroids before hospitalisation, the rates for hospitalisation or death were 11.7% (7/60) in the molnupiravir group and 22.5% (16/71) in the placebo group. For the majority that did not receive corticosteroids, the rates were 6.5% and 12.1%, respectively.

Given that >98% of subjects entering this study had a baseline score of 2 following the WHO-11 point scale score, this study was not powered to detect a difference in reduction in scores by Day 29.

At the time of stopping recruitment, and when data were available for up to Day 29 from the total 1433 enrolled, based on the total 1433 randomised, treatment with molnupiravir significantly reduced the risk of hospitalisation or death through Day 29 but the magnitude of treatment effect was reduced from 6.8 percentage points at IA3/4 to 3 percentage points for the total Part 2 population. Compared to the IA4 data, there were 2 new deaths – one in each group. In the molnupiravir group there were 20 additional instances of hospitalisation (28 vs. 48) compared to an increase by 15 events in the placebo group (52 vs. 67).

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3.3. Uncertainties and limitations about favourable effects

Part 1 did not provide strong support for progressing to Part 2 with 800 mg BID. The applicant conducted some exposure-response analyses to support dose selection, which are found unconvincing. Nevertheless, with no rate-limiting safety concerns, selection of the highest dose tested in Part 1 was reasonable.

There is also no rationale for 5 days of treatment although a 5-day course has been studied repeatedly with antiviral agents for treatment of influenza in outpatients.

The subjects enrolled into the four studies were unvaccinated with respect to SARS-CoV-2.

Since evidence points to an amelioration of COVID-19 by prior vaccination (i.e. vaccinated persons who get breakthrough disease tend to fare better than unvaccinated persons with COVID-19), it is expected that the magnitude of benefit of molnupiravir in vaccinated persons will be less than that documented in MK4482-002 Part 2.

- From IA3/4, the subgroup analyses were generally in keeping with the primary analysis except for the seropositive subgroup. In the seronegative majority (based on SARS-CoV-2 nucleocapsid antibodies) the analysis of the primary endpoint gave rates of 7.7% for molnupiravir and 17.1% for placebo (95% CI -14.9, -4.1). In contrast, in the subgroup seropositive for SARS-CoV-2 anti-N at baseline (approximately 18% in each group), there was no difference between intervention groups in the percentages who were hospitalised or died (2.9% in both groups). Similar findings applied when serostatus was defined by anti-spike NA at baseline.

- In this unvaccinated study population, the presence of anti-N or NA at baseline in persons who presented within 5 days of symptom onset, with ~half within 3 days, is more likely to reflect prior natural infection rather than an early primary immune response to the presenting episode. Prior natural infection would have primed the immune system, giving a rapid immune memory response to the presenting episode with blunting of disease severity. Therefore, the result in the baseline seropositives is as expected, with low and similar progression rates in the molnupiravir and placebo groups.

Based on the total 1433 subjects enrolled into study 002 Part 2, although the final analysis for all 1433 subjects yielded a statistically significant difference between molnupiravir and placebo, the magnitude of effect was very much less than that observed at the time of IA4.

Most importantly, the final estimate of a 30% reduction in hospitalisation/death rates was derived from a ~50% reduction achieved in the IA3/4 population and no demonstrable efficacy in the post-IA3/4 population. Moreover, in the first 40% enrolled the rates for hospitalisation and death were 20/291 (6.9%) for molnupiravir vs. 43/287 (15.0%) for placebo. However, for the latter 60% enrolled, the rates were 28/418 (6.7%) vs. 25/412 (6.1%).

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Table 88: Hospitalisation or Death by D29

	Interim Analysis Population Enrollment Dates: 5/7/2021 – 08/5/2021		Post-Interim Analysis Population[a] Enrollment Dates: 8/6/2021 – 10/2/2021		Full Population Enrollment Dates: 5/7/2021 – 10/2/2021	
	MOV	PBO	MOV	PBO	MOV	PBO
Hospitalization or death by Day 29	28/385 (7.3%)	53/377 (14.1%)	20/324 (6.2%)	15/322 (4.7%)	48/709 (6.8%)	68/699 (9.7%)
Death by Day 29	0 (0%)	8/377 (2.1%)	1/324 (<1%)	1/322 (<1%)	1/709 (<1%)	9/699 (1.3%)

[a]The Post-Interim Analysis Population includes those participants who had not reached Day 29 by the interim analysis data cutoff date of 9/18/2021.

The small difference between IA3/4 and post-IA3/4 populations for hospitalisation/death rates in the molnupiravir group but reduction in the placebo group pointed to a change during the study in the way that the background population responded to natural infection with SARS-CoV-2. It seems that the background progression rate (as estimated in the placebo group) was reduced to such an extent that intervention with molnupiravir was not able to achieve a significant improvement over placebo for the primary endpoint.

The findings for the primary endpoint in the IA3/4 vs. post-IA3/4 populations raised concern that, leaving aside the fact that P002 enrolled only unvaccinated persons, it may be that molnupiravir would not be clinically beneficial in a population with a high rate of natural priming and/or boosting by contact with SARS-CoV-2, with or without clinical illness. It is therefore relevant to note that there was no demonstrable efficacy for molnupiravir in IA3/4 or post-IA3/4 populations in subgroups seropositive at baseline for anti-N or anti-spike NA. However, it is also notable that there was efficacy for molnupiravir among baseline seronegative subjects at IA3/4 but there was no demonstrable efficacy in baseline seronegatives in the post-IA3/4 population. However, persons who have been primed may have a milder course of disease even if they no longer have detectable antibody against nucleocapsid or spike protein when infected because they would have a rapid immune memory response that may involve activation of both humoral and cellular immunity. Therefore, it cannot be ruled out that one contributing factor to the reduction in background progression rates between IA3/4 and post-IA3/4 populations was an increasing natural infection rate with time.

Reflecting the marked drop in rate of hospitalisations/deaths in the placebo group in the non-IA3/4 vs. the IA3/4 population, with no appreciable change in the molnupiravir group, the rates broken down by subgroups mostly reflected the overall finding. Nevertheless, the magnitude of the difference between IA3/4 and post-IA3/4 rates is variable. Some observations of note include:

- In subjects aged 60+ years, the hospitalisation/death rate did not change in the molnupiravir group (10% IA3/4 and 10.3% post-IA3/4) but fell from 21.8% to 5.6% in the placebo group.
- In non-obese subjects, the hospitalisation/death rate hardly changed in the molnupiravir group (11.4% IA3/4 and 10.5% post-IA3/4) but fell from 18.8% to 4.2% in the placebo group.
- In patients with diabetes mellitus, the hospitalisation/death rate changed in the molnupiravir group (18.4% IA3/4 and 13.8% post-IA3/4) but fell from 23.2% to 6.6% in the placebo group.

These data suggest that there was a marked drop in the background (placebo) rate of COVID-19 progression in subjects with and without a risk factor.

- In Latin America, the hospitalisation/death rate hardly changed in the molnupiravir group (7% IA3/4 and 6.1% post-IA3/4) but fell from 14.5% to 3.5% in the placebo group. A reflective pattern occurred in those of Hispanic/Latino ethnicity.
- In contrast, in Europe there were falls in the hospitalisation/death rate in the molnupiravir group (9% IA3/4 and 3.6% post-IA3/4) and in the placebo group (13.8% to 4.1%).

These data suggest that there was a marked drop in the background (placebo) rate of COVID-19 progression in several regions where there was substantial enrolment. The fact that the rate in the molnupiravir group also seemed to drop in Europe is interesting. However, it seems that the majority of subjects in "Europe" were actually enrolled in the Russian Federation since the denominators for FR, DE, ES, IT and UK are very small.

- For those with no detectable anti-N antibody at baseline, the hospitalisation/death rate changed from 8.1% to 6.8% in the molnupiravir group but fell from 16.4% to 6.3% in the placebo group. For those seropositive for anti-N at baseline, there continued to be no discernible benefit for molnupiravir (2.8% vs. 2.9% for placebo at IA3/4 and 4.4% vs. 0% post-IA3/4).
- For those with no detectable anti-spike NA at baseline, the hospitalisation/death rate changed from 8.4% to 7.0% in the molnupiravir group but fell from 16.5% to 7.4% in the placebo group. For those seropositive for anti-spike NA at baseline, there was no discernible benefit for molnupiravir (3.7% molnupiravir vs. 4.2% placebo at IA3/4 and 4.6% vs. 0% post-IA3/4).

In those seronegative based on anti-N or anti-spike NA, the pattern for hospitalisation rates followed that overall, with marked drops only in the placebo group from IA3/4 to post-IA3/4. For those seropositive based on either assay the risk of progression was very low even at IA3/4 and there was no detectable benefit for molnupiravir in the IA3/4 or post-IA3/4 populations.

In the post-IA3/4 population, there is no subgroup found within which the results demonstrate a benefit of molnupiravir treatment vs. placebo. Therefore, even if it were to be considered that some sort of restricted indication based on post hoc analyses in subgroups might be justifiable in the context of the ongoing pandemic, the results of the investigation do not allow identification of a sub-population in which there is clear efficacy for molnupiravir during the entire study.

The applicant's general conclusion that there is no single factor or group of factors identified that explains the change in pattern of hospitalisation/death rates between the IA3/4 and the post-IA3/4 populations was agreed. While there were differences between the IA3/4 and post-IA3/4 populations, most of these occurred in both the molnupiravir and placebo groups to a similar extent. Even these changes could have contributed to the overall finding since any shift towards a population less at risk of hospitalisation/death could have led to the lower rate in the placebo group. With no additive effect on the rate already achieved by molnupiravir, the overall result would be no demonstrable treatment benefit for molnupiravir over placebo.

There were a few imbalances in the IA3/4 population that may have augmented the treatment difference that was seen in the IA3/4 analysis (e.g. higher proportion of males and higher proportion with 2+ risk factors in the placebo group). Any imbalances between treatment groups within the post-IA3/4 population leading to a lower rate in the placebo group and/or a higher rate in the molnupiravir group for any factor predisposing to progression of COVID-19 could contribute to reducing the overall difference between treatments. The applicant's investigation has pointed to several such imbalances that, taken together, may have contributed to the overall result.

There were differences in regional or country-specific enrolment between IA3/4 and post-IA3/4 populations. The IA3/4 population included 66 in Brazil with a marked difference in progression rate favouring molnupiravir.

Other countries with fairly substantial enrolment and rates favouring molnupiravir in the IA3/4 analysis were Colombia, Mexico, Russia and S. Africa. The post-IA3/4 population included very few in Brazil, far fewer in Colombia and fewer in S. Africa. At the same time, numbers in Mexico were not reduced and numbers in Russia increased but both showed a loss of difference in rates between molnupiravir and placebo. Meanwhile numbers enrolled in Guatemala were higher in the post-IA3/4 population with 5 cases of progression in the molnupiravir group and none in the placebo group. There are no obvious explanations for these changing patterns of rates.

Shifts in proportions with mild or moderate COVID-19 at baseline or proportions treated within 3 days do not seem likely to have contributed to the findings.

By region of enrolment, the non-IA3/4 population included >40% Europeans vs. 23% in the IA3/4 population. Since very few EU countries are listed in the appendix tables 14 and 15, it seems that the majority of these "Europeans" were enrolled in the Russian Federation because otherwise the total numbers reported could not be explained. The applicant reported that Europe (including Russia) had the highest rate for positive baseline anti-spike NA (29.1% molnupiravir and 34.3% placebo). As already noted above, there was no benefit of treatment detected in baseline seropositives, whether based on anti-N or anti-spike NA levels.

In the subjects with anti-N at baseline, the change from baseline (log_{10} copies/mL) was comparable between molnupiravir and placebo groups on days 3 and 5 as well as at the post-treatment visits. In the baseline seronegatives, the magnitude of change from baseline was somewhat greater on days 3 and 5 compared to baseline seropositives but this observation applied in molnupiravir and placebo groups and the difference between treatments was very small.

When comparing the IA3/4 and post-IA3/4 populations, there was a slightly higher proportion in the molnupiravir group with low baseline load at IA3/4 and high baseline load at post-IA3/4 vs. the placebo group. However, the hospitalisation/death rates in those with low or high baseline loads were not substantially different between IA3/4 and post-IA3/4 populations in the molnupiravir group (5.4 and 5.6 low; 9.5 and 7.9 high) whereas there were falls in the placebo group (7.7 to 2.9 low; 18.5 to 6.3 high). Furthermore, with a maximum difference between molnupiravir and placebo for change in viral load from baseline of 0.42 log_{10} copies/mL, observed in the IA3/4 population on day 5, none of the differences are notable. Also, the difference between treatments on day 3 was -0.20 in the IA3/4 population and -0.21 in the post-IA3/4 population although the respective differences on day 5 were -0.42 compared to -0.14. Effectively, even the largest difference between molnupiravir vs. placebo in change from viral load from baseline was small in magnitude.

The distribution of clades did change between IA3/4 and post-IA3/4 populations, but the changes were similar in the molnupiravir and placebo groups. Also, up to 30% had missing data. These changes may partly reflect changes in recruitment rates by region and partly shifts in clades over time. At IA3/4 the hospitalisation/death rates were lower with molnupiravir vs. placebo except for delta 21J (11/99 [11.1%] molnupiravir and 12/95 [12.6%] placebo). In the post-IA3/4 population there were too few with gamma or mu variants to comment. For delta 21I a benefit of molnupiravir (8.6 vs. 24.1% at IA3/4) was no longer apparent based on somewhat lower denominators. For delta 21J, with substantial denominators also in the post-IA3/4 population, there continued to be no benefit for molnupiravir although rates were lower in both

treatment groups (6.5% and 5%). Due to the timing of the study there were no infections with omicron treated.

Treatment with molnupiravir did not interfere with the development of anti-spike NA or anti-N antibody to any marked extent based on day 10 and day 29 proportions with detectable antibody with either assay. The proportion with detectable antibody at baseline was higher in the post-IA3/4 population but this observation applied to a broadly similar extent in both molnupiravir and placebo groups.

The applicant considered other factors that could have influenced the changes in the molnupiravir or placebo group hospitalisation/death rates over time. Since the population enrolled was non-hospitalised and not requiring oxygen at baseline, there were no major changes in approved medications during the course of the study given that monoclonal antibodies and investigational agents other than molnupiravir were prohibited. There was some use of corticosteroids in these outpatients (in low percentages) but the pattern of usage does not explain the findings.

Other management modalities could have changed during the period of subject participations in IA3/4 and post-IA3/4 populations but, in a double-blind setting, it is not likely that these would have been applied at different rates in the two treatment groups. Although a major change in management that reduced the background (placebo) rate of hospitalisations/deaths could have contributed to the overall results, there does not seem to have been such a change that can be pinpointed during the course of the study.

In light of the fact that the investigations have failed to pinpoint the reason(s) for the lack of demonstrable treatment effect in the post-IA3/4 population and given the major concern that the efficacy shown at IA3/4 may not be representative of what could be expected in the current EU population, the applicant was requested to consider provision of additional efficacy data that could be regarded as more relevant to the EU in 2022.

Of the studies identified by the applicant as being of relevance, the UK PANORAMIC study included a population enrolled from Dec 8 2021 onwards, when BA.1 and BA.2 were the most common variants in circulation. The vaccination history and natural exposure status of UK residents is broadly in line with that of the majority of EU MS, leading to findings that would most likely also apply across Europe. Although this was an open label study, the decision to hospitalise a subject would have followed general NHS as well as any operative local admission policies and would not likely be affected by knowledge of whether the subject was taking/had taken molnupiravir. With high vaccination rates and prior exposure rates leading to some degree of cross-protection at least against developing severe forms of COVID-19, accompanied by the abovementioned change in predominant circulating variants, the actual hospitalisation and death rate was <1% in the MOV+SOC and SOC groups, such that no benefit for molnupiravir could be demonstrated based on the primary endpoint in a population likely typical for Europe in 2022. The same conclusion applied in the subgroup analysis of the primary endpoint.

In this open-label study, subjects completed online symptom diaries for 28 days and rated a range of symptoms. There was a benefit for molnupiravir of 4.2 (95% BCI: 3.8 – 4.6) days in time-to-first-recovery (TTR) giving a posterior probability of superiority of >0.999. The estimated median TTR for molnupiravir was 10.3 days vs. 14.5 days for SOC, giving a hazard ratio [95% BCI] of 1.36 days, which met the pre-specified superiority threshold. Subgroup analysis demonstrated that this benefit for molnupiravir was consistent across all studied groups.

The results suggest that addition of MOV to SOC is not at all likely to have any important effect on hospitalisation or death rates in a typical current EU population. The study suggests that MOV may be able to shorten the duration of symptomatic disease by several days even in a heavily vaccinated and/or exposed

population infected with omicron variants. However, the study was entirely open-label and the symptom-related endpoints all depend on subjective perceptions recorded by subjects themselves in an online diary. The study is not considered adequate to serve as sole evidence of a potential benefit for MOV in terms of shortening the duration of the illness.

It was therefore potentially relevant to examine the results for symptom resolution in MK-4482-002 since this had a double-blind design. The study had a secondary objective to evaluate the efficacy of MOV compared to placebo as assessed by time to sustained resolution or improvement and time to progression of each targeted self-reported sign/symptom of COVID-19 from randomisation through Day 29. The study did not seek to determine time to resolution of all baseline signs and symptoms or time to self-reported recovery.

For the IA3/4 population, despite a benefit for MOV in terms of the hospitalisation/death rate, there was no consistent benefit for MOV over placebo for improvement or resolution of the individual signs and symptoms captured. In the post-IA3/4 population, there was no apparent benefit for MOV over placebo for improvement or resolution of the individual signs and symptoms captured. Therefore, the findings in the open-label study PANORAMIC are not supported by the data on improvement or resolution of signs and symptoms in the double-blind study MK-4482-002.

The majority of the other studies identified by the applicant was retrospective and concerned outpatients or inpatients not requiring supplemental oxygen due to COVID at time of admission. Not all had necessarily been admitted primarily due to COVID-19. Some were conducted in special populations. Many were conducted during or using data from the omicron wave although the predominant sub-variant varied. None was double-blind and placebo controlled. Several used matched controls using different methods (commonly propensity score matching) and varying ratios for the matching process. Adherence to MOV dosing is not always known or even reported and it is not always known if MOV was started within 5 days of symptom onset. Moreover, different algorithms were in place across the studies regarding selection of patients for treatment.

There was no consistent finding of a benefit for MOV in the populations studied. Some studies suggested a benefit for MOV in preventing disease progression in certain higher risk subgroups, such as those aged >75 years and those inadequately vaccinated for COVID-19. Nevertheless, these published studies must be interpreted with some considerable degree of caution. Taking the reports at face value, MOV may have some benefit vs. no treatment in unvaccinated or inadequately vaccinated persons with risks for progression of COVID-19. Overall, the data do not provide strong or consistent support for the use of MOV to prevent hospitalisation or death in 2022. Furthermore, although there are some suggestions that MOV may be of benefit in some sub-populations, the data cannot be used to identify specific patient groups that might be reflected in a restricted indication for use.

The applicant also reported three randomised, prospective and open-label studies conducted by licensees in India. The populations enrolled were not relevant to the current EU population, not only in terms of age restriction but also in terms of negligible vaccination rates and no requirement for risk factors for progression. In all three studies, the primary endpoint was hospitalisation rate within 14 days, with a different definition of hospitalisation vs. that used in MK-4482-002. Two of the three studies did not show a benefit for MOV vs. SOC for the primary endpoint due to the low number of events. In the Hetero Labs study there was a significant reduction in hospitalisation rate with molnupiravir with an actual difference of <3 percentage points (1.5% vs. 4.3%). The three studies suggested that MOV can shorten the time to recovery, but they were all open-label.

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3.4. Unfavourable effects

At the time of filing the MAA, of the 1069 subjects who had been exposed to molnupiravir at the time of preparing the tables, 593 had received 800 mg BID for up to 5 days and 587 of this number had COVID-19. The vast majority was enrolled in MK4482-002 so they provide safety data for the target population. This total is considered appropriate in light of the intended usage of molnupiravir.

During the procedure, safety data were provided for the total 1433 enrolled. Generally, these additional data did not change the conclusions on safety.

For all AEs and for drug-related AEs there was no clear trend to a major effect of molnupiravir dose on the safety profile. For the most part the overall rates AEs and rates for individual PTs have overlapped between molnupiravir and placebo groups. Relatively few AEs have been Grade 3 or 4 and there has been no excess of these in molnupiravir-treated subjects.

The applicant has paid close attention to any possible effects of molnupiravir on bone marrow, including any events of thrombocytopenia. Thus far, the clinical data do not point to an issue arising from a 5-day treatment course with 800 mg BID.

There was a subject in MK4482-004 with pruritus and rash who discontinued. There have also been AEs of urticaria and rashes not thought to be treatment-related. For example, in MK4482-002, 5 (1.3%) in the molnupiravir 800 mg BID group and 1 in the placebo group had a rash, regardless of relatedness. Although no SAEs likely to represent severe hypersensitivity reactions were reported, there is a risk for hypersensitivity reactions to molnupiravir. Relevant ADRs reported have been reflected in the table in section 4.8 of the SmPC.

In MK4482-001 Part 1, counting AEs that led to death with onset during treatment and the 14-day follow up period regardless of the timing of the death, there were 16 subjects with fatal AEs. This number included 6 in the 200 mg group, 4 in the 400 mg group, 4 in the 800 mg group and 2 in the placebo group. Most deaths occurred in participants who had severe COVID-19 at baseline (12/16), were >60 years of age (13/16), had underlying comorbidities (14/16) and/or had duration of COVID-19 symptoms >5 days before randomisation (12/16). None of the deaths was considered treatment-related by investigators. With small groups and with no dose-related trend, it seems unlikely that molnupiravir contributed to death and the distribution by treatment group may have arisen by chance.

Rates for SAEs have not been higher with molnupiravir and much of the difference vs. placebo in MK4482-002 was driven by the rate of worsening of COVID-19 in the placebo group.

3.5. Uncertainties and limitations about unfavourable effects

The applicant did not conduct a TQT study but did collect ECGs in MK4482-004, which did not suggest any clinically important effect of molnupiravir on cardiac conduction. The safety results from the clinical studies did not indicate an association between molnupiravir and bradycardia. However, 12 reports of bradycardia were submitted and reviewed, as result of the of which four could be considered to have a probable relationship to molnupiravir while two had at least a possible causal relationship. Based on these reports, bradycardia would be an element to be considered as an ADR with an appropriate estimated frequency in the table in section 4.8 of the SmPC and reflected in section 4 of the PIL. However, in light of the negative outcome this is not further pursued.

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An effect of molnupiravir on transaminase levels cannot be ruled out at present but this issue cannot be addressed without additional experience of use in larger numbers.

There is an additional potential safety concern arising from the nonclinical data. In a preliminary embryo-fetal development (EFD) study in rats, significant maternal and developmental toxicity was noted at 1000 mg/kg (margin of exposure of 7.5 fold at RHD). Increases in post-implantation loss as well as reduced fetal body weights were seen. In addition, malformations occurred including abnormal and/or small eye/eye socket, absent kidney, rib malformations and thoracic and lumbar vertebra malformations. The definitive EFD study used a maximum of 500 mg/kg with no molnupiravir-related malformations observed. The only developmental toxicity was decreased fetal weights at 500 mg/kg (margin of exposure of 2.9 fold at RHD). The NOAEL for maternal and developmental toxicity in rats was 250 mg/kg, which represents a margin of exposure of 0.8 fold the NHC exposure measured at the RHD.

In rabbits, the preliminary EFD study identified maternal toxicity at 1000 mg/kg with effects on body weight and food consumption similar to those in rats. No developmental toxicity was reported at any dose level. For the definitive study, the maximum dose used was 750 mg/kg. At doses ≥ 400 mg/kg maternal toxicity was noted and the proposed NOAEL for maternal toxicity was 125 mg/kg (margin of exposure of 1.5 fold).

Developmental toxicity effects in the definitive study in rabbits and attributed to molnupiravir were limited to decreased live fetal weights at 750 mg/kg (margin of exposure of 18-fold at RHD). However, the study report has an increased number of visceral malformations seen in the 400 and 750 mg/kg groups with 6 foetuses from 6 different litters affected in the top dose group compared to 2 in the control group. Although the incidence is low, 2/6 of these malformations were absent kidney, which was also seen in the study in rats. Furthermore, there are effects seen on the gallbladder, which are not evident in control animals. At the applicant's NOAEL for developmental toxicity of 400 mg/kg a margin of exposure of 6.5 fold.

While an absolute contraindication for use in pregnancy and breastfeeding is not thought to be necessary, the draft SmPC recommendation to avoid molnupiravir during pregnancy and lactation is appropriate. The advice that WOCP should use contraception during treatment and for at least 4 days after the last dose is appropriate, along with the advice not to resume breastfeeding for 4 days after the last dose. This 4-day window is based not only on the plasma half-life of NHC but also on recognition that NHC-TP persists in host cells beyond the plasma half-life. Thus, the 4-day window is considered conservative but supportable.

3.6. Effects Table

Table 89: Effects Table for Molnupiravir based on IA3/IA4

Effect	Short Description	Unit	MOV	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects in MK4482-002 Part 2 – 800 mg BID						
Rate of hospitalisation or death					6.8 percentage point hospitalisation or death Consistent across subgroups except in baseline	
	Anti-N Seronegative Seropositive	n/N (%)	 25/307 (8.1%) 2/71 (2.8%)	 49/298 (16.4%) 2/70 (2.9%)	No benefit detectable in baseline seropositive subjects; same applied based on anti-Spike NA serostatus	MK4482-002 Part 2 Tables
	As above but COVID-19-related only		25/385 (6.5%)	50/377 (13.3%)	6.8 percentage point reduction in risk of hospitalisation or death (95% CI: 2.6, 11.1) Consistent with results of primary analysis	
Unfavourable Effects in MK4482-002 Part 2 – 800 mg BID						
AE rates						
	AEs		135/386 (35%)	150/379 (39.6%)		
	SAEs		28/386 (7.3%)	53/379 (14%)		
	Deaths*		0/386	10/379 (2.6%)		

Effect	Short Description	Unit	MOV	Placebo	Uncertainties/ Strength of evidence	References
	Deaths in P001 Part 1 200 mg BID 400 mg BID 800 mg BID		6 (8.2%) 4 (5.5%) 4 (5.6%)	2 (2.7%)		

*There were no deaths in molnupiravir-treated subjects in MK4482-002, 004 or 006

Abbreviations: SAEs: serious adverse events, AEs: adverse events

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In IA3/4 of Part 2 of study 002, molnupiravir 800 mg BID when started within 5 days of symptom onset provided a statistically significant reduction in the rate of hospitalisation or death in subjects who were not receiving supplemental oxygen at study entry and who had at least one of the protocol-listed risk factors for progression to severe COVID-19. The revised indication statement reads: *Lagevrio is indicated 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.*

The results for the total 1433 subjects enrolled raise many questions about the clinical importance of the treatment effect observed for the total population. Moreover, the result for the primary endpoint in the all-randomised population is not robust to alternative assumptions about the missing data mechanism. There were only 3 subjects with an unknown outcome (1 in the MOV group, 2 in the placebo group) in the MITT population and these subjects were already included in IA4. While the point estimate of the treatment effect on incidence of hospitalisation or death through day 29 in the worst-case analysis was generally consistent with the primary efficacy analysis, it is not possible to exclude a conclusion of no treatment effect based on the 95% confidence interval [adjusted risk difference = -2.7% (95% CI: -5.6%, 0.2%); nominal 1-sided p-value = 0.0340]. Thus, the robustness of the treatment effect estimate in the all-randomised population can be questioned, even if poolability of the stage-wise results could be accepted.

The much smaller treatment effect for the full population vs. IA3/4 reflects no demonstrable efficacy in the population that was not included in IA3/4. The result for the post-IA3/4 population reflected no appreciable change from IA3/4 for the hospitalisation/death rate in the molnupiravir group but a marked drop in the background (placebo group) rate.

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This pattern applied across almost all subgroups examined, including those who were seronegative at baseline for anti-N or for anti-spike NA. There was no efficacy demonstrable for molnupiravir in baseline seropositives in IA3/4 or post-IA3/4 populations. The possible reasons for the differences between IA3/4 and post-IA3/4 results for the primary endpoint have been explored but it has not been possible to pinpoint one or a specific group of factors that fully explain the findings.

Since the population enrolled into P002 Part 2 was unvaccinated, the result at IA3/4 (6.8 percentage point reduction in hospitalisation/death rate) likely over-estimates the benefit of molnupiravir in the current EU population.

Adding to this issue the lack of demonstrable efficacy for molnupiravir, reflecting its inability to improve on the relatively low background hospitalisation/death rate in the placebo group in the post-IA3/4 population, there must be a major concern that the post-IA3/4 results are much more relevant to the current EU population (being both highly vaccinated and highly naturally primed) than the IA3/4 results.

The applicant provided additional information from published and unpublished studies conducted in late 2021 or 2022 and potentially of relevance to the targeted patient population. However, these were not prospective randomised and controlled studies and their observational nature raises the potential for bias (e.g. related to measurement of drug exposure, timing and outcomes, selection of comparator and methods of adjustment) as well as various confounding factors. Moreover, the method applied by the applicant to identify, select and appraise the strengths and limitations of each study based on RWD was not clear or consistent. The approaches taken within the studies to mitigate the risk and potential effect of biases on results should have been described in detail to support the selection of studies and the strength of the evidence. Moreover, the relevance of some of the studies to the EU population was not sufficiently justified. In conclusion, the RWD presented were not considered sufficient to address the concerns raised by the inconsistent results of MK4482-002 Part 2.

Therefore, the clinical benefit of MOV in patients with COVID-19 who are not receiving supplemental oxygen and who are at increased risk for progression to severe COVID-19 cannot be determined from the available data. Furthermore, there was insufficient evidence to be able to identify a specific sub-population of patients in whom a clinically important benefit of MOV can be anticipated.

The safety profile of molnupiravir when administered at 800 mg BID for 5 days (10 doses) is generally similar to that of placebo. The potential concerns regarding effects of molnupiravir on bone marrow do not appear to be clinical concerns when treatment is restricted to 800 mg BID for up to 5 days.

An excess of deaths with molnupiravir vs. placebo was seen only in MK4482-001 Part 1 and there is no evidence of a relationship to dose. With relatively small denominators, the differences in numbers may have arisen by chance. The data from treated outpatients does not raise concern about deaths in the molnupiravir groups.

In light of the nonclinical findings, noting that the target population is confined to adults at this time, it is appropriate that Section 4.6 of the SmPC advises that use of molnupiravir is not recommended during pregnancy or breastfeeding with a 4-day post-treatment window for use of contraception and avoidance of breastfeeding. Advice on male and female contraception has also been instituted.

3.7.2. Balance of benefits and risks

There is a marked discrepancy between the results of P002 Part 2 at IA3/4 and for the post-IA3/4 population. Although P002 Part 2 was planned with an interim inferential analysis (IA3/4; 6.8 percentage point difference for the primary endpoint) and a final analysis (3 percentage point difference for the primary endpoint), the final result masks a complete lack of demonstrable efficacy in the post-IA3/4 population (indeed, in the last 60% enrolled into the study). Given the characteristics of the study population and the timing of the study, it cannot be dismissed that the result for the post-IA3/4 population is the more relevant to the current EU population.

Additional published data were provided. However, the clinical benefit of molnupiravir in subjects with COVID-19 who are not receiving supplemental oxygen and who are at increased risk for progression to severe COVID-19 cannot be determined from the available data.

Meanwhile, the applicant maintains that P002 showed a convincing benefit for molnupiravir and uses the RWD to derive a revised indication as follows:

Lagevrio is indicated for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are:

- *aged 65 years and older or*
- *aged 18 to <65 years who are at increased risk of progressing to severe COVID-19 and for whom alternative COVID-19 treatment options are not available or clinically appropriate.*

Healthcare providers should consider local treatment guidelines in assessing whether an individual is at increased risk for progressing to severe COVID-19.

The claimed indications for use in persons older than 65 years and for younger persons with risk for progression are not substantiated by the applicant's study or by RWD. While some studies suggest that there could be a benefit either in terms of preventing hospitalisation and/or death or facilitating faster recovery, the data do not suffice to support these specific statements.

The applicant attended an oral explanation. However, it was considered by the Committee that the uncertainties for efficacy remained after that and therefore that overall, the efficacy of Lagevrio has not been shown with the current data (see conclusion for clinical efficacy). Moreover, in the absence of randomisation, RWD cannot be ascertained that potential bias is controlled. The methodology to select and appraise the quality of the studies presented was not clear. The RWD studies presented are considered not sufficient to override the concerns raised by the inconsistent results of MK4482-002 Part 2.

In conclusion, the clinical benefit of molnupiravir in patients with COVID-19 who are not receiving supplemental oxygen and who are at increased risk for progression to severe COVID-19 cannot be determine based on the totality of the evidence provided. Thus, it is not possible to conclude that MOV can reduce the risk of hospitalisation or death in any population neither to conclude that MOV will shorten the duration of illness/time to recovery in any population.

In addition, it is not possible to identify a specific sub-population of patients in whom a clinically relevant benefit of molnupiravir can be anticipated in order to support an indication for use in an alternative (further restricted) indication statement.

3.7.3. Additional considerations on the benefit-risk balance

N/A

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3.8. Conclusions

The overall benefit/risk balance of Lagevrio is negative.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy for Lagevrio in the proposed indication, the CHMP considers by consensus that:

Th efficacy of the above-mentioned medicinal product is not sufficiently demonstrated and, therefore recommends the refusal of the granting of the marketing authorisation for the above-mentioned medicinal product. The CHMP considers that:

Whereas:

The applicant's conclusion that molnupiravir showed a convincing clinical benefit in patients with COVID-19 who are not receiving supplemental oxygen and who are at increased risk for progression to severe COVID-19 cannot be agreed on. In addition, it is not possible to conclude that molnupiravir can reduce the risk of hospitalisation or death in any population or to conclude that molnupiravir will shorten the duration of illness/time to recovery in any population. Finally, it is not possible to identify a specific sub-population of patients in whom a clinically relevant benefit of molnupiravir can be anticipated in order to support an indication for use in an alternative (further restricted) indication statement. In particular, the CHMP considers:

- While the pivotal study MK4482-002 Part 2 was statistically positive in a pre-planned interim analysis, the concluding part of the trial, of almost a similar size as the pre-interim analysis part, did not show any effect at all on the primary endpoint. Due to this inconsistency of outcomes, MK4482-002 Part 2 did not confirm the efficacy of Lagevrio.
- The open label PANORAMIC study did not show an impact on its primary endpoint, hospitalisation or death. Although the study pointed to a benefit for molnupiravir in terms of time to recovery, this study is not blinded and therefore not adequate to support this claim. Notably, the applicant's double-blind study P002 did not seek to determine time to resolution of all baseline signs and symptoms or time to self-reported recovery. Data were reported from P002 on resolution of individual signs and symptoms. There was not a consistent effect of molnupiravir on time to sustained improvement or resolution of individual signs and symptoms in the IA3/4 or total study population and no effect of molnupiravir on these endpoints in the post-IA3/4 population.
- Data from three randomised, open-label studies conducted by licensees in India were submitted as supportive data. However, these were not considered sufficient to confirm the efficacy of Lagevrio, given the nature of endpoints and questionable external validity for the EU setting.
- RWD were presented to further support efficacy. However, in the absence of randomisation, it cannot be ascertained that potential bias is controlled. Moreover, the methodology to select and appraise the quality of the studies presented was not clear. The approaches taken within and/or across the studies to mitigate the risk and potential effect of biases on results should have been described in detail to support the selection of studies and the strength of the evidence. Moreover, the relevance of some of the studies to the EU population was not sufficiently justified. The studies presented are considered not sufficient to override the concerns raised by the inconsistent results of MK4482-002 Part 2.

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The CHMP is of the opinion that pursuant to Article 12 of Regulation (EC) No 726/2004, the efficacy of the above mentioned medicinal product is not properly or sufficiently demonstrated. Therefore, the CHMP has recommended the refusal of the granting of the marketing authorisation for Lagevrio.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and post-authorisation measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

Furthermore, following review of the available data in the context of the applicant's claim of new active substance status, the CHMP position at the time of this report is reflected in Appendix 5.1. However, in light of the negative recommendation, the CHMP is of the opinion that it is not appropriate to conclude on the new active substance status at this time.

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Document 3A.4

EMA Assessment Report of Lagevrio (January 27, 2022)

Document URL

https://www.ema.europa.eu/en/documents/referral/lagevrio-also-known-molnupiravir-mk-4482-covid-19-article-53-procedure-conditions-use-conditions_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-lagevrio-(also-known-as-molnupiravir-or-mk-4482)-for-treating-covid-19-section

License

Not applicable

27 January 2022
EMA/719664/2021 Rev. 1[1]
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure under Article 5(3) of Regulation (EC) No 726/2004

Use of molnupiravir for the treatment of COVID-19

INN: molnupiravir

Procedure number: EMEA/H/A-5(3)/1512

Note:

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

[1] Statement on BCS classification was updated

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List of abbreviations

Abbreviation	Definition
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase
APaT	all participants as treated
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC0-12	area under the concentration-time curve from time 0 to 12 hours
AUC0-τ	area under the concentration-time curve from time 0 to end of dosing interval
AUC0-inf	area under the concentration-time curve from time 0 to time infinity
AUC0-last	area under the concentration-time curve from time 0 to the time of the last measured concentration
BID	twice a day
BLOQ	below the limit of quantitation
BMI	body mass index
CHMP	Committee for Medicinal Products for Human Use
Cmax	maximum concentration
COVID-19	coronavirus disease 2019
CNS	central nervous system
CSR	clinical study report
CYP	cytochrome P450
DDI	drug-drug interaction
DFC	dry filled capsule
DILI	drug-induced liver injury
ECG	electrocardiogram
ECI	event of clinical interest
eDMC	external Data Monitoring Committee
eGFR	estimated glomerular filtration rate
EIDD	Emory Institute for Drug Development
EMA	European Medicines Agency
EOT	end of treatment
ER	exposure-response
ESRD	end-stage renal disease
EUA	Emergency Use Authorization
FaSSIF	fasted state simulated intestinal fluid
FDA	Food and Drug Administration
IA	interim analysis
IAV	Influenza A virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
IND	Investigational New Drug
IRT	Intervention randomization system
IV	intravenous
LLOQ	lower limit of quantitation
MAA	marketing authorisation application
mAbs	monoclonal antibodies
MAD	multiple-ascending dose
MERS-CoV	Middle East respiratory syndrome coronavirus
MHV	mouse hepatitis virus
MITT	modified intent-to-treat
MOV	molnupiravir (MK-4482)
NEWS	National Early Warning Score
NGS	next generation sequencing
NHC	N-hydroxycytidine
NHC-TP	N-hydroxycytidine-5´-triphosphate
NP	nasopharyngeal

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Abbreviation	Definition
OP	oropharyngeal
PCR	polymerase chain reaction
PIB	powder in bottle
PK	pharmacokinetic(s)
PO	oral administration
PopPK	population PK
Q12H	every 12 hours
RdRP	RNA-dependent RNA polymerase
RNA	ribonucleic acid
RT-PCR	reverse-transcriptase polymerase chain reaction
SAD	single-ascending dose
SAE	serious adverse event
SARS	Severe acute respiratory syndrome
SARS-CoV-2	SARS-associated coronavirus-2
SD	standard deviation
SGF	simulated gastric fluid
t1/2	apparent terminal half-life
Tmax	time of maximum concentration
ULN	upper limit of normal
ULOQ	upper limit of quantitation
US	United States
US FDA	United States Food and Drug Administration
VEEV	Venezuelan equine encephalitis virus
WHO	World Health Organization
WOCBP	women of childbearing potential

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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 can 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 molnupiravir, a prodrug that is metabolised to the ribonucleoside analogue N-hydroxycytidine (NHC) which distributes into cells where it is phosphorylated to form the pharmacologically active ribonucleoside triphosphate (NHC-TP). NHC-TP acts by a mechanism known as viral error catastrophe. NHC-TP incorporation into viral RNA by the viral RNA polymerase, results in an accumulation of errors in the viral genome leading to inhibition of replication.

It has demonstrated an antiviral effect *in vitro*, and in a clinical study, in which it reduced the risk of hospitalisation or death in non-hospitalised COVID-19 patients not requiring supplemental oxygen who were at risk for progressing to severe COVID-19.

These results are of relevance, and their application in the clinical setting before a formal marketing authorisation is granted 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 molnupiravir and on potential conditions for use with a view to supporting national decisions.

On 5 November 2021 the EMA's 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 molnupiravir for the treatment of confirmed COVID-19 in adult patients.

2. Scientific discussion

2.1. Introduction

Molnupiravir (also known as MK-4482, EIDD-2801 and MOV, proposed trade name: Lagevrio) is an investigational medicinal product being developed by Merck Sharp & Dohme in collaboration with Ridgeback for the treatment of COVID-19.

The proposed indication for molnupiravir, by the company, within the marketing authorisation application (MAA) under rolling review, is for the treatment of COVID-19 in adults.

Molnupiravir is presented for clinical use as a 200 mg hard capsule for oral administration. The proposed dosing regimen is molnupiravir 800 mg (administered as four 200 mg capsules) taken orally every 12 hours with or without food for 5 days.

Molnupiravir is the 5´-isobutyrate prodrug of the antiviral ribonucleoside analogue N-hydroxycytidine (NHC).

Molnupiravir is a prodrug that is metabolised to NHC, which distributes into cells where it is phosphorylated to form the pharmacologically active ribonucleoside triphosphate (NHC-TP), which acts by a mechanism known as viral error catastrophe. NHC-TP incorporation into viral RNA by the viral polymerase results in an accumulation of errors in the viral genome leading to inhibition of replication. The error catastrophe mechanism of action for molnupiravir/NHC has been demonstrated for MERS-CoV, VEEV, MHV and IAV. In the presence of NHC, these viruses were observed to have increased errors and concomitant multi-log decreases in the amount of infectious virus produced. The available clinical data further support the mechanism of action of molnupiravir. Sequence analysis of pre- and post-treatment samples showed an increase in mutations across the entire viral genome which were not localised to genes in the viral RdRp complex.

The CHMP considered all available data, including quality data, non-clinical and clinical data from the studies available at the time of this report.

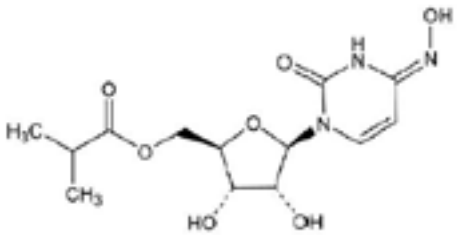
2.2. Quality aspects

2.2.1. Active Substance

General Information

INN: molnupiravir.

The structure is as follows:



The physical and chemical properties are as follows:

Physical characteristics:	white to off-white powder
Solubility:	<table><tr><th>Solvent</th><th>Solubility (mg/mL) at 25°C</th><th>Solubility Description (per USP)</th></tr><tr><td>Water</td><td>39.7</td><td>Soluble</td></tr><tr><td>Ethyl Acetate</td><td>3.9</td><td>Slightly Soluble</td></tr><tr><td>Acetonitrile</td><td>9.0</td><td>Slightly Soluble</td></tr><tr><td>Methyl tert-Butyl Ether</td><td>0.8</td><td>Very Slightly Soluble</td></tr><tr><td>2-propanol</td><td>10.0</td><td>Sparingly Soluble</td></tr><tr><td>Methanol</td><td>> 100</td><td>Freely Soluble</td></tr><tr><td>n-Heptane</td><td>< 0.0005</td><td>Practically Insoluble</td></tr></table>
pK_a-value:	pKa_1, pKa_2, pKa_3 values are 2.2, 10.2, and 12.0.
Partition coefficient:	log D (pH 7) = 0.46.
Hygroscopicity:	Molnupiravir is non-hygroscopic with a moisture gain of 0.1% at 95% RH and 25°C

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Molnupiravir manufactured by the process for products intended to be marketed is crystalline (predominantly Form 1). There is a second non-solvated form (Form 2), with highly comparable physicochemical properties including solubility and stability.

Manufacture, process controls and characterisation

The manufacturing process incorporates one starting material (SM) and several chemical transformations. A detailed description was provided including unit operations, inputs, outputs, yields, how reactions are completed, and process parameters (characterised by a number of PARs, but without listed NORs or set points). The description is acceptable in the context of this procedure, but further information and definition will be expected at the time of MAA.

The detailed justification of SM designation that was provided can be accepted as the steps before the SM do not impact the active substance impurity profile. The provided details of the SM are considered acceptable in the context of this procedure, but further information will be expected at the time of MAA. Several details are requested on the SMs, including definition of suppliers and synthetic routes. The SM specifications and analytical procedures are acceptable in the context of this procedure and include control of incorrect chiral forms. Some tightening of the specifications will be expected at the time of MAA. The specifications for raw materials (including recovered solvents) are acceptable in the context of this procedure, but further details will be expected at the time of MAA.

Detailed specifications are provided for intermediates, which are sufficiently justified with a thorough discussion of impurity carry-over (supported by detailed of spiking studies). Comparative data will be expected at the time of MAA from each proposed intermediate supplier.

The overall manufacturing process of the active substance is unchanged from earlier stages of development, with only minor changes in reagents and additions, which are clearly described. A significant number of batches using the commercial process across a range of batch sizes have been produced, which assures that the process is well-understood and under control. Similarly, the discussion provided on CQAs and the risk assessment is logical and acceptable.

A series of PARs are proposed for each step of the process. While it appears that the ranges have been investigated, a summary of data to justify their use will be expected at the time of MAA, but this is acceptable in the context of this procedure.

Data are presented to support the elucidation of structure of the active substance. A discussion on potential and observed impurities, their carryover and control strategy has been provided and is acceptable, supporting the the controls in place have been also provided. The discussion on potential genotoxic impurities is acceptable in the context of this procedure. All identified potential sources of nitrosamine impurities currently listed in EMA guidance have been considered and no risks could be identified. Characterisation data for specified impurities will be expected at the time of MAA.

The descriptions of the analytical procedures and their validations provided are acceptable in the context of this procedure, but some amendments will be expected at the time of MAA. The related substance method is stability-indicating i.e. determined by forced-degradation studies.

The provided batch data (for 61 batches) demonstrates that the active substance is being manufactured to a consistent quality at each site (and using earlier processes), i.e. for the sites where data are provided. The data support the process being under control and that there are no significant differences between batches from each iteration of the manufacturing process.

Within the rolling review used as a source of information for this procedure, the company provided a justification of the proposed limits, referencing relevant EMA and ICH guidance where appropriate. The

omission of limits for polymorphic form, microbial quality, and particle size distribution (PSD) is acceptable in the context of this procedure, but more data will be expected at MAA (as will some tightening of limits). Note that the limits for related substances will be further discussed during MAA.

The information provided on the reference standard is acceptable in the context of this procedure, but more data will be expected at MAA.

The active substance is stored in double low-density polyethylene (LDPE) liners inside a rigid high-density polyethylene (HDPE) or an alternate container (for example metal or polypropylene (PP) containers) that provides equal or better protection. The provided information is acceptable in the context of this procedure, but specifications for the immediate container will be expected at the time of MAA.

Stability

A retest period of 24 months with no specific storage conditions is proposed. The proposed retest period can be accepted in line with ICH Q1E and is supported by real-time data using an earlier version of the process (which is acceptable as no difference in stability profile is expected and comparability is assured by the provided data). The active substance appears to be very stable under normal storage conditions. The company has demonstrated that the drug substance is photostable.

2.2.2. Finished Product

Description of the product and Pharmaceutical Development

Description of the finished product

The finished product is supplied as a Swedish Orange opaque size 0 dry filled capsule with the corporate logo printed in white ink on one half and "82" printed in white ink on the other half. Each capsule contains 200 mg of molnupiravir active substance and has overall closed length of approximately 21.70 mm and maximum external diameter of approximately 7.64 mm. The qualitative composition of the ink is defined.

Other ingredients than molnupiravir present in the finished product are:

- Granule: hydroxypropyl cellulose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate.
- Capsule: hypromellose, titanium dioxide and red iron oxide
- Printing ink: shellac, potassium hydroxide and titanium dioxide

The product is available in HDPE bottles with a polypropylene closure containing 40 capsules.

Pharmaceutical development

The development strategy was to rapidly develop a physically and chemically stable solid oral dosage form with the intended biopharmaceutical properties consistent with the quality target product profile. Safety and efficacy were used to inform the dosage form selection, design and performance, primary packaging design, and critical quality attributes (CQA) selection.

Active substance physico-chemical and biopharmaceutical properties were evaluated. It is a non-hygroscopic crystalline material with two known anhydrous forms, Form 1 and Form 2, with highly comparable physicochemical properties and no known hydrates. Form 1 is thermodynamically more

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stable. It was demonstrated that the drug substance phase is maintained during the manufacturing process of molnupiravir drug product.

The solubilities of molnupiravir and its active metabolite (NHC) have been determined (NLT 41 mg/ml and 21 mg/ml respectively). Molnupiravir is chemically and physically stable under long-term and accelerated (ICH Q1A) and light (ICH Q1B) conditions.

The sensitivity of the formulation to the active substance particle size distribution (PSD) and bulk density was investigated. Batches with specific PSDs were processed into the finished product, and dissolution profiles demonstrated that PSD did not impact granule dissolution. Relevant physico-chemical and biopharmaceutical properties of the active substance have been identified and are adequately controlled. The active substance attributes that may impact the finished product critical quality attributes have been evaluated.

Excipients were selected to provide a chemically and physically stable formulation with the intended biopharmaceutical properties as well as appropriate process robustness, leveraging prior knowledge of high shear wet granulation formulations. All excipients are of compendial grade apart from printing ink, which is comprised of compendial ingredients. Molnupiravir has been shown to be compatible with the excipients/capsule shell in the proposed commercial formulation. Standard excipients are used in quantities and functions typically seen for oral solid dose products, considering the pharmaceutical form and method of manufacture.

Powder in bottle (PIB) was used for the Phase I single ascending dose study; thereafter dry filled capsule (DFC) was used (25, 100 and 200 mg) in the clinical studies. For Phase II/III, a similar DFC formulation to that Phase I was used, only in 200mg strength.

Commercial and clinical formulations are almost identical (MCC content increased as a filler in lower strengths). The same granulation process was used from Phase I to Phase III.

The impact of compositional changes on in process granule attributes and drug product quality attributes was evaluated, and outputs used to define the final composition. No overages are used.

Dissolution method development has been performed, and the final dissolution method has been adequately justified. The discriminating power of the method has been explored and is limited, considering the very high solubility of the active substance, and its loading (70%) in the composition. Nevertheless, the proposed method is acceptable.

Manufacturing process development is split into several sections, each one representing a unit operation in in the manufacturing process. Experimentation to identify linkages between process variables and process outputs, as well as scale-up and stability studies was performed. Experiments focused on moderate to high risk factors, using both multi-factor designs and one-factor-at-a-time (OFAT) approaches. Typically, process parameters are varied within the unit operation under investigation and are kept constant (as set points) in all other unit operations (upstream and/or downstream). However, it is not always clear what the set points used are, and further clarification will be required for the MAA. The active substance was shown to be stable during granulation.

Based on outcomes from the manufacturing process development (typically) performed at laboratory, pilot and commercial scales, control strategies for each unit operation have been derived. Of note are the large number of PARs proposed, several which have been derived at pilot scale. Further confirmatory data regarding derivation and applicability of PARs at the commercial scale will be expected at time of MAA. Additionally, the overall number of process parameters proposed doesn’t reflect the obtained data, and due to the extensive development work, no CPPs are proposed; this, too, should be addressed in the MAA.

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Overall, the manufacturing process development programme has confirmed that the proposed unit operations have been shown to be appropriate for the product in question; however, several aspects relating to the operation of those unit operations will require further justification at time of MAA.

The commercial proposed package for the finished product is a high-density polyethylene (HDPE) bottle and polypropylene (PP) closure with heat induction seal liner. The packaging configurations studied in the formal stability studies support the use of the commercial container closure system. The provided information is acceptable in the context of this procedure, but additional information will be expected at the time of MAA.

The container closure system has been adequately justified, as have the microbiological attributes. Compatibility is not relevant for oral solid dose products.

Manufacture of the product and process controls

The manufacturers and their operations are defined, and it is confirmed that the manufacturers operate to GMPs. Acceptable evidence of GMP compliance has been provided for each manufacturing site. Batch formulae for maximum and minimum batch sizes are presented, and because granulation batches may be incorporated into single encapsulation batches, further details are required at time of MAA.
Overall, it is considered that the process narrative and schematic lack detail and no critical process parameters have been indicated; the provided information is acceptable in the context of this procedure, but additional information will be expected at the time of MAA.

A satisfactory commitment regarding completion of process validation activities has been provided. The proposed process validation scheme is provided.

All excipients are confirmed to comply with Ph. Eur, except for hypromellose capsules (JP) and printing ink (although all components are stated to be Ph. Eur). Some clarifications will be required at time of MAA. Product specification, analytical procedures, batch analysis

The finished product specifications are proposed for description, identification, uniformity of dosage units, dissolution, and microbial limits. During stability, only description, assay, degradation products, dissolution and microbial limits are performed. For assay and degradation products, different specifications limits are applied for shelf life.

The proposed specification is generally acceptable in the context of this procedure, but some amendments are expected to be addressed at the time of MAA.

In general, the descriptions of the analytical procedures and their validations as provided are acceptable in the context of this procedure, but some amendments and updates are expected to be addressed at the time of MAA.

In particular, it was noted that for one of the methods descriptions and validation are not acceptable, and the method should not be used until comprehensively updated information has been provided at time of MAA. Batch data is presented, and all batches comply with proposed specification, suggesting that the process consistently produces product of the required quality. With respect to comparability of batches from the different manufacturing sites (including dissolution profiles if relevant), batch analysis data from intended production sites has been provided. A summary of method changes implemented between Phase I and Phase III is also presented; method equivalency is demonstrated. Discussion regarding impurities is satisfactory, covering organic impurities (including nitrosamines) and inorganic impurities. There is no risk for formation of nitrosamines, and all elemental impurities are below the ICH Q3D control threshold. Generally acceptable justifications for the proposed specification have been

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provided, referencing ICH and EMA guidance and batch/stability data as appropriate; however, some clarifications will be required at time of MAA, including further discussion regarding the limits for related substances. Note that according to provided batch data, there are no unknown degradation products present at levels above identification thresholds herein. Therefore, these considerations do not preclude the acceptance of batches of DP in the context of this procedure.

Overall, provided information is acceptable in the context of this procedure, but additional information and discussion will be expected at the time of MAA.

The information provided on the reference standard is acceptable in the context of this procedure, but more data will be expected at MAA.

Stability of the product

A shelf life of 18 months when stored at 25°C in 60cc HPDE bottle is proposed. A number of batches manufactured are on stability, and updated data will be required at MAA. It has been demonstrated that the active substance is photostable. The proposed shelf-life can be accepted in line with ICH Q1E and is supported by real-time data using slightly different capsule counts in the same primary container closure system.

Bulk storage study is still on-going, and additional data will be required at MAA.

Overall, the finished product appears stable under the defined storage conditions.

2.3. Non-clinical aspects

Non-clinical data comprising of *in vitro* and *in vivo* studies were conducted to address pharmacodynamics, safety pharmacology, pharmacokinetics and toxicology aspects.

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Pharmacology

Molnupiravir is the 5′-isobutyrate prodrug of a broadly active, antiviral ribonucleoside analogue, N-hydroxycytidine (NHC; also referred to as EIDD-1931. Molnupiravir is hydrolysed by esterases either during or after absorption to deliver NHC into systemic circulation. Once distributed inside cells, NHC is phosphorylated to its corresponding triphosphate anabolite (NHC-TP; also referred to as EIDD-2061), and acts as a competitive alternative substrate for virally encoded RNA-dependent RNA polymerase (RdRp). Owing to the ability of the N4-hydroxycytosine base of NHC to tautomerise, NHC-TP can pair with either guanosine or adenosine, and consequently can substitute for either cytidine triphosphate (CTP) or uridine triphosphate (UTP), respectively. This results in an accumulation of mutations in the viral genome with each cycle of viral replication, referred to as an error catastrophe mechanism of action, in which viral decay acceleration leads to viral extinction by increasing the viral mutation rate beyond a threshold where the virus can replicate.

Primary Pharmacodynamics

In vitro data

In vitro data from the literature have shown that NHC has activity against several RNA viruses, including SARS-CoV-2, in multiple cell types (including Vero E6, HuH-7, Calu-3 lung epithelial cells and A549-ACE2 cells), with EC_{50}s in the sub- to low- µM range. The antiviral activity of NHC was specific and not due to cellular toxicity since CC_{50} values were above the IC_{50} with selectivity index values between 1.24 and >130 depending on the cell line used.

The antiviral activity of NHC against SARS-CoV-2 variants of concern B.1.1.7 (Alpha), B.1351 (Beta), P.1 (Gamma) and B.1.617.2 (Delta) was demonstrated using a cytopathic effect protection assay in Vero E6 cells, with reported IC_{50} values of 1.59 µM, 1.77 µM, 1.32 µM and 1.68 µM respectively, compared with 1.41 µM for WA1 (USA-WA1/2020). The corresponding IC_{50} values for remdesivir were 0.91 µM, 0.96 µM, 0.59 µM and 1.08 µM, for Alpha, Beta, Gamma and Delta variants respectively, and 1.07 µM for WA1.

A non-infectious SARS-CoV-2 reporter replicon assay was used to assess the activity of NHC against replicons encoding specific NSP12 (polymerase) and NSP14 (exonuclease) substitutions. Remdesivir resistance-associated variants in the NSP12 protein (NSP12-F480L, NSP12-D484Y, NSP12-V557L, NSP12-E802A, NSP12-E802D) identified in tissue culture passaging experiments were tested. NHC was similarly active (EC_{50} values <1.6-fold) against replicons with remdesivir resistance-associated amino acid substitutions in NSP12 (polymerase). Moreover, treatment-emergent NSP12 and NSP14 variants NSP12-T739I, NSP14-A220S, NSP14-A220T, NSP14-A220V, NSP14-S503L and NSP14-S503 were evaluated. These variants were observed in NP swab samples from 3 or more participants who had received molnupiravir in Phase 2 studies. NHC was similarly active (EC_{50} values <1.6-fold) against replicons with treatment-emergent NSP12 and NSP14 (exonuclease) variants in the replicon assay.

NHC was evaluated in resistance selection assays against WT mouse hepatitis virus (MHV) and WT MERS-CoV by passage in cell culture and the NHC sensitivity of passage 30 populations was tested. After 30 passages there was a modest change in NHC susceptibility (~2-fold increase in EC90) for MHV and MERS-CoV, suggesting a low likelihood of resistance development to NHC.

In addition, two remdesivir-resistance mutations (F476L and V553L) did not confer cross-resistance to NHC in an *in-vitro* virus replication assay. The activity of molnupiravir was evaluated in Vero E6-ACE2 cells against SARS-CoV-2Engl2 after serial passage in media supplemented with or without remdesivir. Remdesivir, showed 2- to 2.5-fold increase in IC_{50} against the Rem2.5p13.5 strain. Molnupiravir showed a minimal change in IC_{50} against Rem2.5p13.5 (IC50 9.14 µM) compared with SARS-CoV-2Engl2 (IC_{50} 8.92 µM).

NHC exhibits low cytotoxicity (CC_{50}) on mammalian cell lines and was poorly efficient to incorporate into mitochondrial RNA. Molnupiravir inhibited proliferation of myeloid and erythroid colonies at concentrations 296 and 958-fold higher than molnupiravir clinical concentrations.

In vivo data

Molnupiravir 500 mg/kg significantly reduced infectious SARS-CoV-2 levels in lung tissue from infected Lung only Mice (LoM; immunodeficient mice implanted with human lung tissue) when treatment was initiated 12hr pre-infection and 24 or 48 hrs post-infection, although antiviral activity was decreased when treatment was delayed to the 48hour timepoint.

The ability of molnupiravir to mitigate SARS-CoV-2 infection and block transmission was examined in a ferret model of intranasal infection with 1×10^5 pfu of SARS-CoV-2. Treatment of infected ferrets with molnupiravir twice daily via oral gavage (either 5 or 15 mg/kg BID starting 12 hours post-infection, or 15 mg/kg BID starting 36 hours post-infection) significantly reduced the SARS-CoV-2 viral load in the upper respiratory tract within 12h of treatment initiation. In a second study to examine the impact of molnupiravir treatment on viral transmission, ferrets were infected and treated with 5 mg/kg twice daily or vehicle starting 12 h post-infection. After 30 h, each ferret was co-housed with 2 uninfected ferrets. The contact ferrets of vehicle-treated animals began to shed SARS-CoV-2 within 20 h of co-housing but no infectious particles or RNA were detected in the contacts of ferrets that had been treated with molnupiravir.

In a Syrian hamster model of SARS-CoV-2 infection and disease, molnupiravir prophylaxis or treatment gave decreases in viral RNA titres and infectious virus from lungs several days post infection.

In Syrian hamsters infected with 1×10^5 TCID50 units of the B.1-G (Wuhan strain), B.1.1.7 (Alpha) or B.1.351 (Beta) variants of SARS-CoV-2, treatment with molnupiravir 200 mg/kg BID gave statistically significant reductions in viral RNA copies per mg of lung tissue and in infectious virus lung titres regardless of variant.

Secondary Pharmacodynamics

Both molnupiravir and n-hydroxycytidine (NHC) were tested for potential secondary pharmacodynamic *in vitro* activity against a panel of 108 enzymes, receptors and ion channels, with ≥50% inhibitory activity considered significant and reported at only one target, human COX-2. For molnupiravir, a follow-up dose-response assay reported an IC_{50} of 6.33 µM against COX-2, which is not considered clinically relevant given an anticipated clinical Cmax of 0.026µM at the 800 mg BID dose. However, for NHC the anticipated clinical Cmax was 10.8 µM at an 800 mg BID dose, therefore the potential for off-target inhibitory activity could not be excluded based on a maximum concentration of 10 µM NHC used in the *in vitro* assay.

Safety Pharmacology

All pivotal safety pharmacology study reports contain good laboratory practice (GLP) compliance statements, indicating that they have been conducted in accordance with the principles of GLP, in an OECD Mutual Acceptance of Data (MAD) adherent country. Both *in vitro* and *in vivo* studies were conducted to address the safety pharmacology core battery, in line with ICH S7A. *In vitro* hERG assays were conducted with both molnupiravir and NHC applied to HEK cells stably expressing the hERG channel. Greater than 50% inhibition of the hERG current was not achieved in either study at the concentrations of test-article applied. The molnupiravir IC_{50} was estimated at > 30 µM, and the NHC IC_{50} at > 300µM, 1000-fold and 28-fold greater than the respective clinical Cmax at the 800mg BID dose, supporting a low potential for inhibition of IKr and QT prolongation associated with both molnupiravir and NHC at clinically relevant concentrations.

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For the *in vivo* safety pharmacology studies, no TK parameters were included but NHC Cmax values were extrapolated from 28-day TK studies in rats and dogs. Exposure margins are expressed based on population pharmacokinetics analysis in adult patients with COVID-19 from P001 and P002 clinical trials (Part 1), where an 800 mg BID molnupiravir dose resulted in an NHC Cmax of 10.8 µM.

The central nervous system (CNS) and respiratory safety pharmacology studies were conducted in male Sprague Dawley rats and no test-article related findings are reported. A single dose no observed effect level (NOEL) of 500mg/kg for neuropharmacological, body temperature and respiratory changes in male rats is reported, associated with NHC exposures 16-fold higher than the anticipated clinical Cmax. Two cardiovascular safety pharmacology studies were conducted in conscious telemetered beagle dogs and no test-article related findings are reported. A NOEL at the highest dose tested of 17 mg/kg is reported from the first study, associated with a 1.4-fold margin to the anticipated clinical Cmax. However, the second CVS safety pharmacology study also reported no test article-related effects on any BP parameters, HR, ECG parameters, QT-related parameters or body temperature following single oral dosing at 50 mg/kg. Extrapolation from the same available TK data gives a 5-fold safety margin from the reported dog NOEL to the anticipated clinical NHC Cmax.

Pharmacodynamic Drug Interactions

The antiviral activity of NHC against SARS-CoV-2 was evaluated *in vitro* by measuring the reduction of the SARS-CoV-2 cytopathic effect on infected Vero E6 cells. The antiviral activity of lamivudine (3TC), abacavir, emtricitabine (FTC), hydroxychloroquine, nelfinavir, remdesivir, ribavirin, sofosbuvir and tenofovir against SARS-Cov-2 was also determined for each compound alone and in combination with NHC across a range of concentrations. NHC, nelfinavir and remdesivir when tested alone demonstrated antiviral activity against SARS-CoV-2 with EC_{50} values of 1 µM, 0.7 µM and 1.7 µM, respectively. Cytotoxicity in Vero E6 cells was also measured in parallel, in uninfected cells, to quantify compound toxicity. No cytotoxicity was reported for any compound tested (CC_{50} >20 µM) with the exception of nelfinavir, which was cytotoxic at high concentrations (CC50 = 11 µM).

Pharmacokinetics

The pharmacokinetics of molnupiravir were determined in mice, rats, dogs, monkeys and ferrets.

Absorption

Molnupiravir is a 5´-isobutyrate ester prodrug cleaved by esterases present in the intestine and liver during absorption/hepatic first pass, delivering the nucleoside metabolite NHC into systemic circulation, as a result only very low levels of molnupiravir were detected in plasma. Molnupiravir is efficiently absorbed in mice after oral feeding and converted to NHC generating high levels of NHC in animal plasma. The oral bioavailability of NHC in mice is 37-45%. Molnupiravir when orally administered in rats and dogs was well absorbed and resulted in high bioavailability of NHC, and significantly improved the oral exposure to NHC in monkeys when compared to oral administration of NHC itself. The bioavailability of NHC after an oral dose of molnupiravir in rats and dogs was 52% and ≥77%, respectively. Molnupiravir generally provided dose-proportional exposures of NHC in all preclinical species after oral dosing.

Distribution

Molnupiravir, NHC, and NHC-TP were quantified in some tissues (lung, spleen, kidney, liver, heart and brain) from mice, rats, dogs, monkeys and ferrets following single or multiple oral doses of molnupiravir. In general, molnupiravir was either not detected or was near the detection limit in these tissues. NHC and NHC-TP were observed in all tissues and their exposures were generally dose dependent. In most species, NHC-TP typically had the highest exposures in lung and spleen, and the lowest levels in brain.

Distribution to bone marrow was also assessed in rats, but not in dogs where significant bone toxicity was observed. No data are reported for distribution to other tissues which can be considered as relevant, such as bone and cartilage, the GI tract or reproductive tissues.

Protein binding

The plasma protein binding of molnupiravir was not assessed since it is not stable in plasma. The binding of NHC in CD-1 mouse, SD rat, beagle dog, cynomolgus monkey, and human plasma, and in human alpha1-acid glycoprotein and human serum albumin was measured by rapid equilibrium dialysis using 2, 20 and 100 µM. The unbound fraction of NHC was approximately 1 in all matrices and at all concentrations tested.

Metabolism

- *In vivo* metabolism

The *in vivo* metabolism of molnupiravir was studied in male BDC Wistar Han rats and male intact beagle dogs following oral administration of [^{14}C]MOV formulated as a solution in 1% methylcellulose at 30 mg/kg. The majority of the radioactive dose was retained in the body, with 54% recovered from the animal carcasses. The low recovery in faeces (6.8%) indicates molnupiravir -related radioactivity was well absorbed in rats, likely >90%. Given the short t½ of NHC in rat plasma when dosing molnupiravir as well as the low levels of NHC and NHC-TP in tissues observed after 24 hr in a single dose distribution study, the retained radioactivity in the carcass suggests that, as was observed *in vitro*, the majority of the dose was ultimately metabolised to pyrimidine metabolites (uridine, cytidine, etc.), which then enter the endogenous pyrimidine pool.

In human urine following oral administration of molnupiravir, NHC, cytidine, uridine, and an NHC-glucuronide were detected by LC/MS/MS. All exhibited approximate dose-dependent increases in concentration, suggesting that some amount of the endogenous pyrimidines was derived from the oral dose of molnupiravir. Overall, these data are consistent with the expectation that the majority of the molnupiravir -related dose in animals and humans is converted to NHC, NHC-TP, and (or ultimately to) uridine and/or cytidine which then mix with the endogenous nucleoside pool.

- *In vitro* metabolism

Molnupiravir was relatively unstable in mouse, rat, and monkey plasma (all t½ ≤0.4 hr), while more stable in human and dog plasma (t½ 1.05 and 3.2 hr, respectively). Molnupiravir was relatively unstable in mouse, rat, dog, and monkey liver microsomes (t½ 0.02 - 0.08 hr) while more stable in human liver microsomes (t½ 1.2 hr). Molnupiravir was stable in simulated gastric and intestinal fluids (t½ >24 hr).

NHC, the active metabolite of molnupiravir, was stable when incubated with plasma, whole blood, liver microsomes, and liver S9 extracts and intestinal microsomes from mouse, rat, dog, monkey, and human (t½ all ≥3 hr).

Molnupiravir and NHC were taken up by all tissue culture cells tested and converted to NHC-TP.

Intracellular NHC-TP levels were generally concentration-dependent, with Cmax approximately 160-2600 pmol/10^6 in various cell lines cells (at 10-20 µM in culture media). NHC-TP reached Tmax between 1 and 24 h depending on the cell line and concentration tested.

Stable radiolabelled ^{13}C5-NHC was used to quantify the amount of NHC converted to anabolites in the pyrimidine nucleoside phosphorylation pathway. NHC-TP reached high levels within 1-6 h and concentrations in primary lung cells were significantly higher than in primary hepatocytes. The

intracellular stability (t½) of NHC-TP was 4-5 h in human astrocytes and hBTEC but significantly less (0.4-1.1 h) in primary hepatocytes.

Molnupiravir and/or NHC are taken up by all tissue culture cell lines tested, (A549, BEAS-2B, CEM, HepG2, Huh7, PC-3 and Vero cells), at concentrations up to 100 µM, and converted to the pharmacologically active NHC-TP. NHC is also taken up and metabolise to NHC-TP by primary cells such as human astrocytes, hBTEC and hepatocytes (mouse, monkey, and human), at concentrations up to 20 µM.

The *in vitro* metabolism of [^{14}C]molnupiravir (10 µM) was studied in pooled cryopreserved hepatocytes from male SD rats, male beagle dogs, male cynomolgus monkey and humans (mix of genders). After 2h incubation, molnupiravir was extensively metabolised and its metabolic profiles were qualitatively similar across all species. Hydrolysis of molnupiravir to NHC was the major route of metabolism, and NHC accounted for 56, 73, 86, and 71% of the radioactivity in rat, dog, monkey, and human hepatocytes, respectively. Uridine was also a major metabolite detected in human hepatocytes and accounted for 26% of the radioactivity. Minor metabolites (<10% radioactivity) detected included cytidine-monophosphate (except in rat) and uridine-monophosphate. Under the conditions tested and current LCMS/MS method, NHC-TP was not observed following incubation of molnupiravir in hepatocytes suspensions.

All metabolites observed in human hepatocyte incubations were also detected in the nonclinical species. The conversion of NHC to NHC-TP varies between cell lines, therefore the consistency of the phosphorylation not completely characterised. The concentrations of NHC used in some of these studies was higher than the CC50 values provided in a reference. CC50 values were not provided for all cell lines used; therefore, the cytotoxicity of NHC in all the cell lines tested has not been fully established. In addition, a discussion on the potential for reduction of NHC to 2'-deoxy-NHC has not been provided by the company. While this is acceptable for the purpose of this procedure, it will be addressed in more detail as part of the MAA.

Excretion

The recovery of [^{14}C]MOV-related radioactivity in excreta from BDC rats and intact dogs was low (<13%) indicating that the majority of the dose was retained in the body. The low recovery in rats and dog excreta was anticipated given a major route of metabolism of [^{14}C]MOV *in vitro* was the ultimate formation of uridine and/or cytidine, which *in vivo* would mix with the endogenous nucleoside pools and remain in the body.

Pharmacokinetic Drug Interactions

Molnupiravir and NHC as victims

Molnupiravir is hydrolysed to NHC by the high capacity esterases CES1 and CES2. Following the uptake of circulating NHC into cells, host kinases and phosphatases involved in the endogenous pyrimidine nucleoside pathways then anabolise/catabolise NHC to/from NHC-TP. Preclinical *in vitro* and *in vivo* metabolism studies suggest the ultimate route of elimination of molnupiravir/NHC-related material is metabolism to endogenous pyrimidine nucleosides (uridine and/or cytidine). The mitochondrial amidoxime reducing components (mARC1 and mARC2) have been reported to convert NHC to cytidine, and cytidine deaminase readily converts NHC to uridine. *In vitro*, NHC was found to be a substrate of the human nucleoside transporters CNT1, CNT2, CNT3, and ENT2 while molnupiravir was a comparatively weak substrate of CNT1, and neither molnupiravir nor NHC were substrates of human MDR1 P-gp or BCRP. Based on these data, other drugs are not anticipated to affect the tissue levels of NHC-TP resulting from an oral dose of molnupiravir.

Molnupiravir and NHC as perpetrators

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In vitro studies demonstrated that molnupiravir is not an inhibitor of major human CYPs (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4). However, the concentration range of NHC tested in these studies was approximately 10-fold the clinical Cmax (10.8 µM), and therefore not in accordance with EMA guidance (CPMP/EWP/560/95/Rev. 1 Corr. 2**), and it is expected that it will be further followed up in the context of the MAA.

Neither molnupiravir nor NHC inhibited MDR1 P-gp or BCRP. In addition, molnupiravir did not inhibit presystemic OAT and OCT transporters (OATP1B1, OATP1B3, OCT1). However, *in vivo* inhibition of some transporters (OATP1B1, OATP1B3, OCT1, OCT2, OAT1 and OAT3) by NHC, cannot currently be excluded as the observed Ki value (> 100 µM) could be less than the concentrations given for 25*[I]u,inlet,max [2](600 µM), or 50* unbound Cmaxu, (540 µM).

In vitro studies on the potential induction of CYP enzymes (CYP1A2, CYP2B6 and CYP3A4) by molnupiravir or NHC demonstrated that molnupiravir is not and inducer of these major human CYPs. Again, the concentration range on NCH tested was not in accordance with the Guideline on investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**), and it is expected that this will also be further followed up in the context of the MAA.

Toxicology

As a new chemical entity, the nonclinical toxicology package for molnupiravir 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, dogs and rabbits and are considered appropriate based on the similar PK profile seen in these species compared to humans. Furthermore, the pharmacological target of molnupiravir is an exogenous entity and therefore there are no uncertainties related to potential differences in pharmacological activity between species. For some studies the toxicokinetics of molnupiravir and NHC were measured. Considering the rapid conversion of molnupiravir to NHC and the low levels of molnupiravir measured, exposure margins have been calculated to the NHC levels measured.

Single dose toxicity studies

Single dose toxicities studies were incorporated into preliminary non-GLP exploratory studies in mice, rats and dogs with a top dose utilised in each study of 2000 mg/kg. No mortality was seen in any of the studies. For the study in mice, the animals were dosed directly with NHC and not molnupiravir. In mice there was evidence of doses of NHC ≥1500 mg/kg not being tolerated, with decreases in food consumption and body weight gain seen in the days after treatment. Similar signs of weight loss and decreased food consumption were seen in rats at the top dose of 2000 mg/kg. In contrast, GI effects were seen at all dose levels in dogs (from 300 mg/kg). Although the studies are not GLP compliant they provide some limited information in relation to the potential effects associated with overdosing.

Repeat dose toxicity studies

The pivotal nonclinical repeat dose toxicity studies include 28-day studies in rats and dogs as well as a 13-week study in rats only. All of the studies involved daily oral dosing and the 28-day studies included recovery periods of 14-days in rats and 28-days in dogs; however, for the study in dogs the recovery period was more limited for the top dose group because of the toxicity noted, which necessitated the early termination of this group. As outlined in ICH M3 (R2) for a medicinal product 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-day treatment.

[2] Unbound maximum hepatic inlet concentration of drug in blood

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In the 28-day study in rats the test article was generally well tolerated, and findings were limited to slightly lower body weight and food consumption for males at the top dose of 500 mg/kg in the initial weeks of treatment. The only other finding of note was increased liver weight at 500 mg/kg which was not associated with any microscopic findings or changes in any clinical chemistry parameters. In addition, this observation was not seen in the subsequent 13-week study, however, it is noted that increased transaminases have been observed in the clinic. The exposure at this dose level represents a margin of exposure of 7.8 and 4.2-fold respectively for males and females compared to the expected clinical exposure at 800 mg Q12H.

The subsequent 13-week study in rats utilised 1000 mg/kg as the top dose group and without including a recovery group. Based on the previous findings the absence of such recovery groups appears appropriate and in line with 3Rs principles. The lowest dose differed between the sexes with 150 mg/kg used in males and 200 mg/kg because of expected differences in exposure, which did not materialise. In this study with the extended dosing period, much more pronounced effects were seen on body weight, particularly in males, and occurred at all dose levels and in a dose-dependent manner. The effect was less pronounced in females and only seen at the mid- and high-dose groups. The decreases in body weight gain correlated with slight decreases in mean food consumption. Upon necropsy there were significant alterations in the weight of multiple organs in males at the 1000 mg/kg dose which were considered to be secondary to the decreased body weight gain and did not correlate with microscopic findings. The most notable findings from the study were effects on cartilage and bone seen at doses ≥ 500 mg/kg. This included increased thickness of the growth cartilage of the epiphysis of long bones and patella. In the femur and tibia at 1000 mg/kg in males, the increased thickness was associated with decreased osteogenesis and decreased trabecular bone in the metaphysis. In addition to these findings in the long bones, alterations of chondrocyte distribution within the matrix of the cartilage of the trachea were seen in males at doses ≥ 500 mg/kg. Because of the lack of recovery groups there is no information on the potential reversibility of these findings. Such effects were not seen in the previous 28-day study and therefore the effects may only occur with longer duration of treatment. In addition, the rats used were 5 weeks of age at the time of initiation of the 13-week study compared to 8-9 weeks old, which may also have impacted the observations seen. The effects seen on the trachea were minimal in nature and did not have any functional consequence. Based on the bone/cartilage findings the NOAEL was considered 150 mg/kg in males (margin of exposure of 0.7-fold) and 500 mg/kg in females (3.3-fold margin of exposure).

Significant toxicities were seen in the 28-day study in Beagle dogs, which necessitated an interruption of dosing in the mid and top dose groups of 17 and 50 mg/kg on Days 12/14 and Days 21/22 respectively due to marked weight loss, inappetence and critical haematology findings. Upon necropsy the major finding in these groups was discolouration in the GI tract which was adjudged to be secondary to haemorrhaging as a result of thrombocytopenia. The severity of the macroscopic and microscopic findings appeared to be dose related. The haematology findings suggested bone marrow changes affecting all haematopoietic cell lines and causing subsequent haematological abnormalities (including total WBC count, lymphocytes, neutrophils, reticulocytes, RBCs and platelets) at doses ≥ 17 mg/kg. The effects on haematopoietic cells worsened with increased duration of treatment with the most severe effects seen between 14 and 21 days of treatment depending on the dose involved. At the mid dose of 17 mg/kg there was some evidence of reversibility of the bone marrow effects upon treatment cessation. Of note, no effects were seen on bone or cartilage in dogs. There is a margin of exposure of 0.1-fold at the NOAEL of 6 mg/kg with the 17 and 50 mg/kg doses having margins of exposure of 0.4 and 1.6-fold respectively.

Genotoxicity

A summary of the genotoxicity studies is provided in the table below:

Overview Table of Genotoxicity Studies:

Type of test/study ID/GLP	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative/equivocal
Gene mutations in bacteria/Study TT #16-7851/Non-GLP	Salmonella strains TA1535, TA100, TA98 & TA1537; E. coli WP2 uvrA	NHC at 1.5 to 5000 µg/ plate incorporation method +/- S9	Positive in E. coli strain WP2 uvrA ⩾5 µg/plate with and without activation. Negative in strains TA98, TA100, TA1535, and TA1537 with and without activation.
Gene mutations in bacteria/Study TT #19-7810/GLP	Salmonella strains TA98, TA100, TA102 TA1535, & TA1537; E. coli WP2 uvrA	Molnupiravir ranging from 1 to 5000 µg/ plate incorporation method +/- S9	Positive at ⩾ 25.0 µg/plate in strains TA102 and WP2 *uvrA* with metabolic activation; ⩾ 500 µg/plate in strain WP2 uvrA and ⩾ 1000 µg/plate in strain TA102 without metabolic activation. Negative in strains TA98, TA100, TA1535, and TA1537 with and without activation.
Gene mutations in mammalian cells/Study TT #20-7806/GLP	TK6 cells,	- S9 for 4 h: 20.6 to 330 µg/mL with 40-hour recovery + S9 for 4 h: 2.58 to 330 µg/mL with 40-hour recovery -S9 for 27 h: 2.58 to 330 µg/mL	Negative.
Chromosomal aberrations *in vivo*/Study TT #19-7816/GLP	Rat, micronuclei in bone marrow	500, 1000 & 2000 mg/kg once daily for 2 consecutive days	Negative.
Gene mutagens *in vivo*/TT #20-7808/GLP	Peripheral Blood Erythrocyte Pig-a Mutation Assay in Rats	50, 150 or 500 mg/kg once daily for 28 days with sampling Day 29.	Equivocal. Statistically significant increases in the incidence of mutant RBCs and RETs at 500 mg/kg compared to control. Incidence of mutant RBCs was also statistically significant at 50 and 150 mg/kg. Values were typically within the 95% upper limit of the historical control values database. The increase was not dose-related when evaluated with an appropriate trend test.
Gene mutagens *in vivo*/TT #20-9025/GLP	Mutation Assay at the cII Locus male transgenic Fischer 344 Big Blue® rats	50, 150 or 500 mg/kg once daily for 28 days with sampling Day 31	Negative. No significant increase in mutant frequencies seen in any tested tissues (liver and bone marrow).

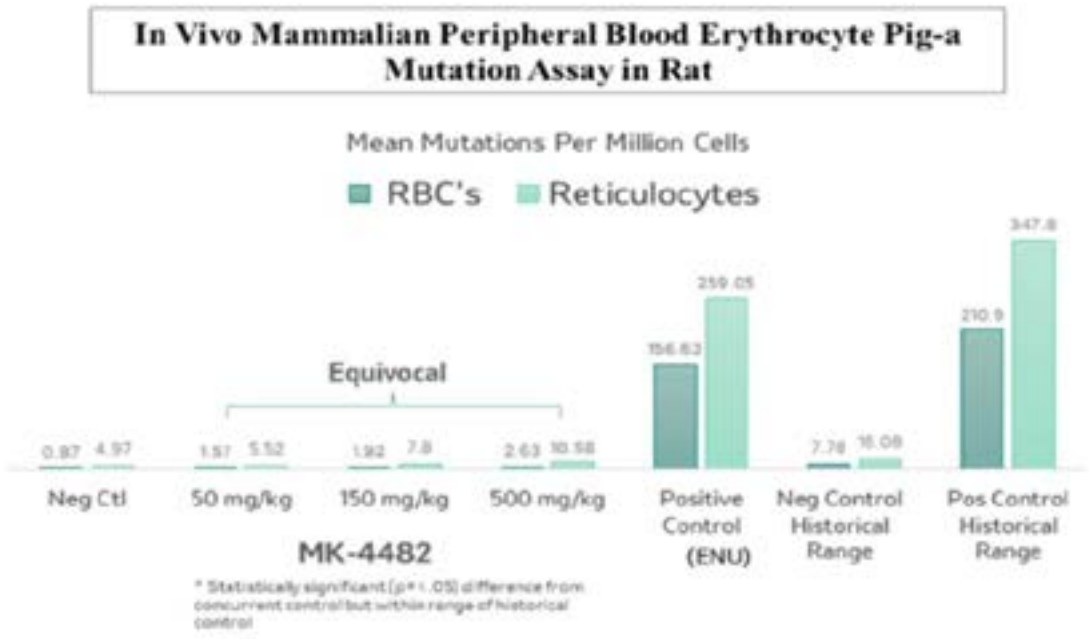
A non-GLP compliant Ames study was performed with NHC and a GLP compliant study with molnupiravir. With NHC in the E. coli WP2 *uvrA* strain all plates ≥5 µg with and without metabolic activation were positive for revertants. With molnupiravir mutagenic potential was also seen in the WP2 uvrA strain, as well as in the TA102 strain, which was not tested in the study with NHC. In contrast to that seen with NHC, metabolic activation reduced the dose level at which mutagenicity was seen with molnupiravir. The company has argued that the positive bacterial mutagenicity result is likely to be a result of incorporation of the NHC-TP into the bacterial DNA. NHC-TP is a ribo- and not deoxy-nucleotide, and thus the ribonucleotide itself is not expected to be significantly incorporated into

eukaryotic cell DNA *in vivo*, therefore the mechanism for the mutagenic effects seen remain unclear for the time being.

The *in vitro* micronucleus test was performed in TK6 cells using levels of molnupiravir up to 330 µg/mL which is equivalent to the maximum concentration of 1 mM in the OECD 487 guideline. Under the conditions of the study there was no increased percent of micronucleated cells noted for the test article with the positive controls functioning as expected.

The *in vivo* micronucleus test was performed in rats after 2 consecutive days of dosing up to 2000 mg/kg. No increase in micronuclei was seen up to the top dose of 2000 mg/kg. The study did not include a measurement of toxicokinetics, although effects were seen on body weight gain and food consumption in both males and females. However, no evidence of bone marrow toxicity was seen up to the top dose.

To better understand if the mutation effects observed in bacteria are relevant in a whole animal mammalian system, the mutagenicity of molnupiravir was assessed using the phosphatidyl inositol glycan class A gene (Pig-a) mutation assay on circulating blood erythrocytes in rats after daily dosing at 50, 150 or 500 mg/kg for 28 days. No substantial reduction in the %RETs was observed for any of the molnupiravir-treated groups when compared to the concurrent negative control value. Therefore, molnupiravir did not cause cytotoxicity following daily oral administration up to 500 mg/kg/day for 28 consecutive days to male rats. Statistically significant differences from control animals were seen at all dose levels for mutant RBCs and at the top dose of 500 mg/kg for mutant RETs (see figure below). However, based on a lack of a dose-related trend and the fact that the values measured fell within the historical control range the study was deemed to be equivocal in-line with the predetermined criteria for positive results.



ENU= N ethyl-N-nitrosourea; MK-4482=Molnupiravir or MOV; Neg Ctl = Negative Control; Pos=Positive; RBCs = Red blood cells

Because of the equivocal findings in the Pig-a mutation assay an additional *in vivo* mutation assay was performed at the cII Locus in Big Blue® Transgenic F344 Rats. Doses of 0 (vehicle control), 50, 150 and 500 mg/kg/day were administered daily for 28 days with sampling on Day 31. The results of the assay met all validity criteria and no significant increase in mutant frequencies were seen in either the

liver or the bone marrow indicating a lack of mutagenic effect in these tissues. No exposure was measured, however, there were some clinical observations noted in the top dose group as well as effects on body weight. Given the assay can utilise any tissue, no justification has been provided in the submission assessed for the rolling review for the choice of tissues examined and it is unknown whether sufficient exposure occurred in these tissues. In the context of a MAA, further information will be required to address this issue and allow for a definitive conclusion on the results of this assay.

A study in the literature has suggested that NHC displays host mutational activity in an animal cell culture assay (Zhou et al. 2001[3]). Using a modified hypoxanthine phosphoribosyl transferase (HPRT) gene mutation assay the authors find that NHC is also mutagenic to the host in the HPRT mutagenesis assay. The mechanism is hypothesised to occur via metabolism of NHC by the host cell to the 2′ -deoxyribonucleotide form by ribonucleotide reductase and then incorporated into DNA, leading to mutagenesis of the host. However, it should be noted that the study is non-GLP, uses a non-standard study design with treatment for 32 days (compared to typical 3-6 h exposure as per OECD guideline) and is lacking any information on the source of NHC and its purity level. For the current submission, data on the extent of metabolism of NHC to its 2-deoxyribonucleoside 5′-diphosphate derivative by ribonucleotide reductase *in vivo* in rat and human are missing.

A complete lack of genotoxic potential cannot be definitively concluded. However, based on the totality of the data and in the context of the proposed clinical use for 5-days duration, the genotoxic risk could be considered justifiable in the context of the clinical benefit.

Carcinogenicity

No carcinogenicity studies have been completed to date. 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 were no microscopic findings from the limited duration repeat dose toxicity studies indicative of pre-neoplastic changes.

Reproductive and developmental toxicity

Separate male and female fertility studies were performed with molnupiravir in rats at oral doses up to 500 mg/kg/day. In both studies no effects were seen on fertility parameters or early foetal development. The male fertility study did not include an examination of sperm parameters. Toxicokinetics were measured in both and suggested that the males achieved exposures approximately 3-fold higher than females at the top dose of 500 mg/kg. Non-adverse clinical effects on weight and food consumption were seen in the study in males only at the top dose. At the NOAEL of 500 mg/kg in the male fertility study there was a margin of exposure of 6.1 and at the NOAEL of 500 mg/kg in females there was a margin of exposure of 2.1 compared to the predicted clinical exposure at 800 mg Q12H.

In a preliminary EFD study in rats, significant maternal toxicity was noted at the top dose of 1000 mg/kg with body weight losses resulting in the early termination of 2 females at GD10. At this dose level an increase in post-implantation loss was seen (22.0%, versus 6.3% in controls) as well as reduced foetal body weights (26.4% for males and 23.5% for females). In addition, internal and skeletal malformations were seen including abnormal and/or small eye/eye socket, absent kidney, rib malformations, thoracic and lumbar vertebra malformations. At the lower dose of 500 mg/kg decreased foetal body weight was seen in the absence of effects on post-implantation loss or molnupiravir related malformations.

Because of the maternal toxicity seen in the preliminary study, the definitive study utilised 500 mg/kg as the top dose. No molnupiravir-related malformations were seen at any dose level and the only

[3] J Infect Dis. 2021. doi: 10.1093/infdis/jiab247

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developmental toxicity noted was decreased foetal weights at the top dose (13% and 11% for males and females respectively) which is comparable to the effects seen at the same dose in the preliminary study. Maternal toxicity was seen at the top dose of 500 mg/kg as evidenced by effects on maternal body weight and food consumption.

Toxicokinetics were measured as part of both studies in rats, however, toxicokinetics were not calculable in the definitive study at the top dose of 500 mg/kg in rats due to a sample volume error. The exposures measured at 100 and 250 mg/kg in the definitive study are largely comparable to that seen in the DRF study. The NOAEL for maternal and developmental toxicity was 250 mg/kg which represents a margin of exposure of 0.8-fold the NHC exposure measured at the RHD of 800 mg Q12H. The effects on foetal weight were seen at a margin of exposure of 2.9-fold and the post-implantation loss and malformations at 7.5-fold (both based on TK from the preliminary study).

In rabbits, the preliminary EFD study identified maternal toxicity at the top dose of 1000 mg/kg with effects on body weight and food consumption similar to that seen in rats. In addition, decreased faecal output was seen at this dose level. No developmental toxicity was reported at any dose level. For the definitive study the top dose used was 750 mg/kg based on the maternal toxicity noted at 1000 mg/kg in the preliminary study. At doses $\geqslant$ 400 mg/kg maternal toxicity was noted (effects on body weight, food consumption and faecal output) and based on these findings the company has concluded that the NOAEL for maternal toxicity is 125 mg/kg. Developmental toxicity effects seen in the definitive study in rabbits and attributed to molnupiravir were limited to decreased live foetal weights (10% and 8.5% for males and females respectively) at the top dose of 750 mg/kg. However, in the study report provided there is an increased number of visceral malformations with molnupiravir treatment in 6 foetuses from 6 different litters in the 750 mg/kg group, compared to 2 in the control group. Although it is acknowledged that the incidence is low, it is notable that 2/6 of these malformations were an absence of kidney, which was also seen in the study in rats. Furthermore, effects seen on the gallbladder, were not evident in control animals. The company's position that these malformations are not molnupiravir-related is not currently accepted and further justification will be requested in the context of a MAA At the NOAEL for maternal toxicity of 125 mg/kg there is a margin of exposure of 1.5-fold, and at the company's NOAEL for developmental toxicity of 400 mg/kg, a margin of exposure of 6.5-fold. At the 750 mg/kg dose level, there is a margin of exposure of 18-fold.

Of note, in the context of this review no data was provided on the placental transfer of molnupiravir and/or NHC and the extent of embryo/foetal exposure in either species, and this aspect will need to be addressed in more detail in the context of the MAA.

Prenatal and postnatal development studies have not been completed. Appropriate warnings as to the lack of animal lactation studies are included in the Conditions for Use.

Local tolerance

Local tolerance was assessed as part of the repeat dose toxicity studies in mice, rats and dogs as is appropriate for an orally administered drug. The significant GI tract issues seen in the dog studies were considered secondary to the thrombocytopenia seen in this species. Additional ocular and dermal irritation studies were performed which concluded that molnupiravir was a mild irritant in both settings, however, given the oral route of administration the significance of these findings is limited.

Phototoxicity

Both molnupiravir and NHC absorb light between 290 and 700 nm with a MEC > 1000 M-1 cm-1. A photoreactivity test using a ROS generation assay was conducted and neither molnupiravir nor NHC generated ROS at an aqueous concentration of 200 µM and in line with ICH S10 were not considered photoreactive.

Impurities

Proposed limits for NHC are justified on the basis of it being a major metabolite in all species. In addition, EIDD-2960, the penultimate intermediate in the drug substance synthesis, is qualified up to levels of 0.22% based on an 800 mg Q12H dosing regime and the levels seen in the batches used in the nonclinical toxicity studies.

Discussion on non-clinical data

Molnupiravir, being the 5'-isobutyrate ester prodrug of NHC, is converted to NHC by esterases (including CES1 and CES2) in intestinal and liver microsomes as well as plasma. After cellular uptake, NHC is triphosphorylated by host kinases to the active moiety NHC-TP (formerly EIDD-2601).

In terms of pharmacodynamics, overall, the specific antiviral effects of NHC were shown against several RNA viruses, including SARS-CoV-2, and demonstrated not to be the result of a cytotoxic effect as a good selectivity index was shown in the *in vitro* cellular models assayed. Molnupiravir reduced infectious SARS-CoV-2 levels in lung tissue from infected Lung only Mice when given 12-48h after infection with a decreased effect at 48h, however, to better define the therapeutic window of opportunity of the drug it would have been desirable if molnupiravir were evaluated at later time points.

While studies to evaluate selection of resistance to NHC with SARS-CoV-2 in cell culture have not been completed, only a modest change in NHC susceptibility (~2-fold increase in EC90) was shown for MHV and MERS-CoV in serial passage resistance selection assays, suggesting a low likelihood of resistance development to NHC.

Off-target pharmacodynamic activity was found only against COX-2, although the maximum concentration tested was below the clinical NHC Cmax, therefore other off-target inhibitory activity cannot be excluded for NHC.

CNS and respiratory safety pharmacology evaluated in rats and two cardiovascular safety pharmacology studies conducted in dogs report no findings of concern.

In terms of pharmacodynamic drug interactions, neither synergy nor antagonism was observed for anti-viral activity *in vitro* against SARS-COV-2 between NHC and lamivudine (3TC), abacavir, emtricitabine (FTC), hydroxychloroquine, nelfinavir, remdesivir, ribavirin, sofosbuvir and tenofovir), supporting a lack of relevant pharmacodynamics drug interactions between NHC and any of the other anti-viral compounds tested.

Pharmacokinetic data available show that molnupiravir generally provided dose-proportional exposures of NHC in all preclinical species after oral dosing. with low exposure levels of molnupiravir measured. Distribution to a limited number of tissues was examined with generally dose dependent exposure of NHC and NHC-TP observed in the tissues examined.

NHC-TP typically had the highest exposures in lung and spleen, and the lowest levels in brain in most species tested. NHC-TP typically had the highest exposures in lung and spleen, and the lowest levels in brain in most species tested. In view of protein binding, molnupiravir could not be assessed due to its instability in plasma, but NHC was found not to be protein bound with an unbound fraction of 1. Molnupiravir excretion was, low indicating that the majority of the dose was retained in the body due to mixing with the endogenous nucleoside pool.

No clinical interaction studies have been performed with molnupiravir. Limitations were identified in the *in vitro* studies assessing molnupiravir and NHC as victims or perpetrators of human metabolic enzymes and transporters. However, currently no substantial risk for clinically important drug

interactions is expected to occur when dosing with molnupiravir 800 mg twice daily for 5 days based on this limited data.

The nonclinical toxicology package is largely complete, and relevant outstanding data are expected to be submitted in the context of the MAA. The repeat dose toxicity studies in rats indicated that daily treatment with molnupiravir was generally well tolerated at dose up to 500 mg/kg for 28 days. Bone and cartilage toxicity were seen in a 3-month study in rats; however, it is possible that these effects may only occur with longer duration of treatment. Furthermore, long-bone growth would be more active in younger rats than in older rats (Zoetis et al, 2003[4]), and considering that the proposed indication is for adults only, where the bone growth plates are closed, the findings are likely of limited relevance.

More significant toxicity was seen with molnupiravir administration in dogs compared to rats, despite the higher dosing and longer durations of treatment in rats. The basis for such differential sensitivity between species is unclear. However, there are deficiencies in the secondary pharmacology screen which may have precluded the identification of potential off targets of molnupiravir. Furthermore, it is noted that exposure levels for NHC and NHC-TP in bone marrow were only quantified in the case of rats. The pronounced effects on bone marrow seen in dogs have to date have not been seen clinically (see clinical section) and were not observed in mice, rats, rabbits or monkeys at exposures in excess of that seen clinically and for durations of at least 7-days up to 3-months.

The most important concern affects the advice on use in women of childbearing potential, pregnancy and breastfeeding, and the Conditions for Use reflect this.

Studies in animals have shown reproductive toxicity. Oral administration of molnupiravir to pregnant rats during the period of organogenesis resulted in embryo-foetal lethality and teratogenicity at 7.5 times the human NHC exposures at the recommended human dose (RHD) and reduced fatal growth at $\geq$ 2.9 times the human NHC exposure at the RHD. Oral administration of molnupiravir to rabbits during the period of organogenesis resulted in reduced foetal body weights at 18 times the human NHC exposure at the RHD. Although maternal toxicity was observed in both rats and rabbits at all dose levels in which developmental toxicity occurred, a substance related effect cannot be excluded.

Overall, the nonclinical studies are considered sufficient for supporting the use of molnupiravir in an emergency setting.

2.4. Clinical Data

The clinical data package for this procedure consists of the following studied with the pivotal study for the purpose of this procedure being MK-4482-002.

Study	**Phase/ Population**	**Study Results Included in Application**
MK-4482-002	Phase 2 (Part 1) Phase 3 (Part 2) non-hospitalised	Phase 2 (Part 1): IA2 results (all Part 1 participants who completed Day 29) for safety, efficacy, virology and Pharmacokinetics (PK) Phase 3 (Part 2): IA3/4 results (50% of randomised

[4] Zoetis T, Tassinari MS, Bagi C, Walthall K, Hurtt ME. Species comparison of postnatal bone growth and development. Birth Defects Res B Dev Reprod Toxicol. 2003 Apr;68(2):86-110. doi: 10.1002/bdrb.10012. PMID: 12866701.

Study	Phase/ Population	Study Results Included in Application
		participants who completed Day 29) for safety, efficacy and virology
MK-4482-006	Phase 2a non-hospitalised	Dose-finding virologic endpoint Final results for safety, virology and PK
MK-4482-001	Phase 2 hospitalised	Phase 2: IA2 results (all Part 1 participants who completed Day 29) for safety, efficacy, virology and PK
MK-4482-004	Phase 1 healthy subjects	Final results for safety and PK

2.4.1. Pharmacokinetics

Before embarking on studies to assess the efficacy of molnupiravir in subjects with COVID-19, a single Phase 1 safety and pharmacokinetics (PK) study was conducted in healthy subjects.

In this study **(MK4482-004)** powder in bottle (PIB) and dry filled capsules were used, and their bioavailability was compared but not in a crossover fashion. No changes to the capsule formulation were made after dose and formulation selection in this study. Molnupiravir is to be supplied commercially as a dry filled hard capsule containing 200 mg of the active substance.

Since this study assessed formulations for efficacy studies and provided the basis for proceeding with 200 mg, 400 mg and 800 mg BID dosing in dose-finding efficacy studies, a brief description of the study and results is included below along with some other pertinent information for use.

MK-4482-004 was conducted in healthy male (84%) and female subjects (16%) aged from 19-60 years (mean 40 years) enrolled at a single site in the UK. The study comprised three parts.

Part 1 (Single Ascending Dose)
Part 1 comprised 8 dose-escalation cohorts and two formulations:
• Cohort 1: 50 mg EIDD-2801 or placebo (powder-in-bottle [PIB] formulation)
• Cohort 2: 100 mg EIDD-2801 or placebo (PIB formulation)
• Cohort 3: 200 mg EIDD-2801 or placebo (PIB formulation)
• Cohort 4: 400 mg EIDD-2801 or placebo (PIB formulation)
• Cohort 5: 600 mg EIDD-2801 or placebo (PIB formulation)
• Cohort 6: 800 mg EIDD-2801 or placebo (PIB formulation)
• Cohort 7: 1200 mg EIDD-2801 or placebo (capsule formulation)
• Cohort 8: 1600 mg EIDD-2801 or placebo (capsule formulation)
Subjects were randomised to receive EIDD-2801 or placebo in a 3:1 ratio (6 active; 2 placebo).

Molnupiravir (EIDD-2801) was quantifiable in samples from all subjects at 0.5 h after 800 mg but was present in low concentrations. Following single doses up to 800 mg (PIB formulation), **NHC (EIDD-1931)** appeared rapidly in plasma, with a median tmax range of 0.5 to 1.5 h. At ≤800 mg the

EIDD-1931 plasma concentrations declined after Cmax in an essentially monophasic manner, with geometric mean half-lives of between 0.907 and 1.29 h.

Table 12: Summary of the Plasma Pharmacokinetic Parameters for EIDD-1931 Following Single Oral Doses of 50 to 800 mg EIDD-2801 (Powder-in-bottle) for Protocol EIDD-2801-1001-UK

Matrix: Plasma; Analyte: EIDD-1931; Profile Day: 1

	EIDD-2801 PIB (fasted)					
Parameter	50 mg (N = 6)	100 mg (N = 6)	200 mg (N = 6)	400 mg (N = 6)	600 mg (N = 6)	800 mg (N = 6)
AUC_{last} (h*ng/mL)	415 (27.4) [6]	917 (27.5) [6]	1810 (20.0) [6]	4000 (20.2) [6]	6120 (21.6) [6]	8720 (10.4) [6]
$DAUC_{last}$ (h*ng/mL/mg)	8.30 (27.4) [6]	9.17 (27.5) [6]	9.05 (20.0) [6]	9.99 (20.2) [6]	10.2 (21.6) [6]	10.9 (10.4) [6]
AUC_{0-inf} (h*ng/mL)	432 (26.5) [6]	932 (27.0) [6]	1830 (19.6) [6]	4010 (20.2) [6]	6130 (21.4) [6]	8740 (10.4) [6]
$DAUC_{0-inf}$ (h*ng/mL/mg)	8.64 (26.3) [6]	9.32 (27.0) [6]	9.13 (19.6) [6]	10.0 (20.2) [6]	10.2 (21.4) [6]	10.9 (10.4) [6]
$\%AUC_{extrap}$ (%)	3.34 (66.6) [6]	1.42 (55.8) [6]	0.931 (68.3) [6]	0.288 (28.2) [6]	0.247 (65.3) [6]	0.245 (40.1) [6]
C_{max} (ng/mL)	223 (46.2) [6]	454 (42.2) [6]	926 (12.6) [6]	1850 (22.7) [6]	2720 (27.0) [6]	3640 (13.4) [6]
DC_{max} (ng/mL/mg)	4.47 (46.2) [6]	4.54 (42.2) [6]	4.63 (12.6) [6]	4.63 (22.7) [6]	4.53 (27.0) [6]	4.55 (13.4) [6]
t_{max} (h)	1.00 (0.517-1.00) [6]	1.00 (0.500-1.50) [6]	1.00 (0.500-1.00) [6]	1.00 (0.500-1.00) [6]	1.00 (1.00-1.00) [6]	1.00 (0.500-1.00) [6]
t_{last} (h)	5.00 (4.00-6.00) [6]	6.00 (6.00-6.00) [6]	7.50 (6.00-9.00) [6]	9.00 (9.00-12.0) [6]	9.00 (9.00-12.0) [6]	12.0 (12.0-12.0) [6]
$t_{1/2}$ (h)	0.945 (12.1) [6]	0.907 (10.1) [6]	1.02 (16.4) [6]	1.03 (8.86) [6]	1.06 (10.3) [6]	1.29 (7.10) [6]
CL_z/F (L/h)	0.747 (72.8) [6]	1.11 (50.5) [6]	0.824 (104) [6]	1.36 (104) [6]	2.35 (51.5) [6]	2.06 (17.9) [6]

AUC_{0-inf} = area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC_{last} = area under the plasma concentration-time curve from time 0 to the last measurable non-zero concentration (t_{last}); CL/F = apparent clearance following an extravascular dose; CLR = renal clearance; C_{max} = maximum observed concentration; CV = coefficient of variation (%); n = number of subjects with valid observations; PIB = powder-in-bottle; $t_{1/2}$ = apparent terminal elimination half-life; t_{last} = time of the last quantifiable concentration; t_{max} = time of the maximum observed concentration; $\%AUC_{extrap}$ = percentage of AUC_{0-inf} that is due to extrapolation from the last quantifiable concentration to infinity.
Parameter starting with 'D' letter signifies the corresponding parameter was normalized by dose administered.
Geometric mean (CV) [n] statistics presented; for t_{max} and t_{last}, median (min-max) [n] statistics presented.

Following single doses of 1200 and 1600 mg (capsule formulation), median tmax was delayed relative to lower doses (1.5-1.75 h) and plasma concentrations were quantifiable until 24 h for 2 and 5 subjects, respectively. Decreases in plasma concentrations after Cmax were biphasic and values of estimated t1/2 were longer (GM t1/2 1.81 and 4.59 h). Where the last quantifiable concentration was at 12 h, t1/2 was consistent with that for the lower dose cohorts.

Table 13: Summary of the Plasma Pharmacokinetic Parameters for EIDD-1931 Following Single Oral Doses of 1200 to 1600 mg EIDD-2801 (Capsule) for Protocol EIDD-2801-1001-UK

Matrix: Plasma; Analyte: EIDD-1931; Profile Day: 1

	EIDD-2801 capsule (fasted)	
Parameter	1200 mg (N = 6)	1600 mg (N = 6)
AUC_{last} (h*ng/mL)	13800 (11.7) [6]	20700 (31.4) [6]
$DAUC_{last}$ (h*ng/mL/mg)	11.5 (11.7) [6]	12.9 (31.4) [6]
AUC_{0-inf} (h*ng/mL)	13800 (11.8) [6]	20700 (31.4) [6]
$DAUC_{0-inf}$ (h*ng/mL/mg)	11.5 (11.8) [6]	12.9 (31.4) [6]
$\%AUC_{extrap}$ (%)	0.196 (37.9) [6]	0.258 (32.1) [6]
C_{max} (ng/mL)	4500 (17.9) [6]	6350 (20.6) [6]
DC_{max} (ng/mL/mg)	3.75 (17.9) [6]	3.97 (20.6) [6]
t_{max} (h)	1.75 (1.00-2.50) [6]	1.50 (1.00-2.00) [6]
t_{last} (h)	12.0 (12.0-24.0) [6]	24.0 (15.0-24.0) [6]
$t_{1/2}$ (h)	1.81 (73.5) [6]	4.59 (71.6) [6]
CL_z/F (L/h)	3.90 (29.8) [6]	4.08 (18.5) [6]

AUC_{0-inf} = area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC_{last} = area under the plasma concentration-time curve from time 0 to the last measurable non-zero concentration (t_{last}); CL/F = apparent clearance following an extravascular dose; CLR = renal clearance; C_{max} = maximum observed concentration; CV = coefficient of variation (%); n = number of subjects with valid observations; PIB = powder-in-bottle; $t_{1/2}$ = apparent terminal elimination half-life; t_{last} = time of the last quantifiable concentration; t_{max} = time of the maximum observed concentration; $\%AUC_{extrap}$ = percentage of AUC_{0-inf} that is due to extrapolation from the last quantifiable concentration to infinity.
Parameter starting with 'D' letter signifies the corresponding parameter was normalized by dose administered.
Geometric mean (CV) [n] statistics presented; for t_{max} and t_{last}, median (min-max) [n] statistics presented.

Maximum observed plasma concentrations of EIDD-1931 were between 229- and 912-fold higher vs. EIDD-2801 in subjects where EIDD-2801 concentrations were quantifiable. The geometric mean EIDD-1931: EIDD-2801 ratio based on Cmax (MRCmax) at doses from 600 to 1600 mg EIDD-2801 was between 476 and 610.

Plasma concentration-time profiles of EIDD-1931 were generally well defined, with a percentage of AUC_{0-inf} that is due to extrapolation from the last quantifiable concentration to infinity (%AUCextrap) of <10% for all subjects. Between-subject variability, as assessed by geometric CV, was generally low (<25%) to moderate (25% to 40%) for AUC_{0-12}, AUC_{last}, AUC_{0-inf} and Cmax.

Part 2 (Food Effect)

Subjects were randomised to a treatment crossover sequence in a 1:1 ratio:

• Sequence 1: 200 mg EIDD-2801 (capsule formulation) in the fed state (within 30 minutes of a high fat breakfast) followed by 200 mg EIDD-2801 (capsule formulation) in the fasted state.

• Sequence 2**:** 200 mg EIDD-2801 (capsule formulation) in the fasted state followed by 200 mg EIDD-2801 (capsule formulation) in the fed state (as above).

There was a 14-day washout period between doses.

Following oral administration of 200 mg EIDD-2801 in the fed state, tmax for EIDD-1931 occurred later, with a median value of 3 h and a range of 2 to 4 h. The first quantifiable concentrations occurred between 0.5 and 1.5 h.

Generally, the slower absorption and later tmax in the fed state was reflected in a lower geometric mean Cmax, with values of 575 ng/mL in the fed state compared to 893 ng/mL in the fasted state. The GLSM ratio for Cmax in the fed state compared to the fasted state was 0.644 and the 90% CI did not include unity. The $AUC_{0\text{-}inf}$ and AUC_{last} were similar in the fed and fasted state. The ratios of GLSMs were 0.955 and 0.959, respectively, and the 90% CIs included unity.

Table 23: Assessment of the Effect of Food on the Pharmacokinetic Parameters of EIDD-1931 Following Single Oral Doses of 200 mg EIDD-2801 (Capsule) for Protocol EIDD-2801-1001-UK

Matrix: Plasma; Analyte: EIDD-1931, Profile Day: 1

Parameter	Treatment	n	GLSM	Fed versus Fasted Ratio of GLSMs (90% CI)
$AUC_{0\text{-}inf}$ (h*ng/mL)	200 mg EIDD-2801 capsule (fasted)	10	1980	
	200 mg EIDD-2801 capsule (fed)	10	1890	0.955 (0.881, 1.03)
AUC_{last} (h*ng/mL)	200 mg EIDD-2801 capsule (fasted)	10	1950	
	200 mg EIDD-2801 capsule (fed)	10	1870	0.959 (0.881, 1.04)
C_{max} (ng/mL)	200 mg EIDD-2801 capsule (fasted)	10	893	
	200 mg EIDD-2801 capsule (fed)	10	575	0.644 (0.535, 0.775)
t_{max} (h)[a]	200 mg EIDD-2801 capsule (fasted)	10	1.00	
	200 mg EIDD-2801 capsule (fed)	10	3.00	1.75 (1.00, 2.50)

[a] The n, median, and Hodges-Lehmann estimate of median difference (90% CI) from the Wilcoxon signed-rank test presented.

$AUC_{0\text{-}inf}$ = area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC_{last} = area under the plasma concentration-time curve from time 0 to the last measurable non-zero concentration (t_{last}); CI = confidence interval; C_{max} = maximum observed concentration; GLSM = geometric least squares mean; n = number of subjects with valid observations; NC = not calculated; t_{max} = time of the maximum observed concentration

Model: ln(parameter) = treatment sequence + period + treatment + subject(treatment sequence) + random error, with subject(treatment sequence) fitted as a random effect

The GLSMs, ratios of GLSMs and corresponding CIs were obtained by taking the exponential of the LSMs, differences and corresponding CIs on the natural log (ln) scale.

The geometric mean t1/2 in the fasted state was 0.977 h and that in the fed state was 1.09 h. The between-subject variability, as judged by geometric CV, was moderate (25% to 40%) for AUC_{last}, $AUC_{0\text{-}inf}$ and Cmax in both the fasted and fed states.

The company claimed that the capsule formulation provided similar systemic exposure to EIDD-1931 (based on AUC0-inf and AUClast) as the PIB formulation at the same dose. However, Cmax was up to 24% lower and tmax was up to 0.75 h later following administration of the capsule formulation.

Part 3 (Multiple Ascending Dose)

Part 3 comprised 7 dose-escalation cohorts, all of which received capsules:

• Cohort 1: 50 mg EIDD-2801 or placebo BID (capsule formulation)

• Cohort 2: 100 mg EIDD-2801 or placebo BID (capsule formulation)

- Cohort 3: 200 mg EIDD-2801 or placebo BID (capsule formulation)
- Cohort 4: 300 mg EIDD-2801 or placebo BID (capsule formulation)
- Cohort 5: 400 mg EIDD-2801 or placebo BID (capsule formulation)
- Cohort 6: 600 mg EIDD-2801 or placebo BID (capsule formulation)
- Cohort 7: 800 mg EIDD-2801 or placebo BID (capsule formulation)

Subjects in each cohort received EIDD-2801 or placebo in a 3:1 ratio. The first dose each day was given in the fasted state. There were no restrictions on, or conditions applied to food before taking the second daily dose. A single dose was administered on the morning of Day 6 for the collection of steady-state PK blood samples.

As in Part 1, very few subjects had quantifiable concentrations of **EIDD-2801** on Day 1. On day 6 after the last dose of 600 mg EIDD-2801 was quantifiable in 3 subjects at 0.5 h with concentrations from 5.62 to 13.6 ng/ml. After the last dose of 800 mg EIDD-2801 was quantifiable for 4 subjects at 0.5 h with concentrations from 5.74 to 14.9 ng/ml.

EIDD-1931 appeared rapidly in plasma and was generally quantifiable from between 0.25 and 0.5 h on Day 1 at all dose levels. Half of those administered 200 mg BID and all except 1 administered ≥300 mg BID had quantifiable pre-dose samples on Day 6. Generally, tmax occurred between 1.00 and 2.50 h on Days 1 and 6.

Table 24: Summary of Plasma Pharmacokinetic Parameters for EIDD-1931 on Day 1 Following the First of Multiple Oral Doses of 50 to 800 mg EIDD-2801 (Capsule) for Protocol EIDD-2801-1001-UK

Matrix: Plasma; Analyte: EIDD-1931; Profile Day: 1

	EIDD-2801 capsule BID (fasted)						
Parameter	50 mg (N = 6)	100 mg (N = 6)	200 mg (N = 6)	300 mg (N = 6)	400 mg (N = 6)	600 mg (N = 6)	800 mg (N = 6)
AUC_{last} (h*ng/mL)	444 (17.3) [6]	835 (19.9) [6]	1640 (15.5) [6]	3080 (17.4) [6]	3790 (19.5) [6]	6110 (26.9) [6]	8180 (21.5) [6]
$DAUC_{last}$ (h*ng/mL/mg)	8.88 (17.3) [6]	8.35 (19.9) [6]	8.18 (15.5) [6]	10.3 (17.4) [6]	9.48 (19.5) [6]	10.2 (26.9) [6]	10.2 (21.5) [6]
AUC_{0-inf} (h*ng/mL)	461 (15.7) [6]	855 (19.8) [6]	1660 (15.3) [6]	3090 (17.4) [6]	3800 (19.5) [6]	6680 (17.6) [5]	8200 (21.6) [6]
$DAUC_{0-inf}$ (h*ng/mL/mg)	9.22 (15.7) [6]	8.55 (19.8) [6]	8.32 (15.3) [6]	10.3 (17.4) [6]	9.51 (19.5) [6]	11.1 (17.6) [5]	10.3 (21.6) [6]
$\%AUC_{extrap}$ (%)	3.36 (43.6) [6]	2.19 (42.6) [6]	1.34 (90.5) [6]	0.395 (22.1) [6]	0.327 (34.4) [6]	0.201 (18.8) [5]	0.214 (52.4) [6]
AUC, (h*ng/mL)	461 (15.7) [6]	854 (19.8) [6]	1660 (15.3) [6]	3080 (17.3) [6]	3800 (19.5) [6]	6110 (26.9) [6]	8190 (21.5) [6]
DAUC, (h*ng/mL/mg)	9.22 (15.7) [6]	8.54 (19.8) [6]	8.31 (15.3) [6]	10.3 (17.3) [6]	9.50 (19.5) [6]	10.2 (26.9) [6]	10.2 (21.5) [6]
$\%AUC_{t,extrap}$ (%)	3.31 (43.8) [6]	2.17 (41.9) [6]	1.25 (104) [6]	0.119 (277) [6]	0.103 (517) [6]	0.00785 (37.0) [6]	0.00933 (47.7) [6]
C_{max} (ng/mL)	223 (19.4) [6]	395 (18.5) [6]	766 (16.3) [6]	1280 (15.2) [6]	1530 (23.2) [6]	2160 (31.4) [6]	2770 (13.3) [6]
DC_{max} (ng/mL/mg)	4.47 (19.4) [6]	3.95 (18.5) [6]	3.83 (16.3) [6]	4.27 (15.2) [6]	3.81 (23.2) [6]	3.60 (31.4) [6]	3.47 (13.3) [6]
t_{max} (h)	1.00 (1.00-1.00) [6]	1.25 (1.00-2.03) [6]	1.50 (1.00-1.50) [6]	1.50 (1.00-1.50) [6]	1.50 (1.00-2.00) [6]	1.75 (1.00-6.00) [6]	1.75 (1.50-2.50) [6]
t_{last} (h)	6.00 (4.00-6.00) [6]	6.00 (6.00-6.03) [6]	6.00 (6.00-9.07) [6]	9.00 (9.00-11.9) [6]	9.03 (9.00-11.9) [6]	11.9 (11.9-12.0) [6]	11.9 (11.9-11.9) [6]
$t_{1/2}$ (h)	0.937 (14.0) [6]	0.918 (9.08) [6]	0.960 (10.4) [6]	1.09 (17.7) [6]	1.05 (13.1) [6]	1.16 (3.50) [5]	1.18 (7.28) [6]
CL/F (L/h)	0.848 (64.2) [6]	1.16 (94.6) [6]	0.833 (80.2) [6]	1.09 (40.4) [6]	1.20 (65.8) [6]	1.95 (21.3) [6]	2.78 (19.5) [6]

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Table 25: Summary of Plasma Pharmacokinetic Parameters for EIDD-1931 on Day 6 Following Multiple Oral Doses of 50 to 800 mg EIDD-2801 (Capsule) for Protocol EIDD-2801-1001-UK

Matrix: Plasma; Analyte: EIDD-1931; Profile Day: 6

	EIDD-2801 capsule BID (fasted)						
Parameter	50 mg (N = 6)	100 mg (N = 6)	200 mg (N = 6)	300 mg (N = 6)	400 mg (N = 6)	600 mg (N = 6)	800 mg (N = 6)
AUC_{last} (h*ng/mL)	414 (16.2) [6]	947 (15.7) [6]	1720 (26.0) [6]	2980 (16.3) [6]	3730 (21.6) [6]	7250 (28.1) [6]	8450 (18.5) [5]
$DAUC_{last}$ (h*ng/mL/mg)	8.29 (16.2) [6]	9.47 (15.7) [6]	8.58 (26.0) [6]	9.92 (16.3) [6]	9.31 (21.6) [6]	12.1 (28.1) [6]	10.6 (18.5) [5]
AUC_∞ (h*ng/mL)	432 (14.9) [6]	968 (15.3) [6]	1730 (25.2) [6]	2960 (16.2) [6]	3710 (21.6) [6]	7110 (28.2) [6]	8330 (17.9) [5]
$DAUC_\infty$ (h*ng/mL/mg)	8.65 (14.9) [6]	9.68 (15.3) [6]	8.65 (25.2) [6]	9.88 (16.2) [6]	9.28 (21.6) [6]	11.9 (28.2) [6]	10.4 (17.9) [5]
$\%AUC_{extrap}$ (%)	3.78 (30.8) [6]	1.82 (81.7) [6]	---	0.370 (NC) [6]	0.367 (NC) [6]	---	---
RA_{AUC}	0.938 (7.80) [6]	1.13 (9.25) [6]	1.04 (18.0) [6]	0.961 (14.7) [6]	0.977 (11.7) [6]	1.16 (12.2) [6]	1.09 (11.8) [5]
C_{max} (ng/mL)	188 (8.67) [6]	434 (14.0) [6]	742 (32.1) [6]	1100 (20.6) [6]	1470 (20.9) [6]	2240 (20.9) [6]	2970 (16.8) [5]
DC_{max} (ng/mL/mg)	3.76 (8.67) [6]	4.34 (14.0) [6]	3.71 (32.1) [6]	3.68 (20.6) [6]	3.67 (20.9) [6]	3.74 (20.9) [6]	3.71 (16.8) [5]
RA_{Cmax}	0.843 (16.0) [6]	1.10 (11.4) [6]	0.969 (23.8) [6]	0.861 (14.3) [6]	0.962 (18.5) [6]	1.04 (20.0) [6]	1.09 (7.15) [5]
t_{max} (h)	1.00 (1.00-1.50) [6]	1.25 (1.00-1.50) [6]	1.50 (0.500-1.50) [6]	1.50 (1.00-2.00) [6]	1.50 (1.00-1.50) [6]	1.75 (1.50-2.50) [6]	1.50 (1.00-2.02) [5]
t_{last} (h)	6.00 (4.00-6.00) [6]	6.00 (6.00-9.00) [6]	9.00 (6.00-12.0) [6]	12.0 (9.00-24.0) [6]	12.0 (9.00-24.0) [6]	24.0 (24.0-24.0) [6]	24.0 (15.1-36.0) [5]
$t_{1/2}$ (h)	0.968 (15.5) [6]	0.970 (15.8) [6]	1.24 (36.4) [6]	1.71 (47.1) [6]	1.20 (9.58) [5]	NC (NC) [1]	7.08 (154) [4]
C_{trough} (ng/mL)	0.0891 (184) [6]	0.230 (170) [6]	1.03 (322) [6]	5.47 (114) [6]	5.13 (109) [6]	18.7 (41.3) [6]	16.7 (42.8) [5]
CL/F (L/h)	0.777 (73.1) [6]	0.945 (52.3) [6]	1.02 (80.9) [6]	1.06 (47.5) [6]	1.43 (41.8) [6]	2.31 (44.5) [6]	2.27 (90.0) [5]

AUC_{last} = area under the plasma concentration-time curve from time 0 to the last measurable non-zero concentration (t_{last}); AUC_∞ = area under the plasma concentration-time curve during a dosing interval hours post dose; CL/F = apparent clearance following an extravascular dose; CLR = renal clearance; C_{max} = maximum observed concentration; C_{trough} = plasma concentration at the end of the dosing interval; C_{trough} = plasma concentration at the end of the dosing interval; CV = coefficient of variation (%); n = number of subjects with valid observations; NC = not calculated; RA_{AUC} = observed accumulation ratio based on AUC_∞; RA_{Cmax} = observed accumulation ratio based on C_{max}; $t_{1/2}$ = apparent terminal elimination half-life; t_{last} = time of the last quantifiable concentration; t_{max} = time of the maximum observed concentration

Parameter starting with 'D' letter signifies the corresponding parameter was normalized by dose administered.

Geometric means (CV) [n] statistics presented; for t_{max} and t_{last} median (min-max) [n] statistics presented.

On Day 6, similar to Day 1, EIDD-1931 concentrations generally declined in a monophasic manner following administration of ≤400 mg BID and were mostly below the LLOQ by ≤12 h. One subject administered 300 mg BID, 1 administered 400 mg BID and all except 2 administered ≥600 mg BID had quantifiable levels up to 24 h and the emergence of a second slower elimination phase was apparent, giving an increase of geometric mean t1/2 with dose. Following 800 mg BID the elimination phase was quantifiable, with a geometric mean t1/2 of 7.08 h (range 1.49 to 19.1 h).

Ctrough was estimated by extrapolation from the last observed concentration where concentrations at the end of the dosing interval were below the LLOQ. Geometric mean Ctrough was 5.47 ng/mL after 300 mg BID dose level and increased to 18.7 and 16.7 ng/mL after 600 and 800 mg BID, respectively.

Across all cohorts and days, Cmax for EIDD-1931 was between 81.6- and 672-fold higher than for EIDD-2801 (where measurable).

There was no evidence of accumulation. The longer secondary elimination phases observed for some subjects at 800 mg BID did not result in consistently higher accumulation ratios as this phase represented only a small amount of the overall AUCT. Between-subject variability, as assessed by geometric CV, was generally low (<25%) on Days 1 and 6 for AUCT and Cmax. The %AUCextrap on Day 1 was <10% for all profiles.

Although this was not a crossover study, the extent of absorption appeared to be similar between the PIB and capsule formulations, but the rate of absorption appeared to be slightly slower for the capsule formulation compared to the PIB formulation, which was reflected in a slightly later median tmax and lower GM Cmax.

Other pharmacokinetic properties

No formal ADME study was conducted in humans, and currently only non-clinical data is available, which is considered acceptable for an emergency use setting.

Data on excretion

After BID dosing in MK4482-004, up to 3.61% of the administered dose was excreted in urine as NHC when assessed by geometric mean percentage of the dose administered recovered in urine over the dosing interval (Fe_{0-T}). The majority (generally >90% of the total amount excreted) was excreted in the first 4 h. The GM CLR ranged from 0.777 to 2.78 L/h across Days 1 and 6. CLR and Fe_{0-T} were

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similar across cohorts and days at doses ≤200 mg BID. At >200 mg BID, there was a trend for CLR and Fe_{0-T} to increase with increasing dose. Over the 4-fold dose range from 200 to 800 mg BID, the amount excreted in urine during a dosing interval (Ae_{0-T}) increased by approximately 16- and 11-fold on Days 1 and 6, respectively. The inter-subject variability in renal PK parameters was generally high (>40%).

Based on a semi-quantitative analysis of pooled human urine samples obtained at 0-12 h on Day 1, NHC, cytidine, uridine and NHC-glucuronide were all detected in urine obtained after dosing with 100 mg or 800 mg. The levels of NHC and NHC-glucuronide in urine increased approximately 18- and 13-fold, respectively, in the 800 mg BID dose group compared to the 100-mg BID dose group. Uridine increased approximately 6-fold in the 800 mg BID dose. The fold-increase in cytidine could not be calculated because little to no cytidine was detected at the lower dose. The company considered that the increase was probably as much or greater than that observed for uridine. The dose dependent increases of these pyrimidine bases in urine suggested that some amount was derived from molnupiravir. It was concluded from the human and nonclinical data that the majority of molnupiravir is converted to NHC, NHC-TP and (or ultimately to) uridine and/or cytidine which then mix with the endogenous nucleoside pool.

Population pharmacokinetic (POPPK) modelling

A population PK model of NHC was developed using plasma concentration data collected in MK4482-001 Part 1, -002 Part 1, -004 and -006. The analysis dataset included 2952 NHC concentrations from 100 healthy participants, 189 inpatients with COVID-19 and 260 outpatients with COVID-19. Modelling used NONMEM, Version 7, Level 3. The first-order conditional estimation with interaction method was used during all stages of model development where possible. The forward selection followed by backward elimination approach was used for covariate evaluation. The final model was a linear 2-compartment model with sigmoid absorption (implemented using a zero-order input process into a depot compartment followed by first-order absorption into the central compartment) and first-order elimination. Covariates included in the final model as statistically significant predictors of PK parameters were:

- A less-than-proportional power function of body weight on CL/F;
- A less-than-proportional power function of BMI on VC/F;
- A 31.3% decrease in VC/F in females compared to males;
- A 568% increase in duration of D1 following a high-fat meal compared to fasting or a standard meal;
- A 64.4% decrease in D1 for oral solution or suspension compared to capsule;
- A 26.5% decrease in D1 for inpatients compared to healthy or outpatient participants.

Attempts were made to harmonise the body size effects on CL/F and VC/F at the stage of the model refinement. The results suggested that the effect of body size on CL/F could be interchangeably described by body weight or by BMI if associated with sex. However, the effect of body size on VC/F was better described by BMI associated with sex compared to body weight alone. Therefore, for reasons of parsimony, the effects identified during covariate analysis were not modified.

Parameter estimates for the final model are presented below. GOF plots indicated that the final model described the data reasonably well. All model parameters were estimated precisely (%RSE < 29% for fixed effects and < 36% for random effects) and without correlation. Based upon the final PK model, shrinkage in the Bayesian estimates of CL/F was small (9.0%), suggesting that individual predictions of CL/F, and thus, individual exposures can be considered reliable. However, shrinkage in VC/F and D1 were reasonably high (36.6% and 39.0%, respectively). Therefore, Cmax predictions should be considered with caution.

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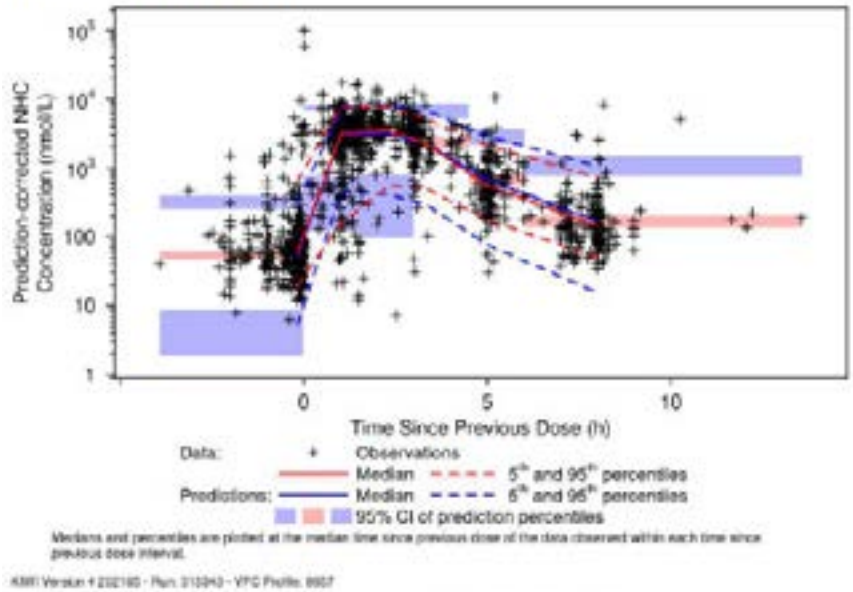
Table 13. Parameter Estimates and Standard Errors for the Final Plasma NHC Pharmacokinetic Model

Parameter		Final Parameter Estimate		Magnitude of Variability	
		Population Mean	%RSE	Final Estimate	%RSE
CL/F	Apparent central clearance in 80-kg participants (L/h)	76.9	2.01	41.1 %CV	14.9
	Power of body weight effect (-)	0.421	20.4		
VC/F	Apparent central volume in 28-kg/m^2 BMI male participants (L)	72.0	6.40	40.0 %CV	35.8
	Proportional shift in female participants (-)	-0.313	18.1		
	Power of BMI effect (-)	0.753	28.4		
Q/F	Apparent distribution clearance (L/h)	3.35	6.73	NE	NA
VP/F	Apparent peripheral volume (L)	70.0	14.8	NE	NA
KA	First-order absorption rate constant (1/h)	0.830	2.81	NE	NA
D1	Zero-order absorption duration (h)	0.802	4.83	42.8 %CV	15.9
	Proportional shift due to high-fat meal (-)	5.68	10.4		
	Proportional shift in oral solution (-)	-0.644	5.71		
	Proportional shift in hospitalized patients (-)	-0.265	22.4		
PHF	Probability of unknown high-fat meal (-)	0.250	FIXED	NE	NA
Residual Variability in Phase 1 Studies		0.123	9.58	35.1 %CV	NA
Residual Variability in Phase 2 Studies		0.268	5.33	51.7 %CV	NA
Minimum Value of the Objective Function = 38916.167					

Abbreviations: BMI, body mass index; %CV, coefficient of variation expressed as a percent; IIV, interindividual variability; NA, not applicable; NE, not estimated; NHC, β-d-N4-hydroxycytidine; %RSE, relative standard error expressed as a percent.
Note: Shrinkage estimates: 9.0% for IIV in CL/F, 36.6% for IIV in VC/F, and 39.0% for IIV in D1.
KIWI Run 320908.
Source: d5pk\tables\doc\d5pk-final-pk-model-mk4482-002664-lah_r320908_mod.docx.

The figure shows that the median concentrations predicted in patients with COVID-19 by the final PK model tracked the median observed concentrations and the variability reasonably.

Figure 19. Visual Predictive Check Plots for the Final Pharmacokinetic Model in Patients With COVID-19



Abbreviations: CI, confidence interval; NHC, β-d-N4-hydroxycytidine.
Source: d5pk\graphs\pnghi\vpc\vpc-r315343-vpc-d5pk-final-pk-model-mk4482-002664-ph2-combined-t1-p8657-s1-001.png.

Simulations were performed based on the final PK model using covariate data from the participants included in the analysis dataset and their individual Bayesian estimates of PK parameters. Simulations assumed hypothetical 800 mg BID dosing for 5.5 days for all individuals in the analysis dataset.

Numerical integration was performed in NONMEM to compute the trough concentration prior to the last dose (Ctrough), Cmax and AUC_{0-12} after the last dose for each individual. Cmax was calculated for participants in which the absorption of NHC could be assessed (individuals for whom IIV was estimated on more than just CL/F). The model-predicted distribution of exposure metrics is shown by study in the tables below, first in nmol/L and then by ng/mL. The tables are specific to the recommended posology of 800 mg BID for 5 days (10 doses).

Table 2. Distribution of Model-Predicted NHC Exposures (Molar Units) After 5.5 Days of 800 mg Twice Daily Dosing, by Study

Variable		MK-4482-P001	MK-4482-P002	MK-4482-P004	MK-4482-P006	Overall	Patients With COVID-19*
Maximum Concentration (nmol/L)	Mean (SD)	9530 (3110)	NA	10600 (2140)	NA	9910 (2840)	9530 (3110)
	Geom. mean (%CV)	8990 (36.9)		10400 (20.7)		9460 (32.6)	8990 (36.9)
	Median	9260		10600		9870	9260
	P5, P95	4580, 15600		7570, 14800		5050, 15400	4580, 15600
	n	178		100		278	178
Trough Concentration (nmol/L)	Mean (SD)	230 (555)	413 (1470)	102 (69.1)	185 (472)	286 (954)	302 (1050)
	Geom. mean (%CV)	110 (123)	132 (141)	87.7 (55.7)	117 (79)	113 (113)	120 (124)
	Median	88.9	102	83.2	102	85.6	97.9
	P5, P95	34.5, 860	41.8, 1280	42.3, 284	59.4, 286	39.2, 582	39.2, 880
	n	189	194	100	66	549	449
AUC_{0-12} (nmol x h/L)	Mean (SD)	32500 (16100)	38000 (30100)	29800 (6880)	34600 (12900)	34200 (21100)	35200 (25000)
	Geom. mean (%CV)	30100 (38)	33200 (46.9)	29100 (22.3)	33200 (27.8)	31300 (38.3)	31900 (41)
	Median	28800	30800	28700	32100	29900	30200
	P5, P95	18800, 56800	19600, 80900	20600, 39800	24400, 49100	19600, 56800	19500, 65200
	n	189	194	100	66	549	449

Abbreviations: AUC_{0-12}, area under the NHC concentration versus time curve from 0 to 12 h postdose; %CV, coefficient of variation expressed as a percent; Geom., geometric; n, number of individuals; NA, not applicable; NHC, β-d-N4-hydroxycytidine; Px, xth percentile; SD, standard deviation.

* Excludes data from Study MK-4482-P004.

Table 3. Distribution of Model-Predicted NHC Exposures (Mass Units) After 5.5 Days of 800 mg Twice Daily Dosing, by Study

Variable		MK-4482-P001	MK-4482-P002	MK-4482-P004	MK-4482-P006	Overall	Patients With COVID-19*
Maximum Concentration (ng/mL)	Mean (SD)	2470 (807)	NA	2740 (554)	NA	2570 (737)	2470 (807)
	Geom. mean (%CV)	2330 (36.9)		2690 (20.7)		2450 (32.6)	2330 (36.9)
	Median	2400		2750		2560	2400
	P5, P95	1190, 4030		1960, 3840		1310, 3980	1190, 4030
	n	178		100		278	178
Trough Concentration (ng/mL)	Mean (SD)	59.6 (144)	107 (382)	26.5 (17.9)	47.9 (122)	68.9 (247)	78.4 (272)
	Geom. mean (%CV)	28.4 (123)	34.3 (141)	22.7 (55.7)	30.4 (73)	29.4 (113)	31.1 (124)
	Median	23.1	26.4	21.6	26.6	24.8	25.4
	P5, P95	8.94, 223	10.8, 333	11, 73.7	15.4, 74.1	10.2, 151	10.2, 223
	n	189	194	100	66	549	449
AUC_{0-12} (ng x h/mL)	Mean (SD)	8430 (4170)	9860 (7810)	7720 (1780)	8980 (3340)	8870 (5480)	9130 (5970)
	Geom. mean (%CV)	7790 (38)	8620 (46.9)	7540 (22.3)	8600 (27.6)	8120 (38.3)	8260 (41)
	Median	7450	8000	7450	8320	7740	7830
	P5, P95	4880, 14700	5080, 21000	5350, 10300	6320, 12700	5070, 14700	5060, 16900
	n	189	194	100	66	549	449

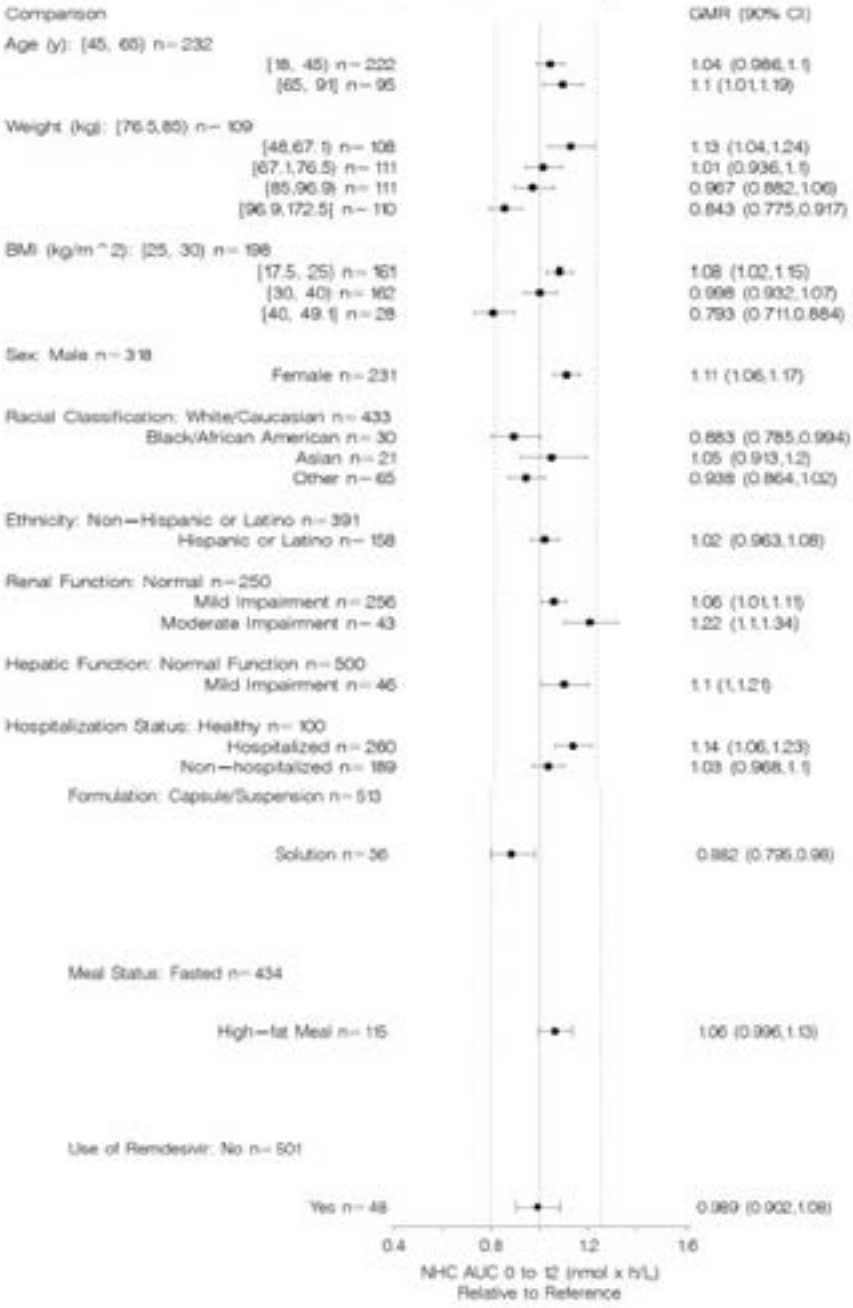
Abbreviations: AUC_{0-12}, area under the NHC concentration versus time curve from 0 to 12 h postdose; %CV, coefficient of variation expressed as a percent; Geom., geometric; n, number of individuals; NA, not applicable; NHC, β-d-N4-hydroxycytidine; Px, xth percentile; SD, standard deviation.

* Excludes data from Study MK-4482-P004.

The impact of the covariate effects included in the final PK model was evaluated on the basis of the geometric mean ratio (GMR) of exposure metrics. The intrinsic factor effects on MK-4482 PK were compared to standard bioequivalence limits (0.8 to 1.25). However, these limits are likely more restrictive than the true range of MK-4482 exposures associated with clinically equivalent efficacy and safety.

For all sub-groups of age, body weight, BMI, sex, racial classification, ethnicity, patient hospitalisation status, renal function, and hepatic function, the GMRs of AUC0-12 were within the 0.8 to 1.25 bioequivalence range, except for BMI ≥40 kg/m2, where the GMR fell just below this range. The company concluded that none of the evaluated intrinsic or extrinsic factors substantially influenced NHC exposures, as most effect sizes were well below 2-fold changes.

Figure 27. Forest Plot of Geometric Mean Ratios (90% Confidence Intervals) for Model-Predicted $AUC_{0\text{-}12}$ After 800 mg MK-4482 Twice Daily



The clinical relevance of covariates is usually established when changes in exposure are greater than 20% and not up to 2-fold as applied by the company.

Based on the figure shown above, subjects with body weight >96.9kg will show >20% less AUC compared to the reference patient (76.5-85 kg). Since body weight and BMI are highly correlated, it also applies to patients with BMI >40 kg/m^2.

In MK4482-002 Part 2 (see next section) the analysis of the primary endpoint by obesity status suggested that the lower AUC (>20%) in obese patients did not translate into reduced efficacy. However, caution is needed due to the low total number of observed events. The company will further

evaluate this matter when PK data from MK4482-002 Part 2 become available and the POPPK analysis has been updated, which is considered appropriate.

In contrast to obese subjects, >50% of subjects with moderate renal impairment are predicted to have a >20% higher AUC with 800 mg BID regimen. Based on the safety profile of molnupiravir, this is not a major concern. However, no information is available in patients with severe renal impairment because they were excluded from the trials. Moreover, relatively few subjects had any degree of hepatic impairment at study entry. With such limited data, including lack of a POPPK analysis that includes the data from MK4482-002 Part 2, a factual statement regarding the lack or paucity of data in subjects with severe renal impairment and subjects with any degree of hepatic impairment has been added to the Conditions for Use (see the appended document).

2.4.2. Efficacy data

The studies of most importance to support the efficacy of molnupiravir are:

- MK4482-006, which was a preliminary dose-finding study
- MK4482-002, which had dose-finding and confirmatory parts

Some other studies completed or ongoing include:

MK4482-001 was a study in hospitalised patients that was stopped at the end of Phase 2 due to lack of clinical effect.

MK4482-005 is an ongoing additional dose finding study (300 mg BID to 800 mg BID) in UK outpatients from which no unblinded data are yet available. MK4482-007 is an ongoing dose-finding study in hospitalised patients. No unblinded data are reported from this study.

2.4.2.1. Dose finding studies

MK4482-006 – dose finding with primary virologic endpoint

This Phase 2 study was conducted in 2020-2021 at 10 sites in the US. It was a randomised, double blind, placebo-controlled escalating dose study. Eligible adult subjects were to start treatment within ≤168 h from first symptom onset of a laboratory-proven episode of COVID-19. Laboratory confirmation for study entry required a positive molecular or non-molecular test conducted at any CLIA-certified laboratory from a sample collected ≤96 hours prior to study entry. Subjects were to have at least one symptom of fever (including feeling feverish or having chills) or signs/symptoms of respiratory illness (including but not limited to upper respiratory congestion, loss of sense of smell or taste, sore throat OR lower respiratory illness – cough, shortness of breath).

Eligible subjects were not in need of hospitalisation or immediate medical attention in the opinion of the investigator. They were not receiving supplemental oxygen at study entry. Hb was to be >10 g/dL in men and >9 g/dL in women with a platelet count >100,000/μL. Subjects with severe renal impairment or on dialysis were excluded along with those having LFTs >3× ULN or any significant liver disease. No therapeutic interventions with possible anti-SARS-CoV-2 activity were allowed within 30 days prior to study entry and subjects were not to have been vaccinated against SARS-CoV-2. The same restrictions applied during the study period.

Up to 172 fully evaluable participants were planned.

In Part 1 up to 44 participants were to be randomised 1:1 to receive molnupiravir 200 mg BID (Arm A) or placebo BID (Arm B) orally for 5 days.

The study then continued to enrol the following study parts:

In Parts 2-4 up to 16 per part were to be randomised 3:1 into Arms C and D (Part 2), Arms E and F (Part 3), and Arms G and H (Part 4) to receive molnupiravir up to 800 mg or placebo orally BID for 5 days.

In Parts 5-9 up to 16 per part were to be randomised 3:1 into Arms I and J (Part 5), Arms K and L (Part 6), Arms M and N (Part 7), Arms O and P (Part 8), and Arms Q and R (Part 9) to receive molnupiravir up to 800 mg or placebo orally BID for 5 days.

The doses for Parts 2 onwards could be the same, higher or lower than the dose(s) studied in previous study parts but could not exceed 800 mg BID. Doses were chosen based on emerging virology and safety data from this and other ongoing studies and were communicated in an official memo/protocol clarification letter. Dosing was without regard to food except that subjects fasted overnight before the PK sampling days.

Study Part	Treatment Description	Treatment Display Code
Part 1	Part1: Molnupiravir 200 mg BID	A
	Part 1: Placebo	B
Parts 2/3/4/5/6/7/8/9	Parts 2-9: Molnupiravir 400 or 800 mg BID	C/E/G/I/K/M/O/Q
	Parts 2-9: Placebo	D/F/H/J/L/N/P/R
Pooled Treatment	Molnupiravir 200 mg BID	1
	Molnupiravir 400 mg BID	2
	Molnupiravir 800 mg BID	3
	Placebo	9

In Part 1, randomisation was stratified by time (days) from symptom onset defined by:

• Early presentation: randomisation 0 to ≤60 h from symptom onset

• Late presentation: randomisation >60 to ≤168 h from symptom onset

Randomisation was not stratified in subsequent study parts.

The primary efficacy objective was to determine if molnupiravir reduces the time to viral RNA negativity, defined by RT-PCR applied to nasopharyngeal (NP) swabs. NP swabs were required to be collected at all sites. On Day 1, the sample was collected prior to the first dose of study treatment. The site at which virology testing was performed (UNC-CH) collected 1 NP swab per time point and divided the sample in preparation for analysis by infectivity vs. RT-PCR assay. All other study sites collected 2 NP swabs (1 per nostril) at each time point and 1 swab was prepared and shipped for analysis by infectivity assay and the other swab was sent for analysis by RT-PCR assay.

The RT-PCR assay was based on the US CDC 2019-nCoV EUA assay, which uses primers specific to the N1 region of the SARS-CoV2 RNA with LLOQ of 1018 copies/mL. The infectivity assay was that described by Sheahan (2020) in which Vero E6 cell monolayers were infected with an aliquot from the sample for 1 h. Culture medium was analysed for viral load at 2 and 5 days post infection by RT-PCR. A positive culture resulted when viral RNA was >1,000 copies/mL at Day 2 or increased from Day 2 to Day 5 by 0.5 $\log_{10}$ copies/mL. Missing values were imputed by the laboratory if positive cultures were demonstrated at the following time point. The GenoSure SARS CoV-2 RdRp assay (next-generation sequencing assay) was used to amplify and sequence the complete RdRp coding region of the SARS-

CoV-2 RNA. Minor variants detected at 1% of the viral population were reported. Paired samples from Baseline and Day 5 were sequenced. If the sample on Day 5 was below the LLOQ, then the sample from Day 3 was sequenced.

The following analysis sets were defined for this study:

Intent-to-Treat (ITT) = all randomised.

Modified Intent-to-Treat (mITT) = all treated with at least 1 post-baseline viral RNA assessment.

Per Protocol (PP) = no important protocol deviations and completed the Day 28 follow-up visit.

Blood samples were collected on Days 1, 7 and 28 for SARS-CoV-2 antibodies determined using a spike receptor binding domain (RBD) antigen capture ELISA. Samples were recorded as positive if they produced an absorbance value greater than the assay cut-off (0.376), which was determined based on testing of large numbers of reference samples.

Results

Subject disposition is shown in the figure and the populations analysed are shown in the table.

Figure 1: Disposition of Participants

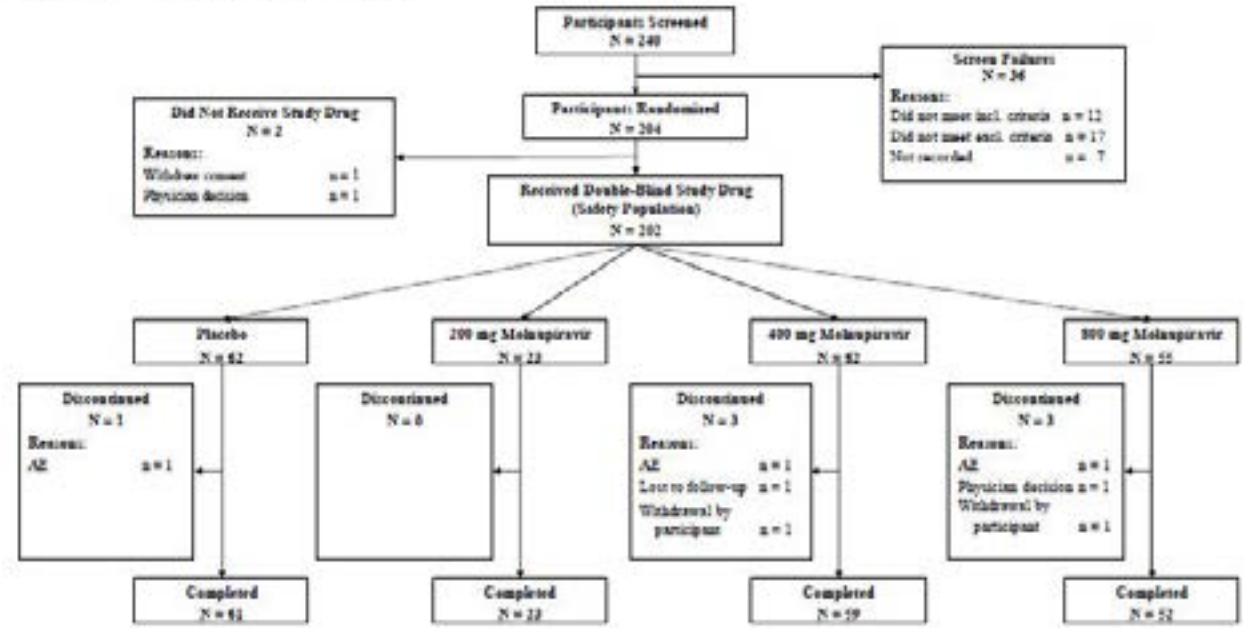


Table 2: Summary of Participant Populations (Randomized Participants)

Category	Molnupiravir 200 mg (N=23) n (%)	Molnupiravir 400 mg (N=64) n (%)	Molnupiravir 800 mg (N=55) n (%)	All Molnupiravir (N=142) n (%)	Placebo (N=62) n (%)
Number of Subjects Randomized (ITT)	23	64	55	142	62
Number of Subjects in the Safety Population [a]	23	62	55	140	62
Number of Subjects in the mITT Population [a]	23 (100.0)	61 (98.4)	53 (96.4)	137 (97.9)	61 (98.4)
Number of Subjects in the PK Population [a]	18 (78.3)	27 (43.5)	28 (50.9)	73 (52.1)	0
Number of Subjects in the PP Population [a]	23 (100.0)	58 (93.5)	52 (94.5)	133 (95.0)	61 (98.4)

On average, participants in the molnupiravir 200 mg group were slightly younger, with a mean age of 36.5 years, compared with mean ages of 42.4, 42.2 and 39.7 years in the 400 mg, 800 mg and placebo groups, respectively. About 50% were of each gender.

The 800 mg group had the lowest mean viral load at baseline at 5.80 $\log_{10}$ copies/mL, compared with viral loads of 6.69, 6.38 and 6.11 $\log_{10}$ copies/mL in the 200 mg, 400 mg and placebo groups, respectively.

Table 3: Summary of Key Demographic and Baseline Characteristics (Full Safety Population)

Category	Molnupiravir 200 mg (N=23)	Molnupiravir 400 mg (N=62)	Molnupiravir 800 mg (N=55)	All Molnupiravir (N=140)	Placebo (N=62)
Age (years)					
N	23	62	55	140	62
Mean (SD)	36.5 (15.34)	42.4 (14.88)	42.2 (14.36)	41.3 (14.80)	39.7 (14.10)
Median	32.0	42.5	42.0	41.0	39.0
Min, Max	19, 65	19, 82	18, 68	18, 82	19, 71
Baseline Viral Load (Log_{10} copies/mL)					
N	23	59	54	136	58
Mean (SD)	6.69 (1.888)	6.38 (1.837)	5.80 (1.823)	6.20 (1.859)	6.11 (1.794)
Median	7.25	6.72	6.12	6.52	6.40
Min, Max	3.0, 9.5	3.0, 9.9	3.0, 9.4	3.0, 9.9	3.0, 9.3
Days from Symptom Onset					
N	23	62	55	140	62
Mean (SD)	4.22 (1.308)	4.74 (1.236)	4.44 (1.309)	4.53 (1.283)	4.63 (1.326)
Median	4.00	4.85	4.60	4.60	4.55
Min, Max	1.8, 7.0	2.5, 7.1	1.4, 7.1	1.4, 7.1	1.8, 7.5

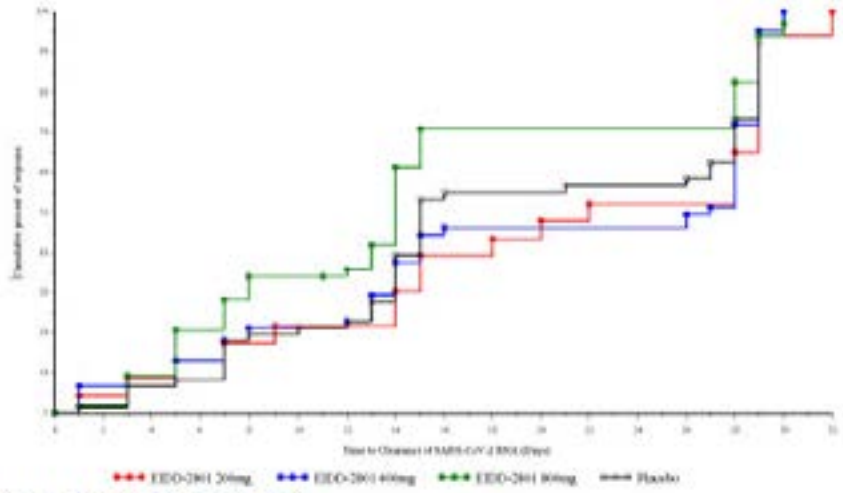
The majority had at least 1 risk factor for severe illness from COVID-19 (60.7% in the combined molnupiravir group and 57.7% in the placebo group). The most common risk factor for severe illness was smoking (30.7% molnupiravir and 32.3% placebo) while 39.3% and 40.3% in respective groups had no known risk factors for the development of severe COVID-19.

Results for the primary endpoint of time to clearance of viral RNA in NP swabs showed a median of 14 days with 800 mg molnupiravir and 15 days with placebo. The proportion with SARS-CoV-2 RNA negativity by EOS was greater with 800 mg molnupiravir (92.5%) vs. placebo (80.3%). The proportion of participants who achieved undetectable SARS-CoV-2 RNA at each time point was greater in the

molnupiravir 800 mg group compared with the placebo group (p=0.0373 on Day 5 and p=0.0343 on Day 28).

Table 4. Summary of Time to Undetectable SARS-CoV-2 Viral RNA (Full mITT Population)

	Molnupiravir 200 mg (N=23)	Molnupiravir 400 mg (N=61)	Molnupiravir 800 mg (N=53)	All Molnupiravir (N=137)	Placebo (N=61)
Number (%) Participants with Response	21 (91.3)	48 (78.7)	49 (92.5)	118 (86.1)	49 (80.3)
Number (%) Participants Censored	2 (8.7)	13 (21.3)	4 (7.5)	19 (13.9)	12 (19.7)
Time to Response (days)					
Median (95% CI)	22.0 (15.0, 28.0)	27.0 (15.0, 28.0)	14.0 (13.0, 14.0)	15.0 (14.0, 20.0)	15.0 (15.0, 27.0)
Log Rank p-value	0.5551	0.7270	0.0128	0.4216	



Source: [P006MK4482: adam-adsl; adtte]

Figure 2 Kaplan-Meier Plot of Time to Clearance of SARS-CoV-2 RNA by Treatment (Full mITT Population)

Table 5 Summary of SARS-CoV-2 Viral Load Results Below the Limit of Detection at Each Time Point - (Full mITT Population)

Visit Stat / Response	Molnupiravir 200 mg (N=23)	Molnupiravir 400 mg (N=61)	Molnupiravir 800 mg (N=53)	All Molnupiravir (N=137)	Placebo (N=61)
Day 3					
Undetectable	2/23 (8.7)	6/60 (10.0)	11/53 (20.8)	19/136 (14.0)	6/61 (9.8)
p-value	>.9999	>.9999	0.1199	0.4041	
Day 5					
Undetectable	5/23 (21.7)	15/59 (25.4)	16/53 (30.2)	36/135 (26.7)	8/61 (13.1)
p-value	0.3304	0.1067	0.0373	0.0419	
Day 7					
Undetectable	4/23 (17.4)	16/58 (27.6)	22/52 (42.3)	42/133 (31.6)	17/61 (27.9)
p-value	0.4051	>.9999	0.1173	0.7370	
Day 14					
Undetectable	12/23 (52.2)	31/59 (52.5)	38/51 (74.5)	81/133 (60.9)	40/61 (65.6)
p-value	0.3166	0.1936	0.4095	0.6324	
Day 28 (EOS)					
Undetectable	21/23 (91.3)	45/55 (81.8)	46/48 (95.8)	112/126 (88.9)	46/56 (82.1)
p-value	0.4924	>.9999	0.0343	0.2389	

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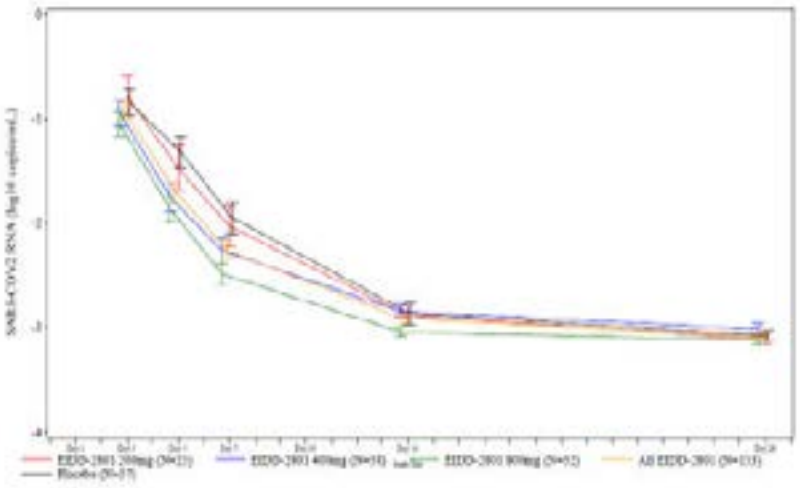
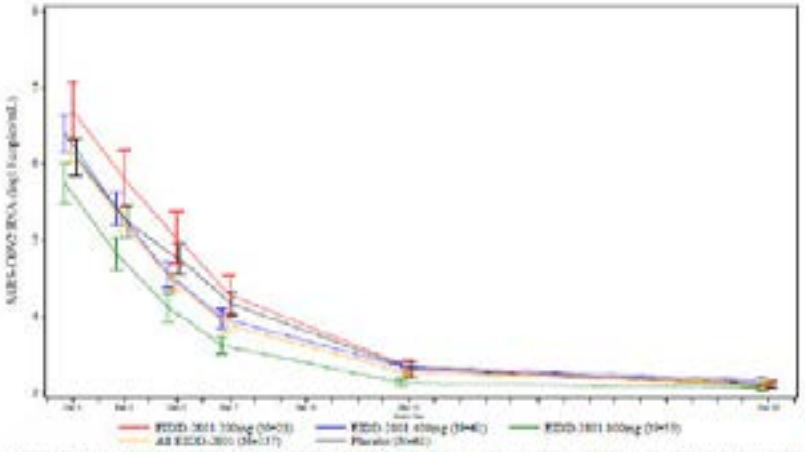


Abbreviations: COVID-19 = coronavirus disease 2019; mITT = modified Intent-to-Treat; MMRM = mixed model repeated measures; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SE = standard error.
Source: [P006MK4482: adam-adsl; adeff]

Figure 3 Least Squares Mean (SE) Change from Baseline in SARS-CoV-2 RNA (Log_{10} copies/mL) – MMRM (Full mITT Population)



Abbreviations: mITT = modified Intent-to-Treat; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SE = standard error.
Source: [P006MK4482: adam-adsl; adeff]

Figure 4 Mean (SE) Absolute SARS-CoV-2 RNA (Log_{10} copies/mL) by Treatment (Full mITT Population)

At baseline, the proportions with positive SARS-CoV-2 infectivity results varied across treatment groups. The proportion with positive cultures decreased faster in the 800 mg dose group compared with lower doses and placebo such that the change from baseline in viral load showed a larger decrease in the 800 mg group compared with other groups from Days 3 to 28.

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Table 6 Summary of SARS-CoV-2 Infectivity Results (Full mITT Population)

	Molnupiravir 200 mg	Molnupiravir 400 mg	Molnupiravir 800 mg	All Molnupiravir	Placebo
Category	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Day 1					
Number of Participants with Positive Infectivity	11/22 (50.0)	18/43 (41.9)	20/52 (38.5)	49/117 (41.9)	25/53 (47.2)
p-value [a]	>.9999	0.6816	0.4320	0.6167	
p-value [b]					0.3144
Day 3					
Number of Participants with Positive Infectivity	4/22 (18.2)	5/43 (11.6)	1/53 (1.9)	10/118 (8.5)	9/54 (16.7)
p-value [a]	>.9999	0.5691	0.0161	0.1225	
p-value [b]					0.0095
Day 5					
Number of Participants with Positive Infectivity	1/22 (4.5)	0/42 (0.0)	0/53 (0.0)	1/117 (0.9)	6/54 (11.1)
p-value [a]	0.6658	0.0335	0.0270	0.0043	
p-value [b]					0.0025
Day 7					
Number of Participants with Positive Infectivity	1/21 (4.8)	0/47 (0.0)	0/52 (0.0)	1/120 (0.8)	2/56 (3.6)
p-value [a]	>.9999	0.4990	0.4960	0.2379	
p-value [b]					0.092

Mutation rate

Analysis of nucleotide changes in the RdRp region at levels ≥1% of the viral population compared with the Wuhan consensus sequence indicated an increased mutation rate in molnupiravir-treated subjects compared with those given placebo. The result indicated a mean of 10.9 nucleotide changes in the RdRp among molnupiravir-treated subjects compared with 5.7 in the placebo group (p=0.024).

The effect of the increased number of nucleotide changes was also reflected in the analysis of amino acid changes where the mean number of changes observed among molnupiravir treated participants was 7.5 compared with 4.2 for the placebo participants (p=0.0367). An analysis of mutations leading to amino acid changes in the RdRp gene demonstrated that the amino acid changes occurred throughout the protein sequence. There were no apparent differences across treatment groups in the pattern and/or position in the RdRp of the amino acid changes observed.

Correlation of viral load and infectivity

Based on published data, infectious SARS-CoV-2 virus can only be cultured when the SARS-CoV-2 RNA viral load as measured by RT-PCR is above approximately 106 copies/mL. The correlation between SARS-CoV-2 viral load and SARS-CoV-2 infectivity was explored at baseline and for all study samples.

Table 10. Agreement Between SARS-CoV-2 Infectivity and SARS-CoV-2 Viral Load at Baseline (All Participant Data)

	SARS-CoV-2 Viral Load		
SARS CoV-2 Infectivity by RT-PCR	Negative (BLQ)	Positive	Kappa Statistic
Negative	13 (7.5%)	82 (47.4%)	0.1251
Positive	0	78 (45.1%)	

Table 11. Agreement Between SARS-CoV-2 Infectivity and SARS-CoV-2 Viral Load Assessments (All Participant Data)

	SARS-CoV-2 Viral Load		
SARS CoV-2 Infectivity by RT-PCR	Negative (BLQ)	Positive	Kappa Statistic
Negative	127 (18.6%)	450 (65.8%)	0.0811
Positive	0	107 (15.6%)	

Samples that had negative infectivity had much lower viral load at baseline and throughout the study. For both analyses, infectivity results were negative for every sample that had a negative SARS-CoV-2 RNA result. Infectivity results were only positive for 45.1% of samples that had a positive SARS-CoV-2 RNA result at baseline and 15.6% of all samples that had a positive SARS-CoV-2 RNA result throughout the study. The kappa statistics of 0.1251 at Baseline and 0.0811 overall indicate a very low level of agreement between the assays.

The proportion with positive infectivity at baseline was somewhat higher among those who had no risk factors for severe COVID-19 illness, and the proportion decreased over time more quickly in the molnupiravir-treated groups compared with placebo-treated group, without a consistent difference between the subgroups (risk factors for severe COVID-19 = 0 or ≥1).

Impact of serostatus on infectivity

The proportion with any (IgG, IgM, IgA, total Ig or composite) positive anti-SARS-CoV-2 antibody result at baseline were 15.0%, 30.0%, 35.3% and 18.2% in the molnupiravir and placebo groups, respectively. The proportions increased over time and by Day 28 nearly all participants were seropositive (at least 96.5%). There were no obvious differences in the proportions of participants with IgG on Days 7 and 28 between those treated with placebo vs molnupiravir.

There was a clear effect of antibody status at baseline on infectivity. In the seronegative subjects, 59% molnupiravir and 55.8% placebo subjects had a positive infectivity result at baseline compared to 3% and 11% in respective groups who were seropositive at baseline.

Among baseline seronegative subjects all except one treated with 800 mg achieved negativity for infectious virus on Day 3 vs. 20.9% treated with placebo. On Days 5 and 7, all subjects treated with 400 mg or 800 mg had negative infectious virus compared to 14.0% and 4.7% of those treated with placebo.

Table 12. Summary of SARS-CoV-2 Infectivity Results for Participants with Negative Composite Antibody Status at Baseline (Full mITT Population)

	Molnupiravir 200 mg	Molnupiravir 400 mg	Molnupiravir 800 mg	All Molnupiravir	Placebo
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Day 1 No. of participants with positive infectivity	9/17 (52.9)	17/29 (58.6)	20/32 (62.5)	46/78 (59.0)	24/43 (55.8)
Day 3 No. of participants with positive infectivity	2/17 (11.8)	5/29 (17.2)	1/32 (3.1)	8/78 (10.3)	9/43 (20.9)
Day 5 No. of participants with positive infectivity	0/17 (0.0)	0/29 (0.0)	0/32 (0.0)	0/78 (0.0)	6/43 (14.0)
Day 7 No. of participants with positive infectivity	1/16 (6.3)	0/30 (0.0)	0/32 (0.0)	1/78 (1.3)	2/43 (4.7)

In the subgroup enrolled ≤4.5 days after onset of COVID-19 symptoms positive infectivity was 15.1% in the molnupiravir groups and 25.9% in the placebo group. In the subgroup enrolled >4.5 days after

onset of COVID-19 symptoms, 3.1% of molnupiravir and 7.4% of placebo participants tested positive for infectious virus.

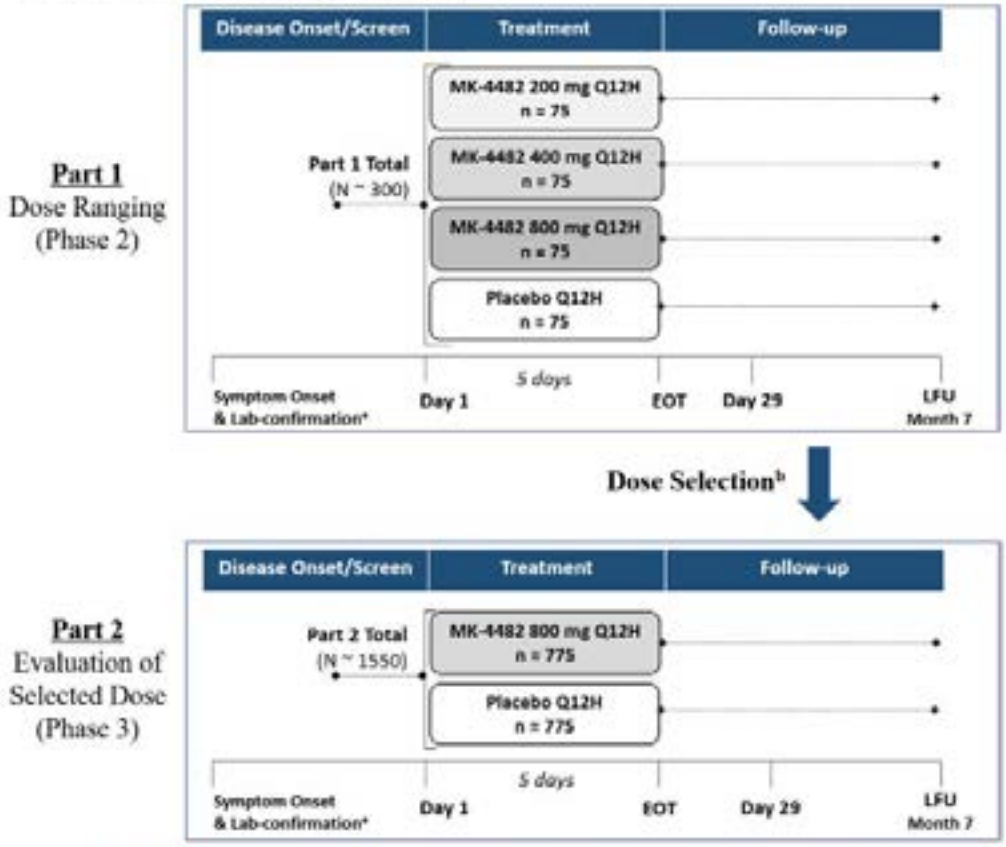
Overall, there was a high degree of variability between groups and over time in COVID-19 symptoms recorded in patient diaries. Among the summaries and analyses prepared, there were no consistent or meaningful differences between the treatment groups at any time during the study. There were 4 participants hospitalised during the study (2 in the 400 mg group, 1 in the 800 mg group and 1 in the placebo group).

Based on the 8-point WHO Ordinal Scale, all participants were ambulatory with no limitation of activities or with limitation of activities at baseline. The proportions rated as having limitation of activities at baseline varied from 63.6%, 75.4%, 90.2% and 74.1% in the 200 mg, 400 mg, 800 mg and placebo groups, respectively. The proportions rated as having limitation of activities decreased over time in all of the treatment groups to a similar degree.

2.4.2.2. Pivotal efficacy study

The study MK4482-002 was carried out in two distinct parts as shown below.

Figure 1 Study Schema and Treatment Plan



EOT=end of treatment; LFU=Late Follow-up Visit; N=total number of participants in each study part; n=number of participants per group; Q12H=administered once every 12 hours.

*Eligible participants will have laboratory-confirmed SARS-CoV-2 infection with signs/symptoms attributable to COVID-19 for ≤7 days in Part 1 and ≤5 days in Part 2 prior to randomization (Section 5.1). Calculation of the 7-/5-day symptom onset window does not include the date of randomization (Section 5.1).

[b] Dose selection will be based on Part 1 interim analysis(es) in combination with the totality of data available across the MK-4482 clinical program prior to initiating Part 2 (Section 4.3.3 and Section 9.7).

The results of Part 1, in which there was no formal hypothesis testing, are provided in a full CSR and are described below quite separately from those for Part 2.

The current assessment commenced after the company had obtained the top line results from an interim analysis of Part 2, for which a full CSR is not available. A statistical report was provided, followed by a summary report and efficacy tables and figures along with a Clinical Overview. Results from Part 2 obtained from these documents are described below.

- **Study participants**

Male or female subjects aged ≥18 years with laboratory-confirmed SARS-CoV-2 infection with sample collection ≤7 days (Part 1) or ≤5 days (Part 2) prior to the day of randomisation were eligible. RT-PCR confirmation was the preferred method, but eligibility could be based on other molecular or antigen tests that detect viral RNA or protein if authorised for use in the country. Eligible subjects were also to have initial onset of signs/symptoms attributable to COVID-19 ≤7 days (Part 1) or ≤5 days (Part 2) prior to randomisation. Signs/symptoms attributable to COVID-19 present at randomisation were to include at least one of: fever >38.0ºC, chills, cough, sore throat, shortness of breath or difficulty breathing with exertion, fatigue, nasal congestion, runny nose, headache, muscle or body aches, nausea, vomiting, diarrhoea, loss of taste or loss of smell. Furthermore, subjects were to have mild or moderate COVID-19 based on the below protocol definitions.

Mild COVID-19:

Must have **ALL** of the following:

- Respiratory rate <20 breaths per minute
- Heart rate <90 beats per minute
- SpO_2 >93% on room air or on supplemental oxygen for a reason other than COVID-19 which HAS NOT increased since onset of COVID-19 signs/symptoms

AND

Must **NOT** have shortness of breath **at rest** or **with exertion** as assessed by the investigator, respiratory failure, shock, or multi-organ dysfunction/failure (see definitions in Critical COVID-19 below)

Moderate COVID-19:

Must have **ONE or MORE** of the following:

- Shortness of breath **with exertion** as assessed by the investigator
- Respiratory rate >20 to <30 breaths per minute
- Heart rate ≥90 to <125 beats per minute

AND

Must have SpO_2 >93% on room air or on supplemental oxygen for a reason other than COVID-19 which HAS NOT increased since onset of COVID-19 signs/symptoms [or only on ≤4 liters/min supplemental oxygen for COVID-19 (but was not previously on supplemental oxygen), regardless of SpO_2]

AND

Must **NOT** have shortness of breath **at rest** as assessed by the investigator, respiratory failure, shock, or multi-organ dysfunction/failure (see definitions in Critical COVID-19 below)

Subjects with mild COVID-19 in Part 1 and all subjects in Part 2 were to have at least 1 characteristic or underlying medical condition associated with an increased risk of severe illness from COVID-19, listed in the protocol as:

- Age >60 years
- Active cancer (if associated with immunosuppression or significant morbidity/mortality)
- Chronic kidney disease (excluding dialysis or eGFR <30 mL/min/1.73 m^2)
- Chronic obstructive pulmonary disease
- Obesity (BMI 30 or higher)
- Serious heart conditions (heart failure, coronary artery disease, or cardiomyopathies)
- Diabetes mellitus

Immunocompromised state from solid organ transplant and sickle cell disease were high-risk conditions in Part 1 but were removed from Part 2.

Excluded subjects included those who:

- Were hospitalised or expected to need hospitalisation for COVID-19 within 48 h
- Had any of the following conditions:
  - HIV with a recent viral load >50 copies/mL (regardless of CD4 count) or an AIDS-defining illness in the past 6 months
  - Chemotherapy required within 6 weeks before randomisation (Part 1 only)
  - A neutrophilic granulocyte absolute count <500/mm^3
  - Autologous or allogeneic hematopoietic stem cell transplant recipient (Part 1 only)
- Had a platelet count <100,000/µL or received a platelet transfusion in the 5 days prior to randomisation.
- Had acute pancreatitis within 3 months prior to randomisation or a history of chronic pancreatitis (Part 1 only)

In addition, the table shows concomitant therapies that were not permitted for the specific time frames listed. If a subject is hospitalise, medications intended as treatment for COVID-19 were permitted.

Table 2 Prohibited and Allowed Therapies

COVID-19 Vaccines	• SARS-CoV-2 vaccines are prohibited any time prior to randomization and through Day 29.
COVID-19 Monoclonal Antibodies	• Monoclonal antibodies are prohibited for treatment of the current SARS-CoV-2 infection, including prior to randomization and through Day 29.
Other COVID-19 Therapeutic	• Sponsor-designated standard of care for treatment for COVID-19* is permitted (eg, corticosteroids) but may require additional safety monitoring as determined by the treating clinician. o If guidelines for local standard of care conflict with Sponsor-designated standard of care, site should consult with Sponsor. o Unless designated by the Sponsor as acceptable standard of care for COVID-19, concomitant use of other therapies intended as specific treatment for COVID-19 are prohibited from randomization through Day 29. If a participant is hospitalized during the study, other therapies intended as treatment for COVID-19 are permitted. • Supportive therapies (including but not limited to anti-pyretic and anti-inflammatory agents) to manage COVID-19 signs/symptoms are allowed.
Non-COVID-19 Investigational Agents	All non-COVID-19 investigational agents including devices are prohibited within 30 days prior to randomization and through Day 29.

- **Treatments**

In Parts 1 and 2 the following treatments were administered as multiples of 200 mg capsules, taken without regard to food:

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Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
MK-4482	Experimental	MK-4482	Drug	Capsule	200 mg	Part 1: 200 mg, 400 mg, 800 mg; Part 2 800 mg	Oral	Q12H 5 days (10 doses total)	Experimental	IMP	Central
Placebo	Placebo Comparator	Placebo Matching MK-4482	Drug	Capsule	0 mg	Part 1: N/A Part 2: N/A	Oral	Q12H 5 days (10 doses total)	Placebo	IMP	Central

N/A= not applicable, Q12H= every 12 hours.
The classification of Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) in this table is based on guidance issued by the European Commission and applies to countries in the European Economic Area (EEA). Country differences with respect to the definition/classification of IMP/NIMP may exist. In these circumstances, local legislation is followed.

- **Objectives**

The primary and secondary endpoints were as follows:

Objectives	Endpoints
Primary	
• To evaluate efficacy of MOV compared to placebo as assessed by the percentage of participants who are hospitalized and/or die from randomization through Day 29.	• Hospitalization or death
• To evaluate the safety and tolerability of MOV compared to placebo.	• Adverse events • Adverse events leading to discontinuation of study intervention
Secondary	
• To evaluate the efficacy of MOV compared to placebo as assessed by time to sustained resolution or improvement, and time to progression of each targeted self-reported sign/symptom of COVID-19 from randomization through Day 29.	• COVID-19 signs/symptoms
• To evaluate the efficacy of MOV compared to placebo as assessed by the odds of a more favorable response on the WHO 11-point ordinal scale on Day 3, EOT, Day 10, Day 15, and Day 29.	• WHO 11-point scale score

- **Outcomes/endpoints**

The primary endpoint was all-cause hospitalisation (≥24 h of acute care in a hospital or similar acute care facility, including emergency rooms or facilities created to address hospitalisation needs during the COVID-19 pandemic) or death in the 28 days after the day of randomisation (i.e. to Day 29).

Two secondary endpoints were defined to document the effect of treatment on signs/symptoms associated with COVID-19 infection and on shifts in clinical status as measured on the WHO 11-point ordinal outcome scale through Day 29.

- **Sample size**

Part 1

The sample size for Part 1 was not determined based on a specific hypothesis for a selected endpoint.

The plan for 300 participants (75 per group) was deemed sufficient to provide reasonable precision to discriminate between treatment groups with regard to the virology endpoints. Approximately 80% of this cohort (60/group) was expected to have a baseline VL of at least 106 copies/mL. A 1 log10 difference between treatment groups in the population mean was considered clinically relevant. The table shows the power calculations for true log differences of 0.75 to 1.25 and for various assumptions about the true underlying standard deviation.

Table 9 Power by Detectable Difference and Standard Deviation Viral RNA change from baseline (log10 copies/mL) N=60/group, α=0.025, 1-sided

	Between-Group Difference (log_{10} copies/mL)		
Standard Deviation	-0.75	-1.00	-1.25
1.25	90%	99%	>99%
1.5	78%	95%	>99%
1.75	64%	87%	97%

Part 2

The primary analysis was planned to include ~1550 participants (~775 for each group) meeting the criteria for inclusion in the MITT population. The study was to have overall power of 97% to demonstrate superiority of MK-4482 800 mg over placebo at an overall one-sided, 2.5% alpha level, if the underlying treatment difference (MK-4482 minus placebo) in the percentage hospitalised and/or dying through Day 29 is -6 percentage points.

The power and sample size were based on the following assumptions:

1) An underlying percentage hospitalised/dying of 12% for placebo and 6% for MK-4482 (50% reduction in the relative risk) and

2) A futility/efficacy interim analysis at 50% information

To meet the statistical criterion for success (one-sided p ≤0.019 at the final analysis), the observed treatment difference must be approximately -3.0 percentage points or lower, assuming a percentage of 12% for placebo. Based on subgroup results in Part 1 and the modification to the study population for Part 2, the assumption of 12% for placebo and a 50% reduction in the relative risk was deemed to be reasonable. The study power for different assumptions of the underlying percentage hospitalised/dying are shown in the table, where all scenarios are based on a total sample size of 1550 participants and an overall one-sided, 2.5% alpha level.

Table 8 Study Power by Percentage Hospitalized/Dying
N=1550 participants (775 for MK-4482 800 mg and 775 for placebo), alpha=0.025, 1-sided

Placebo Rate (%)	MK-4482 Rate (%)	Absolute Difference (percentage points)	Power
18%	12%	6	88%
16%	10%	6	92%
14%	8%	6	95%
12%	7%	5	89%
10%	5%	5	95%
8%	4%	4	89%
6%	2%	4	97%

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- **Randomisation**

Randomisation was performed centrally using an IRT system.

In Part 1, there was assignment in a 1:1:1:1 ratio to one of the three molnupiravir dose groups or to placebo with stratification according to:

1. Time from symptom onset prior to the day of randomisation (≤5 days, >5 days)

2. At increased risk of severe illness from COVID-19 (yes, no)

At least 75% of participants overall were to have at least 1 characteristic or underlying medical condition associated with being at increased risk for severe illness from COVID-19. Enrolment of participants with moderate COVID-19 was limited to 50% of total planned sample size.

In Part 2, there was assignment 1:1 to molnupiravir 800 mg BID or placebo with stratification according to:

1. Time from symptom onset prior to the day of randomisation (≤3 days, >3 days)

This difference vs. Part 1 resulted from the amendment to require randomisation within ≤5 days from symptom onset in Part 2 (reduced from 7 days in Part 1).

Also, all participants in Part 2 were to have at least 1 characteristic or underlying medical condition associated with being at increased risk for severe illness from COVID-19. There was no set minimum for enrolment of participants >60 years of age.

- **Blinding (masking)**

A double-blind design was used with in-house blinding.

- **Statistical methods**

The MITT population was the primary population for the analysis of efficacy data for both parts of this study. The MITT population consisted of all randomised participants who received at least 1 dose of study intervention and excluded any hospitalised before treatment started. The MITT population for Part 2 did not include Part 1 participants.

For the primary endpoint, superiority of MK-4482 compared to placebo was to be assessed using the stratified Miettinen and Nurminen method. For the primary analysis of this endpoint in the MITT population, incomplete data on Day 29 survival and hospitalisation status were treated as follows:

- unknown Day 29 survival status was treated as failure

- early withdrawal from the study with known Day 29 survival status as alive but unknown Day 29 hospitalisation status was not treated as failure.

A sensitivity analysis treating unknown Day 29 survival status as failure and early withdrawal from the study with known Day 29 survival status as alive but unknown Day 29 hospitalisation status as failure was also planned.

A sensitivity analysis for the primary endpoint was planned to include only COVID-19 related hospitalisations or death by Day 29 in the MITT population using the stratified Miettinen and Nurminen method. An additional sensitivity analysis excluding hospitalisations that occurred early (within a certain time from randomisation) was also planned.

Two additional sensitivity analyses of time to hospitalisation/death and time to COVID-related hospitalisation/death were planned for the MITT population using the stratified log-rank test to compare MK-4482 with placebo and the same stratification factors as for the primary endpoint. Hazard ratios were based on the stratified Cox Proportional Hazards regression model.

The table below summarises the main features of the planned efficacy analyses.

Primary Endpoints	**Efficacy**: Proportion of participants with hospitalization or death by Day 29. **Safety**: Number of participants with AEs, and discontinuing study intervention due to AEs
Key Secondary Endpoints	• Time to sustained resolution or improvement, and time to progression of each targeted self-reported sign/symptom of COVID-19 through Day 29 • Odds of a more favorable response on the WHO 11-point ordinal scale on Day 3, EOT, Day 10, Day 15, and Day 29
Statistical Methods for Key Efficacy Analyses	For the evaluation of the primary hypothesis, superiority of MK-4482 compared to placebo with respect to the percentage of participants with hospitalization or death by Day 29 will be calculated using the stratified Miettinen and Nurminen method [Miettinen, O. 1985].
Statistical Methods for Key Safety Analyses	P-values (Tier 1 endpoints) and 95% CIs (Tier 1 and Tier 2 endpoints) will be provided for between-treatment differences in the percentage of participants with AEs; these analyses will be performed using the unstratified Miettinen and Nurminen method [Miettinen, O. 1985].
Interim Analyses	**IA1 – Part 1 Dose Evaluation** This IA will be used to review data to inform dose selection models and analyses. **IA2 – Part 1[b] Dose Selection** This IA will be used to evaluate the dose/exposure-response to select the dose for Phase 3. **IA3 – Part 2 Sample Size Re-estimation** This IA will be an unblinded sample size re-assessment. The conditional power approach will be employed in which the overall sample size can be adjusted upwards if the interim result is sufficiently promising without inflation of the type I error. **IA4 – Part 2 Futility/Early Efficacy** The purpose of this IA is to allow for early stopping in the case of futility and to allow for the initiation of marketing authorization applications in the case of a positive efficacy finding. Additional details about interim analyses are in Section 9.7.
Multiplicity	There are no adjustments for multiplicity other than the type I error control for interim analyses described in Section 9.7.

Sample Size and Power	The total sample size for the primary efficacy assessment (Part 2) will be ~1550 participants (~775 for MK-4482 800 mg and ~775 for the placebo group). The study has overall power of 97% to demonstrate the superiority of MK-4482 over placebo at an overall one-sided, 2.5% alpha level, if the underlying treatment difference (MK-4482 minus placebo) in the percentage of participants who are hospitalized and/or die through Day 29 is -6 percentage points. Additional details and assumptions for sample size and power calculation are in Section 9.9.
[a] Stratification in Part 1 included: 1) Time from symptom onset prior to the day of randomization (≤5 days, >5 days); and 2) At increased risk of severe illness from COVID-19 (Appendix 10) (yes, no)	

There were four interim analysis planned initially with details as shown in the table below.

Interim Analysis	Timing	MK-4482-002 Primary Data for Analysis	Committee Action
IA1 – Part 1 Dose Evaluation	Targeted to occur during Phase 2 after ~300 participants complete EOT combined in MK-4482-001[a] and MK-4482-002.	PK, available virologic, safety & efficacy data through EOT	eDMC recommendation for discontinuation of the study or protocol modifications Sponsor siDMC review of interim safety data and review of preliminary virology data Review by an unblinded team to inform dose selection models and analyses
IA2 – Part 1[b] Dose Selection	Targeted to occur at the completion of Phase 2 after ~300 participants complete Day 29 (includes participants from IA1).	PK, safety & efficacy data through Day 29 and available virologic data	eDMC recommendation for discontinuation of the study or protocol modifications Sponsor siDMC approval of proposed MK-4482 dose for Part 2
IA3 – Part 2 Sample Size Re-estimation	Targeted to occur no earlier than at 30% of the full planned Part 2 enrollment and no later than IA4. Final timing to be based on enrollment timelines.	Primary efficacy endpoint at Day 29	Sample size re-estimation to be assessed by eDMC based on review of conditional power for primary endpoint with potential to increase Part 2 sample size
IA4 – Part 2 Futility/Early Efficacy	Targeted to occur during Phase 3 after ~775 participants complete Day 29 across the MK-4482 group and the placebo group (~50% of total enrollment).	Safety & efficacy data through Day 29	Futility and early efficacy to be assessed by eDMC per eDMC Charter and guided by statistical criteria
eDMC=external Data Monitoring Committee; EOT=End of Treatment; IA=Interim Analysis; PK=pharmacokinetics; siDMC=standing internal Data Monitoring Committee. [a] MK-4482-001 is a companion MK-4482 dose-ranging study in hospitalized adults with COVID-19 [b] IA2 represents the analysis of the full Part 1 cohort of participants through Day 29.			

There were no adjustments for multiplicity other than controlling type I error for interim analyses of the primary endpoint in part 2 of the study. The p-value boundary for efficacy at the final analysis was anticipated to be 0.0194, corresponding to an absolute difference of -0.03.

IA3 – Part 2: Sample size re-estimation

IA3 was to occur no earlier than at 30% of the full planned Part 2 enrolment and no later than IA4. The conditional power approach was to be employed in which the overall Part 2 sample size could have been adjusted upwards by 450 participants to a total of 2000 if the interim result was sufficiently promising (conditional power >51% but <80%, assuming continuing the interim analysis trend) without inflation of the type I error [Chen, Y. H. J., et al 2004[5]]. The potential increase in total Part 2 sample size was designed to maintain adequate study power in the event that the observed treatment effect at the interim analysis was smaller than the original assumption but still clinical meaningful.

[5] Chen G, Wang YC, Chi GY. Hypotheses and type I error in active-control noninferiority trials. J Biopharm Stat. 2004 May;14(2):301-13. doi: 10.1081/BIP-120037181. PMID: 15206528.

Based on enrolment timelines, the supplemental SAP stated that IA3 and IA4 were to be conducted at a single time point (once 50% of planned participants are enrolled and followed through the Day 29 visit). Based on an expected information fraction of 50%, the promising zone for adjusting the overall sample size upwards by 450 participants is between 0.0703 and 0.0299 in the 1-sided p-value scale.

IA4 – Part 2: Futility/Early Efficacy IA

IA4 was to be triggered when ~50% of participants in the molnupiravir group and the placebo group had completed the Day 29 visit. The purpose of this interim analysis was to allow for early stopping in the case of futility and to allow for the initiation of MAAs in the case of a positive efficacy finding. There were no plans to discontinue enrolment prior to the planned final sample size in the case of a positive efficacy outcome.

The Gamma family spending function with γ = -1 was to be used to set both efficacy and futility boundaries for the primary endpoint as a guide for the eDMC in order to control overall type I error rate of 0.025, 1-sided. Assuming the information fraction of 50%, the non-binding futility boundary expressed on the absolute difference scale is -0.011. The boundary crossing probabilities for futility are 71% under H0 and 0.8% under H1 (absolute difference of -0.06). The p-value boundary for efficacy is 0.0094, corresponding to an absolute difference of -0.048. The boundary crossing probabilities for efficacy are 0.9% under H0 and 72% under H1 (absolute difference of -0.06). Had sample size re-estimation resulted in an increase in the total planned sample size to 2000, the p-value boundary for efficacy at the final analysis would have been 0.0184.

The company provided a separate SAP for this study dated 16 September 2021 (version 2). This document included summaries of changes from the protocol SAP (protocol amendment 04) and version 1 of the SAP (dated 16 June 2021).

- **Results – MK-4482 Part 1 (based on the interim CSR)**

Participant flow

Disposition of Participants
All Randomized Participants
MK-4482-002 IA2

	MK-4482 200 mg		MK-4482 400 mg		MK-4482 800 mg		MK4482 Combined		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Not Randomized											66	
Participants in population	75		77		76		228		74		302	
Status for Study Medication												
Started	74		77		74		225		74		299	
Completed	69	(93.2)	73	(94.8)	70	(94.6)	212	(94.2)	71	(95.9)	283	(94.6)
Discontinued	5	(6.8)	4	(5.2)	4	(5.4)	13	(5.8)	3	(4.1)	16	(5.4)
Adverse Event	0	(0.0)	0	(0.0)	3	(4.1)	3	(1.3)	1	(1.4)	4	(1.3)
Non-Compliance With Study Drug	2	(2.7)	1	(1.3)	0	(0.0)	3	(1.3)	1	(1.4)	4	(1.3)
Physician Decision	0	(0.0)	2	(2.6)	0	(0.0)	2	(0.9)	0	(0.0)	2	(0.7)
Withdrawal By Subject	1	(1.4)	1	(1.3)	1	(1.4)	3	(1.3)	1	(1.4)	4	(1.3)
Other	2	(2.7)	0	(0.0)	0	(0.0)	2	(0.9)	0	(0.0)	2	(0.7)
Status for Day 29 Milestone[a]												
Started	74		77		74		225		74		299	
Completed	71	(95.9)	75	(97.4)	71	(95.9)	217	(96.4)	72	(97.3)	289	(96.7)
Discontinued	3	(4.1)	2	(2.6)	3	(4.1)	8	(3.6)	2	(2.7)	10	(3.3)
Lost To Follow-Up	2	(2.7)	0	(0.0)	1	(1.4)	3	(1.3)	1	(1.4)	4	(1.3)
Withdrawal By Subject	1	(1.4)	2	(2.6)	2	(2.7)	5	(2.2)	1	(1.4)	6	(2.0)
Status for Trial Through LFU												
Started	75		77		76		228		74		302	
Discontinued	4	(5.3)	2	(2.6)	5	(6.6)	11	(4.8)	4	(5.4)	15	(5.0)
Death	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.3)
Lost To Follow-Up	2	(2.7)	0	(0.0)	1	(1.3)	3	(1.3)	1	(1.4)	4	(1.3)
Withdrawal By Subject	2	(2.7)	2	(2.6)	4	(5.3)	8	(3.5)	2	(2.7)	10	(3.3)
Status Not Recorded	71	(94.7)	75	(97.4)	71	(93.4)	217	(95.2)	70	(94.6)	287	(95.0)

Status Not Recorded = Ongoing
[a] Only participants who receive at least 1 dose will be included.

There were 302 subjects randomised into Part 1, of which 299 were treated. The majority of subjects completed the 5-day treatment regimen (94.6%) and the Day 29 visit (96.7%) and few (3.3%) had discontinued after Day 29. Based on the CSR dated 19 July 2021, the majority of participants had not yet completed the 7-month LFU visit.

Recruitment

The study was conducted at 82 sites in 12 countries.

Conduct of the study

Important and not important protocol deviations associated with the pandemic were reported for 51 participants. No subject was excluded from the MITT analyses due to an important protocol deviation.

Baseline data

The majority of participants was male (52.6%) and the mean age was 49.2 years (range 18 to 84 years) with 52% aged 18 to 50 years. The majority (66.9%) started treatment ≤5 days after COVID-19 sign/symptom onset across all groups and 75.2% had at least one factor for increased risk of severe COVID-19, most commonly due to obesity (48.7% BMI ≥30), age >60 years (23.5%) and diabetes mellitus (16.6%).

At baseline, COVID-19 severity was moderate for 57.0% and mild for 43.0%. SARS-CoV-2 baseline antibody testing was positive for 12.6% and 81.1% had detectable SARS-CoV-2 RNA (rather than a positive antigen detection test) in a baseline NP sample.

No subjects required oxygen supplementation at study entry.

Participant Characteristics – Oxygen Saturation
Modified Intent-To-Treat Population
MK-4482-002 Part 1 - IA2

	MK-4482 200 mg	MK-4482 400 mg	MK-4482 800 mg	MK-4482 Combined	Placebo	Total
Participants in population	74	77	74	225	74	299
Participants with data	73	77	74	224	74	298
Mean	97	96.9	96.9	96.9	97.3	97
SD	1.58	1.51	1.55	1.54	1.61	1.56
Median	97	97	97	97	97	97
Range	(94, 100)	(94, 100)	(94, 100)	(94, 100)	(94, 100)	(94, 100)

Numbers analysed

The MITT population included 299 randomised and treated subjects.

Outcomes and estimation

For the primary endpoint, there were only 11 events across all groups with no statistically significant difference between molnupiravir groups vs. placebo or between molnupiravir dose levels.

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Incidence of Death or Hospitalization Through Day 29
Modified Intent-To-Treat Population
MK-4482-002 IA2

Treatment	N	n (%)	Treatment vs. Placebo		
			Unadjusted Difference	Adjusted Difference in Rates % (95% CI)*	p-Value
MK-4482 200 mg	74	1 (1.4)	-4.1	-4.1 (-12.2, 2.5)	0.1676
MK-4482 400 mg	77	3 (3.9)	-1.5	-1.5 (-9.9, 6.2)	0.6668
MK-4482 800 mg	74	3 (4.1)	-1.4	-1.3 (-9.6, 6.4)	0.7141
Placebo	74	4 (5.4)			
Pairwise Comparison among MK Treatment Groups			Unadjusted Difference	Adjusted Difference in Rates % (95% CI)*	p-Value
MK-4482 400 mg vs. MK-4482 200 mg			2.5	2.5 (-3.9, 9.8)	0.3351
MK-4482 800 mg vs. MK-4482 200 mg			2.7	2.7 (-3.7, 10.1)	0.3121
MK-4482 800 mg vs. MK-4482 400 mg			0.2	0.3 (-7.3, 8.3)	0.9342

* Adjusted differences, the corresponding confidence intervals and p-values are based on Miettinen & Nurminen method stratified by randomization strata.
Unknown Day 29 survival status is treated as failure.

The 11 events reported all involved hospitalisations, with no deaths in Part 1. All of the 11 subjects hospitalised had at least one of the protocol-listed risk factors for severe COVID-19 including obesity (n=8), >60 years of age (n=5) and diabetes mellitus (n=5).

Post hoc subgroup analyses of the primary endpoint for participants >60 years of age, time from COVID-19 symptom onset ≤5 days and increased risk for severe COVID-19 indicated improved outcomes with molnupiravir. Among those who started treatment within 5 days of symptom onset and were at increased risk of severe COVID-19, there were 4/107 (3.7%) hospitalised in the combined molnupiravir groups vs. 4/34 (11.8%) in the placebo group.

Ancillary analyses

Time to sustained resolution or improvement and time to progression of each self-reported

COVID-19 sign/symptom was similar across groups. The observed median time to sustained improvement or resolution was ≤12 days for all symptoms and the sustained resolution or improvement rate was generally comparable across the groups through Day 29. There were no clear trends in treatment effect between intervention groups as assessed by the WHO 11-point ordinal scale. With >94% having a baseline score of 2, 74.3% achieved a score of 0 or 1 by Day 29.

There were comparable decreases in mean SARS-CoV-2 RNA titres from to baseline across the groups.

Higher viral sequence mutation rates (per 10,000 bp) were observed at Day 5 in NP samples from molnupiravir-treated subjects (6.7 to 8.7) compared with placebo (2.0).

The highest RNA mutation rate was at Day 5 in the 800 mg BID group. SARS-CoV-2 mutations observed post-baseline were distributed across the entire 30,000 bp genome with no increase of treatment-emergent mutations in the RdRp active site.

- **Results – MK-4482 Part 2 (Statistical Report, Clinical Overview and Tables)**

Participant flow

There were 775 participants randomised and eligible for inclusion in IA4, of which 765 (98.7%) had received study treatment and 94.9% had completed assigned treatment. Also, 95.0% completed the Day 29 visit. The most common reason for discontinuation was withdrawal by subject (2.7%). At the time of IA4, disposition was as shown below.

Disposition of Participants
All Randomized Participants
MK-4482-002 Combined IA3/IA4

	MK-4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	387		388		775	
Status for Study Medication						
Started	386		379		765	
Completed	371	(96.1)	355	(93.7)	726	(94.9)
Discontinued	15	(3.9)	24	(6.3)	39	(5.1)
Adverse Event	5	(1.3)	13	(3.4)	18	(2.4)
Lost To Follow-Up	1	(0.3)	1	(0.3)	2	(0.3)
Non-Compliance With Study Drug	4	(1.0)	6	(1.6)	10	(1.3)
Withdrawal By Subject	4	(1.0)	2	(0.5)	6	(0.8)
Other	1	(0.3)	2	(0.5)	3	(0.4)
Status for Day 29 Milestone*						
Started	386		379		765	
Completed	369	(95.6)	358	(94.5)	727	(95.0)
Discontinued	17	(4.4)	21	(5.5)	38	(5.0)
Death	0	(0.0)	8	(2.1)	8	(1.0)
Lost To Follow-Up	5	(1.3)	3	(0.8)	8	(1.0)
Withdrawal By Subject	12	(3.1)	9	(2.4)	21	(2.7)
Other	0	(0.0)	1	(0.3)	1	(0.1)
Status for Trial Through LFU						
Discontinued	18	(4.7)	31	(8.0)	49	(6.3)
Death	0	(0.0)	9	(2.3)	9	(1.2)
Lost To Follow-Up	5	(1.3)	3	(0.8)	8	(1.0)
Randomized By Mistake Without Study Treatment	1	(0.3)	1	(0.3)	2	(0.3)
Withdrawal By Subject	12	(3.1)	17	(4.4)	29	(3.7)
Other	0	(0.0)	1	(0.3)	1	(0.1)
Status Not Recorded	369	(95.3)	357	(92.0)	726	(93.7)

LFU=Late Follow-up Visit
Status Not Recorded = Ongoing
* Only participants who receive at least 1 dose will be included.

Recruitment

Subjects were recruited across 5 continents with the majority in Latin America (~56%) followed by Europe (~23%).

Conduct of the study

As indicated in the statistical analysis plan, dated 16 September 2021, there were changes made compared to the description outlined in the protocol. The most important was as follows:

3.7	Added additional details for IA3 and IA4	IA3 and IA4 were combined into a single timepoint based on enrollment timelines. As such, the information fraction for the interim analysis for sample size re-estimation is fixed at 50% (timing was flexible between 30% and 50% per protocol).

Initially, two IAs (IA3 and IA4) were planned for Part 2 (Phase 3) of the study:

- IA3 was to assess the need for sample size re-estimation when 30% to 50% of the planned Phase 3 enrolment had reached the Day 29 visit.
- IA4 was to assess futility/early efficacy when 50% of the planned Phase 3 enrolment had reached the Day 29 visit.

Because of enrolment timelines, IA3 and IA4 were conducted simultaneously when 775 of 1550 planned subjects had reached the Day 29 visit.

Baseline data

There was an approximate equal gender split at baseline with a median age just over 40 years. Less than 15% of subjects were aged >60 years. Most participants (99.2%) had at least 1 risk factor for severe illness from COVID-19, with the most common being obesity (BMI ≥30, 76.5%). The baseline COVID-19 severity was moderate for 43.4% and mild for 56.0%. All subjects had symptom onset within 5 days prior to randomisation and about half had onset within ≤3 days.

All Randomized Participants
MK-4482-002 Combined IA3/IA4

	MK-4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	387		388		775	
Sex						
Male	187	(48.3)	217	(55.9)	404	(52.1)
Female	200	(51.7)	171	(44.1)	371	(47.9)
Age (years)						
18 to 49	274	(70.8)	271	(69.8)	545	(70.3)
50 to 64	82	(21.2)	80	(20.6)	162	(20.9)
65 to 74	24	(6.2)	24	(6.2)	48	(6.2)
≥75	7	(1.8)	13	(3.4)	20	(2.6)
≤60	336	(86.8)	333	(85.8)	669	(86.3)
>60	51	(13.2)	55	(14.2)	106	(13.7)
Participants with data	387		388		775	
Mean	43.2		44.2		43.7	
SD	13.5		14.3		13.9	
Median	41.0		43.0		41.0	
Range	18 to 87		18 to 88		18 to 88	

Time from Symptom Onset to Randomization						
≤3 Days	188	(48.6)	184	(47.4)	372	(48.0)
>3 Days	198	(51.2)	203	(52.3)	401	(51.7)
Unknown[a]	1	(0.3)	1	(0.3)	2	(0.3)
Participants with data	386		387		773	
Mean	3.5		3.5		3.5	
SD	1.1		1.0		1.1	
Median	4.0		4.0		4.0	
Range	1 to 5		1 to 5		1 to 5	
Risk Factors for Severe Illness from COVID-19						
At least one risk factor	385	(99.5)	384	(99.0)	769	(99.2)
Age >60 years	51	(13.2)	55	(14.2)	106	(13.7)
Active Cancer	6	(1.6)	11	(2.8)	17	(2.2)
Chronic Kidney Disease	14	(3.6)	20	(5.2)	34	(4.4)
Chronic Obstructive Pulmonary Disease	7	(1.8)	22	(5.7)	29	(3.7)
Obesity (BMI ≥ 30)	306	(79.1)	287	(74.0)	593	(76.5)
Serious Heart Condition	42	(10.9)	36	(9.3)	78	(10.1)
Diabetes Mellitus	48	(12.4)	57	(14.7)	105	(13.5)
Baseline COVID Severity						
Mild	222	(57.4)	212	(54.6)	434	(56.0)
Moderate	162	(41.9)	174	(44.8)	336	(43.4)
Severe	2	(0.5)	0	(0.0)	2	(0.3)

No subject required supplemental oxygen at study entry.

Participant Characteristics – Oxygen Saturation
Modified Intent-To-Treat Population
MK-4482-002 Part 2 - Combined IA3/IA4

	MK-4482 800 mg	Placebo	Total
Participants in population	385	377	762
Oxygen Saturation (%)			
Participants with data	385	377	762
Mean	96.8	96.8	96.8
SD	1.56	1.51	1.54
Median	97	97	97
Range	(93, 100)	(94, 100)	(93, 100)

At baseline, 85.5% had detectable SARS-CoV-2 RNA (by NP sample) and 18.2% had positive SARS-CoV-2 antibody results. Of those with sequence data available (277/775; 35.7%), the most common genotype clades at baseline were 21H (Mu, 35.0%), 21A (Delta, 22.4%) and 20J (Gamma, 22.4%).

All Randomized Participants
MK-4482-002 Combined IA3/IA4

	MK-4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Stratification Factor at Randomization Collected via IRT: Time from Symptom Onset to Randomization						
≤3 Days	191	(49.4)	190	(49.0)	381	(49.2)
>3 Days	196	(50.6)	198	(51.0)	394	(50.8)
SARS-CoV-2 RNA at Baseline in Nasopharyngeal Sample (Qualitative Assay)						
Detectable	332	(85.8)	331	(85.3)	663	(85.5)
Undetectable	28	(7.2)	29	(7.5)	57	(7.4)
Unknown[a]	27	(7.0)	28	(7.2)	55	(7.1)
SARS-CoV-2 Baseline Antibody						
Positive	71	(18.3)	70	(18.0)	141	(18.2)
Negative	299	(77.3)	288	(74.2)	587	(75.7)
Unknown[a]	17	(4.4)	30	(7.7)	47	(6.1)

[a] Missing data, invalid sample, tests not done, or results reported as "Unknown" are categorized as Unknown.

Number of Participants Infected With Different Viral Clades Based on Nextstrain Clade Designation
Nasopharyngeal Sample
All Randomized Participants
MK-4482-002 Combined IA3/IA4

Clade Designation	MK-4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants with evaluable sequence data available	132		140		277	
19B	1	(0.8)	0	(0.0)	1	(0.4)
20A	1	(0.8)	2	(1.4)	3	(1.1)
20B	3	(2.3)	3	(2.1)	6	(2.2)
20C	0	(0.0)	1	(0.7)	1	(0.4)
20D	1	(0.8)	0	(0.0)	1	(0.4)
20H	4	(3.0)	5	(3.6)	9	(3.2)
20I	12	(9.1)	8	(5.5)	20	(7.2)
20J	27	(20.5)	35	(24.1)	62	(22.4)
21A	33	(25.0)	29	(20.0)	62	(22.4)
21G	8	(6.1)	6	(4.1)	14	(5.1)
21H	41	(31.1)	56	(38.6)	97	(35.0)
Unknown	1	(0.8)	0	(0.0)	1	(0.4)

Unknown: The sequence could not be classified by Nextstrain into a currently known clade.
Percentage is based on the number of participants with evaluable sequence data available.

Numbers analysed

The MITT population comprised 762/775 (98.3%) of randomised subjects, with 385 in the molnupiravir 800 mg BID group and 377 in the placebo group. Ten subjects were excluded because of no treatment taken and 3 were hospitalised before the first dose.

	MK-4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
All Randomized Participants	387		388		775	
All Participants As Treated						
Yes	386	(99.7)	379	(97.7)	765	(98.7)
No	1	(0.3)	9	(2.3)	10	(1.3)
Modified Intent-To-Treat						
Yes	385	(99.5)	377	(97.2)	762	(98.3)
No	2	(0.5)	11	(2.8)	13	(1.7)

* Includes randomized participants who were not treated and randomized participants who were hospitalized before the first dose of study medication based on the definition of modified intent-to-treat population.

Outcomes and estimation

The percentage who were hospitalised or died through Day 29 in the molnupiravir 800 mg BID group (7.3%) was statistically significantly lower than in the placebo group (14.1%). Molnupiravir met the protocol-defined criterion (1-sided p-value boundary <0.0092 at IA4) for demonstration of superiority to placebo for the primary efficacy endpoint.

Incidence of Hospitalization or Death Through Day 29
Modified Intent-To-Treat Population
MK-4482-002 Combined IA3/IA4

Treatment	N	n (%)	Treatment vs. Placebo		
			Unadjusted Difference	Adjusted Difference in Rates % (97% CI)*	p-Value
MK-4482 800 mg	385	28 (7.3)	-6.8	-6.8 (-11.3, -2.4)	0.0012
Placebo	377	53 (14.1)			

* Adjusted differences, the corresponding confidence intervals and the one-sided p-values are based on Miettinen & Nurminen method stratified by randomization strata.
Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.
The p-value boundary for early efficacy is 0.0092 using the Gamma family spending function with γ = -4 based on the final evaluable sample size for the IA3/IA4 timepoint (n = 762 in the MITT population out of a total of 1130 planned; information fraction = 40%).

All 8 participants who died through Day 29 were in the placebo group and were hospitalised prior to death. One participant in the placebo group was imputed as a failure for the primary endpoint due to unknown mortality status at the time of database lock.

Summary of Hospitalization or Death Through Day 29
Modified Intent-To-Treat Population
MK-4482-002 Combined IA3/IA4

	MK-4482 800 mg		Placebo	
	n	(%)	n	(%)
Participants in population	385		377	
Hospitalization or Death	28	(7.3)	53	(14.1)
Hospitalization	28	(7.3)	52	(13.8)
Death	0	(0.0)	8	(2.1)
Unknown Day 29 Survival Status[a]	0	(0.0)	1	(0.3)

n= number of participants with the corresponding event.
Every participant is counted a single time for each applicable row and column. Participants who died were hospitalized prior to death; such participants are counted once each in the Hospitalization and Death rows.
[a] Unknown Day 29 survival status is treated as failure, i.e., counted as hospitalization or death in the primary analysis for the primary efficacy endpoint.

The percentages with *COVID-related* hospitalisation or death through Day 29 was 6.5% for molnupiravir vs. 13.3% for placebo, giving a 6.8 percentage point reduction [95% CI: -11.1, -2.6].

Incidence of COVID-related Hospitalization or Death Through Day 29
Modified Intent-To-Treat Population
MK-4482-002 Combined IA3/IA4

Treatment	N	n (%)	Treatment vs. Placebo	
			Unadjusted Difference	Adjusted Difference in Rates % (95% CI)[a]
MK-4482 800 mg	385	25 (6.5)	-6.8	-6.8 (-11.1, -2.6)
Placebo	377	50 (13.3)		

[a] Adjusted differences and the corresponding confidence intervals are based on Miettinen & Nurminen method stratified by randomization strata.
N= number of participants in the modified intent-to-treat population.
n= number of participants died or hospitalized through Day 29.
Unknown survival status at Day 29 was not counted as having an outcome of COVID-related hospitalization or death.

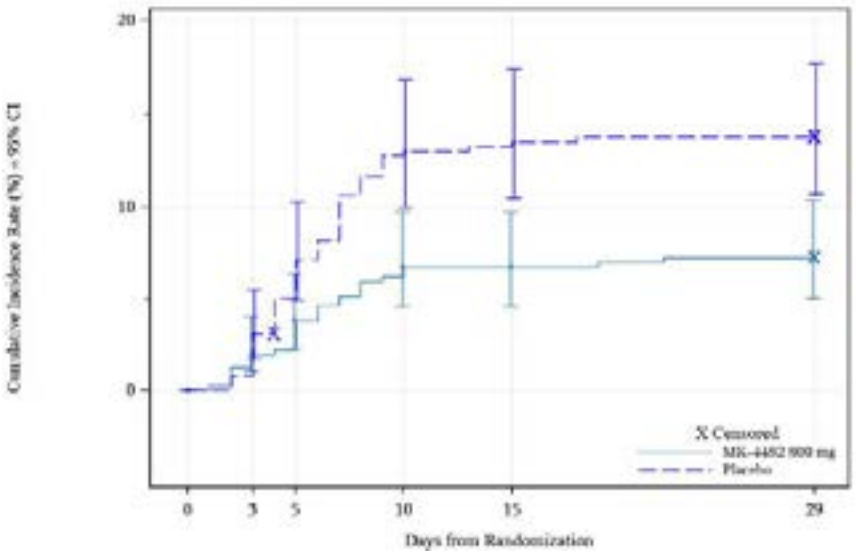
Results of time-to-event sensitivity analyses were consistent with the results of the primary analysis.

Analysis of Time to Hospitalization or Death Through Day 29
Modified Intent-To-Treat Population
MK-4482-002 Combined IA3/IA4

Treatment	N	Number of Events (%)	Person-day	Event Rate/ 100 Person-days	Median Time to Hospitalization or Death[a] (days) (95% CI)	Hospitalization or Death Rate at Day 29 in %[a] (95% CI)
MK-4482 800 mg	385	28 (7.3)	10531.0	0.3	NR (NA, NA)	7.3 (5.1, 10.4)
Placebo	377	52 (13.8)	9712.0	0.5	NR (NA, NA)	13.8 (10.7, 17.7)
Comparison					Hazard Ratio[b] (95% CI)[b]	p-Value[c]
MK-4482 800 mg vs. Placebo					0.51 (0.32, 0.81)	0.0017

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on stratified Cox regression model with Efron's method of tie handling with treatment as covariate and randomization stratum as stratification factor. Hazard ratio < 1 favors the MK-4482 800 mg group.
[c] One-sided p-value based on log-rank test stratified by randomization stratification stratum.
NR = Not reached; NA = Not applicable.
N= number of participants in the Modified Intent-To-Treat population.

Kaplan-Meier Plot for Hospitalization or Death Through Day 29
Modified Intent-To-Treat Population
MK-4482-002 Combined IA3/IA4



Results of a sensitivity analysis which excluded participants who did not receive at least 48 h treatment (<5 doses) or who were hospitalised or died before their 5th dose were consistent with the results of the primary analysis based on the MITT population.

Incidence of Hospitalization or Death Through Day 29
Sensitivity Analysis: Excluding Participants Who Received < 5 Doses of Study Intervention or Were Hospitalized Before Receipt of 5 Doses of Study Intervention
Modified Intent-To-Treat Population
MK-4482-002 Combined IA3/IA4

Treatment	N	n (%)	Treatment vs. Placebo	
			Unadjusted Difference	Adjusted Difference in Rates % (95% CI)[a]
MK-4482 800 mg	370	21 (5.7)	-5.8	-5.8 (-10.0, -1.7)
Placebo	358	41 (11.5)		

[a] Adjusted differences and the corresponding confidence intervals are based on Miettinen & Nurminen method stratified by randomization strata.
N= number of participants in the modified intent-to-treat population.
n= number of participants died or hospitalized through Day 29.
Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.
Participants who took less than 5 complete doses through end of treatment and participants who were hospitalized before the 5th complete dose are excluded from the analysis.

Results of subgroup analyses were consistent with the results of the primary analysis for the following:

RETURN TO PACKAGE TABLE

- Time from symptom onset to randomisation (≤3 days; >3 [4-5] days)

Incidence of Hospitalization or Death Through Day 29 by Time From Symptom Onset to Randomization
Modified Intent-To-Treat Population
MK-4482-002 Combined IA3/IA4

	MK-4482 800 mg		Placebo		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)*
Participants in population	385		377			
Time from Symptom Onset to Randomization						
≤3 days	16/189	(8.5)	23/185	(12.4)	-4.0	(-10.4, 2.3)
>3 days	12/196	(6.1)	30/192	(15.6)	-9.5	(-16.0, -3.0)

* The corresponding confidence interval is based on Miettinen & Nurminen method.
m= number of participants in the modified intent-to-treat population with the corresponding group.
n= number of participants died or hospitalized through Day 29.
Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.
Time from symptom onset to randomization is based on the value of the stratification factor collected at randomization.

- Age group (≤60 years; >60 years)

Incidence of Hospitalization or Death Through Day 29 by Age Group
Modified Intent-To-Treat Population
MK-4482-002 Combined IA3/IA4

	MK-4482 800 mg		Placebo		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)*
Participants in population	385		377			
Age Group						
≤60 years	23/335	(6.9)	41/322	(12.7)	-5.9	(-10.6, -1.4)
>60 years	5/50	(10.0)	12/55	(21.8)	-11.8	(-26.1, 2.5)

* The corresponding confidence interval is based on Miettinen & Nurminen method.
m= number of participants in the modified intent-to-treat population with the corresponding group.
n= number of participants died or hospitalized through Day 29.
Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.

- Obesity (BMI ≥30; yes, no)

Incidence of Hospitalization or Death Through Day 29 by Obesity Status
Modified Intent-To-Treat Population
MK-4482-002 Combined IA3/IA4

	MK-4482 800 mg		Placebo		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)*
Participants in population	385		377			
Obesity (BMI ≥ 30)						
Yes	19/306	(6.2)	35/281	(12.5)	-6.2	(-11.2, -1.6)
No	9/79	(11.4)	18/96	(18.8)	-7.4	(-18.0, 3.7)

* The corresponding confidence interval is based on Miettinen & Nurminen method.
m= number of participants in the modified intent-to-treat population with the corresponding group.
n= number of participants died or hospitalized through Day 29.
Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.

- Diabetes mellitus (yes, no)

Incidence of Hospitalization or Death Through Day 29 by Diabetes Mellitus Status
Modified Intent-To-Treat Population
MK-4482-002 Combined IA3/IA4

	MK-4482 800 mg		Placebo		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)*
Participants in population	385		377			
Diabetes Mellitus Status						
Yes	9/48	(18.8)	13/56	(23.2)	-4.5	(-20.1, 11.8)
No	19/337	(5.6)	40/321	(12.5)	-6.8	(-11.4, -2.5)

* The corresponding confidence interval is based on Miettinen & Nurminen method.
m= number of participants in the modified intent-to-treat population with the corresponding group.
n= number of participants died or hospitalized through Day 29.
Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.

- Viral clades (20J [Gamma], 21A [Delta], 21H [Mu])

Incidence of Hospitalization or Death Through Day 29 by Baseline Clade
Modified Intent-To-Treat Population
MK-4482-002 Combined IA3/IA4

	MK-4482 800 mg		Placebo		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)*
Participants in population	385		377			
Baseline Clade						
20J	0/27	(0.0)	4/34	(11.8)	-11.8	(-28.8, 1.5)
21A	5/33	(15.2)	9/29	(31.0)	-15.9	(-36.9, 5.3)
21H	3/43	(7.1)	6/35	(10.9)	-3.6	(-15.9, 10.0)

* The corresponding confidence interval is based on Miettinen & Nurminen method
n= number of participants in the modified intent-to-treat population with the corresponding baseline clade.
n= number of participants died or hospitalized through Day 29.
Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.
This table only presents baseline clade that with ≥ 25 participants in both treatment groups.

- COVID-19 severity (mild, moderate)

Incidence of Hospitalization or Death Through Day 29 by Baseline COVID Severity
Modified Intent-To-Treat Population
MK-4482-002 Combined IA3/IA4

	MK-4482 800 mg		Placebo		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)*
Participants in population	385		377			
Baseline COVID Severity						
Mild	12/222	(5.4)	21/203	(10.3)	-4.9	(-10.5, 0.2)
Moderate	16/161	(9.9)	31/173	(17.9)	-8.0	(-15.5, -0.5)
Severe	0/2	(0.0)	0/0	(0.0)		

* The corresponding confidence interval is based on Miettinen & Nurminen method.
n= number of participants in the modified intent-to-treat population with the corresponding group.
n= number of participants died or hospitalized through Day 29.
Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.

- Region (North America, Latin America, Europe, and Africa)

Incidence of Hospitalization or Death Through Day 29 by Region
Modified Intent-To-Treat Population
MK-4482-002 Combined IA3/IA4

	MK-4482 800 mg		Placebo		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)*
Participants in population	385		377			
Region						
North America	1/13	(6.7)	3/22	(13.6)	-7.0	(-28.6, 18.6)
Latin America	15/214	(7.0)	30/207	(14.5)	-7.5	(-13.7, -1.6)
Europe	8/89	(9.0)	12/87	(13.8)	-4.8	(-14.8, 4.8)
Asia Pacific	1/5	(20.0)	3/6	(50.0)	-30.0	(-71.6, 28.8)
Africa	3/62	(4.8)	3/55	(5.5)	-0.7	(-15.5, 5.6)

* The corresponding confidence interval is based on Miettinen & Nurminen method.
n= number of participants in the modified intent-to-treat population with the corresponding group.
n= number of participants died or hospitalized through Day 29.
Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.

- Seronegative participants (based on SARS-CoV-2 nucleocapsid antibodies)

In the subgroup of participants positive for SARS-CoV-2 antibodies at baseline (approximately 18% in each group), there was no difference between intervention groups in the percentage of participants who were hospitalised or died (2.9% in both groups).

Incidence of Hospitalization or Death Through Day 29 by SARS-CoV-2 Baseline Antibody
Modified Intent-To-Treat Population
MK-4482-002 Combined IA3/IA4

	MK-4482 800 mg		Placebo		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)*
Participants in population	385		377			
SARS-CoV-2 Baseline Antibody						
Positive	2/70	(2.9)	2/69	(2.9)	-0.0	(-7.5, 7.3)
Negative	23/299	(7.7)	49/287	(17.1)	-9.4	(-14.9, -4.1)

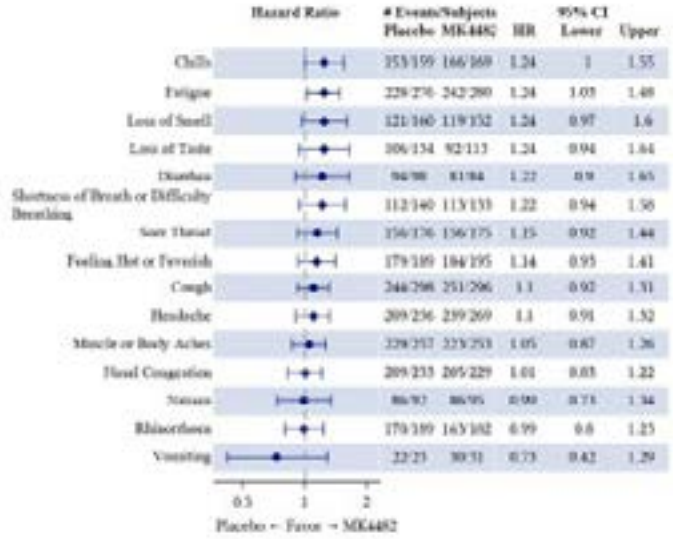
* The corresponding confidence interval is based on Miettinen & Nurminen method.
n= number of participants in the modified intent-to-treat population with the corresponding group.
m= number of participants died or hospitalized through Day 29.
Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.

- **Ancillary analyses**

Most participants (>98%) in both intervention groups had a baseline score of 2 on the WHO ordinal scale. The majority in both intervention groups (66.3%) improved to a score of 0 (uninfected; no viral RNA detected) or 1 (asymptomatic; viral RNA detected) by Day 29.

Although subjects were not severely ill at baseline, the overall picture of effect of treatment on resolution of baseline signs and symptoms suggested some benefit for molnupiravir, as summarised in the figure.

Hazard Ratio of Time to Sustained Improvement or Resolution of Signs and Symptoms
Through Day 29
Modified Intent-To-Treat Population
MK-4482-002 Combined IA3/IA4



At the time of the database lock for IA3/IA4, qualitative and quantitative SARS-CoV-2 RNA PCR for most participants were available through Day 10. Post-baseline SARS-CoV-2 viral sequence data were available from 92 participants (n=42 molnupiravir; n=50 placebo).

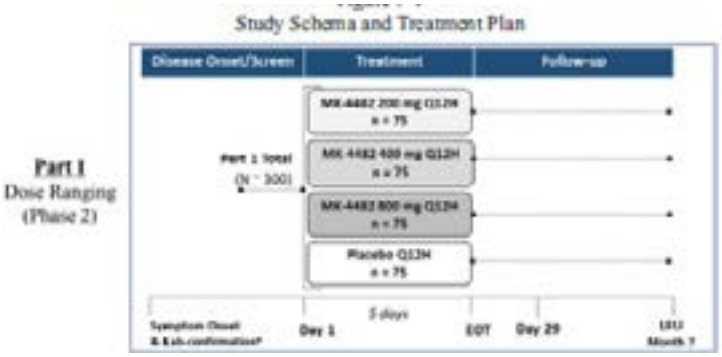
Molnupiravir was associated with a greater reduction in SARS-CoV-2 RNA from baseline compared with the placebo group at Days 3 and 5 but not at later time points. Results stratified by baseline SARS-CoV-2 RNA titre ($>10^6$ and $\leq 10^6$ copies/mL) were generally consistent with the overall results for the mean change from baseline in SARS-CoV-2 RNA.

After adjusting for baseline RNA titre, the adjusted mean difference in SARS-CoV-2 RNA (in $\log_{10}$ scale) was -0.24 at Day 3 and -0.44 at Day 5, which corresponds to a 42% and a 64% relative reduction in the geometric mean SARS-CoV-2 RNA titre. Among those with $>10^6$ copies/mL, after adjusting for

baseline RNA titre, the largest difference was a 70% relative reduction observed at Day 5. Among those participants with ≤10^6 copies/mL, the largest difference was a 70% relative reduction at Day 3. The percentages with undetectable SARS-CoV-2 RNA in NP samples by qualitative PCR was comparable between treatment groups and regardless of baseline SARS-CoV-2 RNA titre. Molnupiravir was associated with a higher mutation rate vs. placebo (7.4 vs. 3.4) in those with paired baseline and Day 5 SARS-CoV-2 viral sequences. Mean numbers of transversion mutations were low in both groups.

2.4.2.3. Study MK4482-001 in hospitalised patients

The study was initiated in October 2020 and the CSR reports data to March 2021 that supported interim analysis 2 (IA2), at which time all Part 1 participants had completed to Day 29 or had otherwise discontinued. There was no formal hypothesis testing in Part 1 of the study. Part 1 of the study was a dose-finding exercise in which three doses of molnupiravir were compared to placebo. Based on IA2, following the recommendation of the eDMC, the decision was taken not to proceed with the planned Part 2 of the study (see below).



Eligible subjects were adults with laboratory-confirmed SARS-CoV-2 infection from a sample collected ≤10 days prior to randomisation who had signs/symptoms attributable to COVID-19 for ≤10 days and ≥1 sign/symptom attributable to COVID-19. They were to require in-hospital care for COVID-19 that could be classed as mild, moderate or severe but not critical. There was no selection criterion related to requirement for oxygen supplementation at study entry. Appendix 9 of the protocol categorised patients into mild, moderate and severe based on respiratory and heart rate and oxygen saturation. In addition to meeting the RR and HR criteria, mild and moderate cases were to have >93% saturation on room or on oxygen prior to hospitalisation that had not further increased since hospitalisation whereas severe cases may have had saturation ≤93%. Patients considered to be in respiratory failure, including those needing mechanical ventilation or other means of delivering high flow oxygen, were excluded.

Subjects were excluded if they were on dialysis or had eGFR <30 mL/min/1.73 m^2, had HIV with >50 copies/mL or CD4 <200 cell/mm^3, had an absolute neutrophil count <500/mm^3, a platelet count <100,000/µL, had acute pancreatitis within 3 months or a history of chronic pancreatitis. Standard of care treatments of COVID-19 were allowed including remdesivir, systemic corticosteroids and convalescent plasma.

There were 304 subjects randomised across 86 study sites in 15 countries, as shown below. The majority (93.6% combined molnupiravir; 96.0% placebo) received 9 to 10 doses with a mean duration of treatment of 4.4 days.

Disposition of Participants
All Randomized Participants
MK-4482-001 1A2

	MK-4482 200 mg		MK-4482 400 mg		MK-4482 800 mg		MK4482 Combined		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Not Randomized											16	
Participants in population	75		75		76		226		78		304	
Status for Study Medication												
Started	73		73		72		218		75		293	
Completed	70	(95.9)	66	(90.4)	69	(95.8)	205	(94.0)	72	(96.0)	277	(94.5)
Discontinued	3	(4.1)	7	(9.6)	3	(4.2)	13	(6.0)	3	(4.0)	16	(5.5)
Adverse Event	0	(0.0)	1	(1.4)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.3)
Lost To Follow-Up	1	(1.4)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.3)
Non-Compliance With Study Drug	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.5)	0	(0.0)	1	(0.3)
Withdrawal By Subject	2	(2.7)	6	(8.2)	2	(2.8)	10	(4.6)	3	(4.0)	13	(4.4)
Status for Day 29 Milestone*												
Started	73		73		72		218		75		293	
Completed	62	(84.9)	60	(82.2)	66	(91.7)	188	(86.2)	70	(93.3)	258	(88.1)
Discontinued	11	(15.1)	13	(17.8)	6	(8.3)	30	(13.8)	5	(6.7)	35	(11.9)
Death	5	(6.8)	4	(5.5)	3	(4.2)	12	(5.5)	1	(1.3)	13	(4.4)
Lost To Follow-Up	1	(1.4)	1	(1.4)	1	(1.4)	3	(1.4)	1	(1.3)	4	(1.4)
Physician Decision	0	(0.0)	1	(1.4)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.3)
Withdrawal By Subject	5	(6.8)	7	(9.6)	2	(2.8)	14	(6.4)	3	(4.0)	17	(5.8)

Baseline demographic and disease characteristics were comparable across the groups. The majority was male (56.5%) and the mean age was 57.0 years (range 19 to 94 years); 41.4% of the study population was >60 years of age. Most participants (76.3%) received study intervention >5 days after symptom onset and the median time from symptom onset to randomisation was 8.0 days.

The baseline COVID-19 severity was moderate or severe for 86.5% of participants (13.5% mild, 43% moderate and 43% severe). The most common risk factors for severe COVID-19 were age >60 years (41.4%), obesity (BMI ≥30, 40.1%) and diabetes mellitus (23.0%). Most participants (87.5%) had detectable SARS-CoV-2 RNA in the baseline NP sample. SARs-CoV-2 baseline antibody was positive for 31.9% at baseline.

Efficacy analyses were based on the MITT population, which included 293 randomised and treated participants. For the primary efficacy endpoint in Part 1, which was the time to sustained recovery through Day 29, there was no clear effect of molnupiravir treatment.

Analysis of Time to Sustained Recovery Through Day 29
Modified Intent-To-Treat Population
MK4482-001 1A2

Treatment	N	Number of Events (%)	Person-day	Event Rate/ 100 Person-days	Median Time to Recovery [a] (days) (95% CI)	Recovery Rate at Day 29 in % [a] (95% CI)
MK-4482 200 mg	73	56 (76.7)	867.0	6.5	9.0 (7.0, 10.0)	81.5 (71.4, 89.7)
MK-4482 400 mg	73	56 (76.7)	788.0	7.1	9.0 (8.0, 10.0)	85.2 (75.4, 92.0)
MK-4482 800 mg	72	59 (81.9)	874.0	6.8	9.0 (8.0, 11.0)	84.3 (74.8, 91.6)
Placebo	75	61 (81.3)	896.0	6.8	9.0 (8.0, 11.0)	84.7 (75.5, 91.9)
Pairwise Comparison					Hazard Ratio[b] (95% CI)[b]	p-Value
MK-4482 200 mg vs. Placebo					0.99 (0.68, 1.45)	0.3620[c]
MK-4482 400 mg vs. Placebo					1.13 (0.78, 1.65)	0.3145[c]
MK-4482 800 mg vs. Placebo					1.01 (0.69, 1.47)	0.4894[c]
MK-4482 400 mg vs. MK-4482 200 mg					1.12 (0.76, 1.66)	0.3034[c]
MK-4482 800 mg vs. MK-4482 200 mg					1.00 (0.69, 1.47)	0.4523[c]
MK-4482 800 mg vs. MK-4482 400 mg					0.89 (0.61, 1.31)	0.6685[c]

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment and randomization stratification factors as covariates. Hazard ratio >1 favors the first group in the pairwise comparison.
[c] One-sided p-value based on log-rank test stratified by randomization stratification factors.

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The median time to sustained recovery was 9 days in active and placebo groups and the recovery rate ranged from 81.5% to 85.2% in each intervention group at Day 29.

The results for the primary endpoint in participants >60 years of age, without remdesivir use prior to or at randomisation, at increased risk of severe COVID-19, and with symptom onset of ≤5 days prior to randomisation were consistent with those in the overall population

Overall, 17 (5.8%) deaths were reported during the 29-day follow-up period. A higher proportion of participants died in each of the molnupiravir groups (200 mg – 4, 5.5%], 400 mg – 8, 11.0% and 800 mg - 3, 4.2%]) compared with placebo [2, 2.7%]). Results from post-hoc analyses of all-cause mortality in participants >60 years of age, without remdesivir use prior to or at randomisation, with risk factors for severe COVID-19 and with symptom onset of ≤5 days prior to randomisation were consistent with the results in the overall population. Similar improvements in outcomes over time and up to Day 29 were observed across groups based on the WHO 11-point ordinal scale.

A similar decrease from baseline in SARS-CoV-2 RNA mean titre was observed in all groups at all time points in NP and OP samples (assessed by quantitative PCR). There were no differences in response across the dose groups and placebo group for participants with high (>10^6 copies/mL) or lower (≤10^6 copies/mL) baseline RNA titres.

A higher mutation rate was observed in post-baseline viral sequences from NP swabs in all molnupiravir groups compared with placebo. Additionally, the proportion of participants with >3 per 10,000 post-baseline sequence mutations (threshold defined post-hoc) from NP swabs was higher in all the molnupiravir groups compared with placebo.

Analysis of mutation rate associated with molnupiravir treatment

A report dated 28 September 2021 describes the available virology data concerning minor variants derived from next generation sequencing (NGS) of NP and oropharyngeal swabs obtained during MK4482-001 Part 1 and MK4482-002 Part 1.

Samples included NP and/or OP swabs with RNA ≥22,000 copies/mL. NGS was only performed on samples from individuals who had an evaluable baseline sample and at least one post-baseline (Study Day 3 and/or Study Day 5/EOT) sample for comparison. Samples from the same individual were batched in the same sequencing run to minimise potential sequence differences due to batch variability.

Minor variant analysis in P002 Part 1

At Day 1, there were no differences detected in the geometric mean number of minor variants (NMV) between the molnupiravir (MOV) and placebo groups for both NP and OP samples, as assessed by linear trend analysis. In contrast, at Day 3 and Day 5, there was a linear dose-response relationship with increasing molnupiravir dose in the geometric mean NMV in both NP and OP samples. At Day 3, this represented an approximate 5- and 8-fold increase in the geometric mean number of mutations for the 800 mg molnupiravir group compared with placebo in the NP and OP samples, respectively. At Day 5, the respective increases were by 11- and 10-fold.

The effect of viral RNA titre on minor variant detection by NGS was evaluated because RT-PCR and sequencing artefacts can manifest as minor variants and the number of artefacts can be affected by the amount of input RNA during NGS library construction. To control for this, NMV was compared between intervention groups while controlling for viral RNA titre.

On Day 1, the samples with lower viral RNA titres tended to be those with higher NMV across all intervention groups, which does suggest that the NMV can be affected by sample viral RNA titre. At

Day 3 and Day 5, there was a linear dose-response relationship in adjusted geometric mean NMV in both NP and OP samples.

Table 3 Number of Minor Variants (Adjusted for Viral RNA Titer) in SARS-CoV-2 RNA Genome Sequence by Visit and Dose: P002 Part 1 Nasopharyngeal Swabs

Visit	Placebo		MOV 200mg		MOV 400mg		MOV 800mg		
	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	P-value for Linear Trend
Day 1	37	**10.5** (7.6, 14.5)	36	**8.7** (6.3, 12.0)	36	**10.5** (7.5, 14.5)	33	**10.5** (7.4, 14.8)	0.8286
Day 3	35	**11.2** (8.0, 15.5)	39	**23.4** (17.1, 31.6)	37	**38.0** (27.8, 52.5)	35	**52.5** (37.4, 72.4)	<.0001
Day 5 (EOT)	24	**14.8** (10.0, 21.9)	24	**56.2** (37.8, 83.2)	20	**66.1** (43.0, 102.3)	16	**102.3** (62.2, 166.0)	<.0001

CI=confidence interval; EOT=end of treatment; MOV=Molnupiravir; N= number of participants with available data.
Day 3 includes post-baseline records up to Day 4 relative to randomization. Day 5 (EOT) includes post-baseline records from Day 5 (relative to randomization) up to Day 7. EOT visits occurring earlier than Day 5 (relative to randomization) are included in the Day 3 visit.

Table 4 Number of Minor Variants (Adjusted for Viral RNA Titer) in SARS-CoV-2 RNA Genome Sequence by Visit and Dose: P002 Part 1 Oropharyngeal Swabs

Visit	Placebo		MOV 200mg		MOV 400mg		MOV 800mg		
	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	P-value for Linear Trend
Day 1	22	**17.8** (11.9, 26.3)	22	**10.2** (7.0, 15.1)	17	**13.5** (8.7, 21.4)	17	**14.8** (9.5, 22.9)	0.7882
Day 3	19	**13.5** (8.9, 20.4)	20	**27.5** (18.5, 41.7)	15	**42.7** (26.9, 67.6)	15	**97.7** (60.8, 154.9)	<.0001
Day 5 (EOT)	12	**15.8** (9.3, 26.3)	14	**77.6** (48.1, 125.9)	8	**39.8** (21.2, 75.9)	5	**128.8** (57.7, 288.4)	0.0003

CI=confidence interval; EOT=end of treatment; MOV=Molnupiravir; N= number of participants with available data.
Day 3 includes post-baseline records up to Day 4 relative to randomization. Day 5 (EOT) includes post-baseline records from Day 5 (relative to randomization) up to Day 7. EOT visits occurring earlier than Day 5 (relative to randomization) are included in the Day 3 visit.

Minor variant analysis in P001 Part 1

A linear trend in the geometric mean NMV with increasing drug dose was observed in NP samples at Day 3, but not at Day 5. No linear trends in the geometric mean NMV with increasing drug dose were observed in OP samples at either visit. Controlling for viral RNA titre, treatment-emergent differences between molnupiravir and placebo groups were evident in NP samples at Day 3, but not Day 5. No differences were observed in OP samples at either visit.

Table 7 Number of Minor Variants (Adjusted for Viral RNA Titer) in SARS-CoV-2 RNA Genome Sequence by Visit and Dose: P001 Part 1 Nasopharyngeal Swabs

Visit	Placebo		MOV 200mg		MOV 400mg		MOV 800mg		
	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	P-value for Linear Trend
Day 1	26	**25.1** (16.2, 38.9)	26	**15.8** (10.2, 24.5)	29	**20.0** (12.9, 30.2)	24	**16.2** (10.2, 25.7)	0.2860
Day 3	25	**23.4** (14.8, 36.3)	20	**34.7** (20.9, 56.2)	26	**49.0** (31.6, 75.9)	21	**78.9** (46.8, 123.0)	0.0004
Day 5 (EOT)	13	**32.4** (17.4, 58.9)	13	**69.2** (38.0, 128.8)	14	**63.1** (34.7, 112.2)	14	**67.6** (38.9, 117.5)	0.1021

CI=confidence interval; EOT=end of treatment; MOV=Molnupiravir; N= number of participants with available data.
Day 3 includes post-baseline records up to Day 4 relative to randomization. Day 5 (EOT) includes post-baseline records from Day 5 (relative to randomization) up to Day 7. EOT visits occurring earlier than Day 5 (relative to randomization) are included in the Day 3 visit.

Table 8 Number of Minor Variants (Adjusted for Viral RNA Titer) in SARS-CoV-2 RNA Genome Sequence by Visit and Dose: P001 Part 1 Oropharyngeal Swabs

Visit	Placebo		MOV 200mg		MOV 400mg		MOV 800mg		
	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	P-value for Linear Trend
Day 1	15	**17.0** (10.7, 26.9)	15	**22.9** (14.5, 36.3)	16	**14.5** (9.3, 22.4)	15	**21.9** (13.8, 34.7)	0.7652
Day 3	12	**25.1** (15.1, 42.7)	11	**53.7** (31.6, 91.2)	13	**51.3** (30.9, 85.2)	11	**31.6** (18.6, 53.7)	0.5938
Day 5 (EOT)	10	**41.7** (24.0, 74.1)	5	**208.9** (95.5, 457.1)	9	**79.4** (43.7, 144.5)	10	**58.9** (33.9, 104.7)	0.9596

CI=confidence interval; EOT=end of treatment; MOV=Molnupiravir; N= number of participants with available data.
Day 3 includes post-baseline records up to Day 4 relative to randomization. Day 5 (EOT) includes post-baseline records from Day 5 (relative to randomization) up to Day 7. EOT visits occurring earlier than Day 5 (relative to randomization) are included in the Day 3 visit.

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Conclusions

The report concluded that molnupiravir treatment was associated with a dose-dependent increase in minor variants in both NP and OP samples at Day 3 and Day 5 in study P002. The NMV in the SARS-CoV-2 viral RNA was inversely associated with the viral RNA titre. Controlling for viral RNA titre, there was a linear dose-response relationship in adjusted geometric mean NMV in both NP and OP samples in study P002. In study P001, a dose-dependent increase in minor variants in NP samples was observed at Day 3, with or without the adjustment for viral RNA titre.

molnupiravir treatment increases viral mutations in SARS-CoV-2 in a dose-dependent fashion, consistent with the error catastrophe mechanism of action.

2.4.2.4. Discussion on clinical efficacy

Demonstrated benefits

The studies were double blind and placebo-controlled in design, which is considered appropriate by CHMP.

In MK4482-002 Part 2, in contrast to MK4482-006 and MK4482-002 Part 1, eligible subjects were to be enrolled within 5 days of symptom onset and all were to have at least one underlying condition listed in the protocol as potentially predisposing them to develop severe COVID-19. The change in selection criteria reflected Part 1 data suggesting that the maximum benefit of molnupiravir occurs when it is started within 5 days of symptom onset in a population that could be regarded as being at increased risk of progressing to severe COVID-19 (according to criteria in the WHO 11-point ordinal scale for clinical progression). The protocol for MK4482-002 also attempted to subdivide patients at baseline into those with mild or moderate disease mainly based on presence of one of shortness of breath on exertion, tachypnoea or tachycardia.

Very importantly, the protocol for MK4482-002 required that subjects were not receiving supplemental oxygen to treat COVID-19 or were on no more than 4L/min. On request, the company confirmed that no subjects in Parts 1 or 2 were receiving oxygen at study entry, which fits with the baseline WHO scale status of the study population. Moreover, the majority of subjects in Part 1 had at least one protocol-listed risk factor for progression of COVID-19 and all subjects in Part 2 were to have at least one such risk factor. The company's initial proposed indication statement *for treatment of coronavirus disease 2019 (COVID-19) in adults* was not accepted by the CHMP, since efficacy was shown in a defined population not requiring oxygen in MK-4482-002 Part 2 and since MK4482-001 Part 1 failed to show any clinical benefit in a hospitalised population that had a range of oxygen requirements.

In the selected study population, the primary endpoint of all-cause hospitalisation (as defined by the company) or death up to Day 29 was appropriate. There was no pre-planned hypothesis testing in Part 1 and subjects enrolled into Part 1 were not included in analyses of Part 2, which stands alone. Part 2 was planned to have overall power of 97% to demonstrate superiority of molnupiravir 800 mg BID over placebo at an overall one-sided 2.5% alpha level, if the underlying treatment difference (molnupiravir minus placebo) in the percentage hospitalised and/or dying through Day 29 was -6 percentage points. These assumptions were based on emerging evidence from various clinical trials and were considered reasonable.

Part 2 involved stratification at randomisation according to time from symptom onset (TSSO) prior to the day of randomisation (≤3 days, >3 days), having reduced the maximum TSSO allowed for eligibility to 5 days based on Part 1. This stratification seems appropriate since Part 1 had already pointed to the potential importance of TSSO (≤5 days, >5 days) for outcomes.

A primary analysis in the MITT (all-treated) population, in which unknown survival was counted as failure, is acceptable.

The four planned interim analyses were generally appropriate given the lack of any prior evidence of efficacy based on a clinical endpoint. In the final event, IA3 was not required since enrolment into Part 2 progressed quickly, so IA3 and IA4 were merged.

Selection of 800 mg BID for 5 days for MK4482-002 Part 2

MK4482-006 provided some preliminary evidence that molnupiravir had an antiviral effect in a population similar to that enrolled into MK4482-002 Part 1. There was no effect of active treatment at any dose tested for the pre-defined primary endpoint of median time to viral clearance. However, the proportion with undetectable SARS-CoV-2 RNA was greater in the molnupiravir 800 mg group (but not in the 200 mg and 400 mg groups) compared with the placebo group (p=0.0373 on Day 5 and p=0.0343 on Day 28). With 35.3% in the 800 mg group vs. 18.2% in the placebo group seropositive at baseline and with a very clear effect of baseline seropositivity on positive cultures (e.g. 56% of seronegative and 11% of seropositive subjects were culture positive in the placebo group at baseline), the results based on positive cultures over time are difficult to interpret. At the same time, there did not seem to be rate-limiting safety issues, such that progression to MK4482-001 Part 1 and MK4482-002 Part 1 with doses up to 800 mg BID was a reasonable choice.

MK4482-002 Part 1 enrolled a population in which ~75% had at least one of the protocol-listed risk factors for severe COVID-19 (mostly obesity, diabetes and age >60 years) and ~66% had a TSSO within 5 days. Just over half met the company's criteria for moderate disease, a low percentage (<15%) was already seropositive for SARS-CoV-2 and most (>80%) had PCR confirmation of the virus as opposed to a positive antigen test at study entry. None received oxygen at study entry.

Among 299 included in the MITT population, there were only 11 primary endpoint events and no statistically significant differences between the four treatment groups with rates from 1.4% to 5.4%. However, among those who started treatment within 5 days of symptom onset and were at increased risk of severe COVID-19, there were 4/107 (3.7%) hospitalised in the combined molnupiravir groups vs. 4/34 (11.8%) in the placebo group. While Part 1 was not intended to address specific hypotheses, it did suggest that a benefit of molnupiravir might be more evident when it was started within 5 days of symptom onset and in those at increased risk of severe COVID-19.

The results of Part 1 led the DSMB to recommend continuation to Part 2, which seems appropriate. Part 1 did not provide good support for progressing to Part 2 with 800 mg BID. Nevertheless, with no rate-limiting safety concerns, selection of the highest tested dose was reasonable.

Efficacy of 800 mg BID for 5 days in MK4482-002 Part 2

With slightly different selection criteria vs. Part 1, >99% of the population enrolled into Part 2 had at least one of the protocol-listed risk factors for developing severe COVID-19, the most common by far being obesity. Just under 15% were aged >60 years. Using the company's definitions, ~44% had moderate and 56% mild disease and about half had TSSO within 3 days. Overall, 18.2% were already seropositive for SARS-CoV-2 at baseline and 85.5% had a positive RT-PCR result rather than a positive antigen detection test. None received oxygen at study entry.

The tables for Part 2 report the variant distributions for 36% of the total enrolled for which data are currently available. The most common genotype clades at baseline were 21H (Mu, 35.0%), 21A (Delta, 22.4%) and 20J (Gamma, 22.4%). While such data are limited, the nonclinical data suggest that molnupiravir has similar in-vitro activity against the EU-predominant delta variant as against "wild type" virus, which is reassuring.

In the MITT population, which comprised 98.3% of those enrolled, there was a statistically significantly lower rate of all-cause hospitalisations and deaths through Day 29 in the molnupiravir group, with a reduction from 14.1% to 7.3%. The 95% confidence intervals around the difference did not span zero and the p-value was 0.0012.

There were 8 documented deaths in the placebo group and none in the molnupiravir group. One additional placebo group subject had an unknown outcome at day 29. Unsurprisingly, the rates show that those who are known to have died did so after being hospitalised.

In the planned sensitivity analysis in which only hospitalisations and deaths considered to be COVID-related were counted, the totals in each group were reduced by 3 subjects, giving rates of 6.5% vs. 13.3% and 95% CI around the difference that did not span zero. Results of a sensitivity analysis which excluded those who received <5 doses or who were hospitalised or died before their 5th dose were consistent with the results of the primary analysis. The Kaplan-Meier curve showed separation between groups for primary endpoint events from Day 3 onwards.

The subgroup analyses were generally in keeping with the primary analysis.

In the seronegative majority (based on SARS-CoV-2 nucleocapsid antibodies) of the study population the analysis of the primary endpoint gave rates of 7.7% for molnupiravir and 17.1% for placebo (95% CI -14.9, -4.1). In contrast, in the subgroup seropositive for SARS-CoV-2 antibodies at baseline (approximately 18% in each group), there was no difference between intervention groups in the percentage of participants who were hospitalised or died (2.9% in both groups).

In this unvaccinated study population, the presence of anti-N antibody at baseline in persons who presented within 5 days of symptom onset, with ~half presenting within 3 days, is more likely to reflect prior natural infection rather than an early primary immune response to the acute episode. Prior natural infection would have primed the immune system, giving a rapid immune memory response to the presenting episode with blunting of severity resulting in a low progression rate in the placebo group that could not be improved by active treatment. Therefore, the result in the baseline seropositive patients is to be expected.

Uncertainty about benefits

Reflecting the timing of initiation of the study and the enrolment window, the study populations in MK4482-002 Parts 1 and 2 were unvaccinated with respect to SARS-Cov-2 and the baseline seropositivity rates (based only on anti-N antibody) suggest that less than one fifth had experienced prior natural infection. Published data point to an amelioration of COVID-19 by prior vaccination (i.e. vaccinated persons who get breakthrough disease tend to fare better than unvaccinated persons with COVID-19). Moreover, MK4482-002 Part 2 showed that the rate of hospitalisation or death among baseline seropositive subjects was very low and similar in the molnupiravir and placebo groups, reflecting some degree of protection afforded by prior natural priming.

The magnitude of benefit of molnupiravir documented in MK4482-002 in unvaccinated and seronegative subjects is not expected to be applicable to a population comprising vaccinated and/or naturally primed seropositive subjects.

Similar issues regarding the efficacy shown in studies confined to, or predominantly including, unvaccinated and seronegative subjects apply to several antiviral agents and monoclonal antibodies that have been investigated for the treatment of COVID-19. The company has mentioned in the draft conditions for use that the study population consisted of unvaccinated persons, which is appropriate. However, as the baseline serostatus based on anti-N antibody should also be mentioned in the conditions for use, a statement was included to the effect that progression rates in baseline seropositive patients were very low and similar between molnupiravir and placebo groups.

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The study allowed use of corticosteroids. However, the proportion of subjects who did receive steroids specifically to prevent progression of COVID-19 is not reported in the data. Other antiviral agents against SARS-CoV-2 (including monoclonal antibodies) were not allowed.

At this time, information on protocol deviations is lacking. Also, numbers included in the per protocol population, which would have excluded those with important deviations, are not reported, and these aspects will need to be further explored in the context of the MAA.

Based on next generation sequencing (NGS) applied to samples obtained in MK4482-001 Part 1 and MK4482-002 Part 1, molnupiravir treatment increases viral mutations in SARS-CoV-2 in a dose-dependent fashion, consistent with the error catastrophe mechanism of action. This raises the question whether virus that emerges during treatment and/or in subjects who fail treatment with molnupiravir could harbour mutations with significant consequences for the success of other products intended for prevention or treatment of COVID-19. This is not a question that can be answered from available data and it will likely require some prospective monitoring in the post-approval period. Therefore, this issue will be further explored in the MAA.

Importance of the MK4482-001 Part 1 data

MK4482-001 Part 1 was intended to identify a potentially efficacious dose regimen to be used in Part 2, which was cancelled following review of Part 1 results. There was no plan for formal hypothesis testing in Part 1. This study enrolled hospitalised subjects at up to 10 days after symptom onset and about 75% started treatment >5 days after onset. Most (~85%) met the company's criteria for moderate or severe COVID-19 at baseline; thus, not all subjects required supplemental oxygen when enrolled and the proportion that did has not been reported. With a delay up to 10 days since symptom onset, ~32% had anti-N antibody at study baseline. In this rather mixed population and with a primary endpoint of time to sustained recovery through Day 29, there was no clear effect of molnupiravir. Both the median time to recovery as defined in the protocol and percent reaching the endpoint were comparable between each of the molnupiravir dose groups and placebo.

Given the difference in population and the TSSO, the results do not really conflict with those of MK4482-002 Part 2. There was a higher death rate in each molnupiravir group vs. placebo but the actual numbers were 2-8 per group, with the highest number and rate in the 400 mg group, so there was no trend to death by increasing molnupiravir dose. The data and the available information do not suggest that molnupiravir itself was responsible for these deaths and, with such small numbers per group, the result could have arisen by chance. Overall, as MK4482-001 Part 1 was also carried out in a different patient population its results are not thought to detract from the results of MK4482-002.

Virological data from MK4482-002 Part 2

Although no relationship has been established between effect on viral load based on RT-PCR applied to NP samples, it is of interest that there was an effect of molnupiravir vs. placebo on days 3 and 5 but not thereafter, reflecting natural recovery rates in the majority of subjects in the placebo group. The seronegative subjects would have had higher viral loads at baseline. Molnupiravir was effective in baseline seronegative patients, suggesting that baseline viral load might not have a significant effect on efficacy.

2.4.2.5. Conclusions on clinical efficacy

Molnupiravir 800 mg BID when started within 5 days of symptom onset provided a statistically significant reduction in the rate of hospitalisation or death in the population enrolled into MK4482-002 Part 2.

The company's initial proposed indication statement was for treatment of coronavirus disease 2019 (COVID-19) in adults. This was not considered appropriate since a very restricted population was included and, especially, since MK4482-001 Part 1 failed to show any clinical benefit in a hospitalised population that had a range of oxygen requirements. The population in which efficacy was demonstrated (i.e. MK4482-002 Part 2) was not receiving supplemental oxygen at baseline and all subjects had at least one protocol-listed risk factor for progression of COVID-19.

Therefore, the recommended indication is:

> *Lagevrio is indicated 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.*

The draft Conditions for Use states that treatment should start within 5 days of symptom onset and Section 6 clarifies that the study population was unvaccinated.

2.4.3. Safety data

Across clinical trials 1069 subjects have been exposed to any dose of molnupiravir, of which 593 were allocated to 800 mg BID for 5 days and received at least one 800 mg dose. Of these 593, 587 had COVID-19.

Participants Who Received molnupiravir (P002, P006, P001, and P004)

Study	Number of Participants	
	Any Dose of MOV	**MOV 800 mg Q12H[a]**
P002 (Phase 2/3)	Part 2: 386	Part 2: 386
	Part 1: 225	Part 1: 74
P006 (Phase 2a)	140	55
P001 (Phase 2)	218	72
P004 (Phase 1)	100	6
Total	**1069**	**593**

MOV=molnupiravir, Q12H=once every 12 hours

[a] participants received at least 1 dose of MOV 800 mg in a dosing regimen of Q12H for 5 days

Adverse events

MK4482-004

The table below summarises the safety profile observed after BID dosing of healthy subjects.

Table 32: Summary of Treatment-emergent Adverse Events for Part 3 of Protocol EIDD-2801-1001-UK (Multiple Ascending Doses)

	Placebo capsule BID (fasted) (N = 14) n/% (*/o) [nE]	EIDD-2801 capsule BID (fasted) 50 mg (N = 6) n/% (*/o) [nE]	100 mg (N = 6) n/% (*/o) [nE]	200 mg (N = 6) n/% (*/o) [nE]	300 mg (N = 6) n/% (*/o) [nE]	400 mg (N = 6) n/% (*/o) [nE]	600 mg (N = 6) n/% (*/o) [nE]	800 mg (N = 6) n/% (*/o) [nE]
TEAEs								
Overall	7 (50.0%) [11]	2 (33.3%) [2]	3 (50.0%) [3]	3 (50.0%) [9]	2 (33.3%) [3]	3 (50.0%) [5]	2 (33.3%) [2]	3 (50.0%) [5]
Serious	---	---	---	---	---	---	---	---
Leading to Discontinuation	---	---	---	---	---	---	---	---
Life-threatening	---	---	---	---	---	---	---	---
Leading to Death	---	---	---	---	---	---	---	---
Severity								
Mild (Grade 1)	7 (50.0%) [11]	2 (33.3%) [2]	3 (50.0%) [3]	3 (50.0%) [6]	2 (33.3%) [3]	3 (50.0%) [5]	2 (33.3%) [2]	3 (50.0%) [5]
Moderate (Grade 2)	---	---	---	1 (16.7%) [3]	---	---	---	---
Severe (Grade 3)	---	---	---	---	---	---	---	---
Treatment-related TEAEs								
Overall	3 (21.4%) [4]	---	---	2 (33.3%) [3]	1 (16.7%) [1]	---	1 (16.7%) [1]	3 (50.0%) [4]
Serious	---	---	---	---	---	---	---	---
Leading to Discontinuation	---	---	---	---	---	---	---	---
Life-threatening	---	---	---	---	---	---	---	---
Leading to Death	---	---	---	---	---	---	---	---
Severity								
Mild (Grade 1)	3 (21.4%) [4]	---	---	2 (33.3%) [3]	1 (16.7%) [1]	---	1 (16.7%) [1]	3 (50.0%) [4]
Moderate (Grade 2)	---	---	---	---	---	---	---	---
Severe (Grade 3)	---	---	---	---	---	---	---	---

Fewer subjects had TEAEs following administration of EIDD-2801 BID than following placebo. There were no apparent treatment- or dose-related trends. The TEAEs reported were typical of those usually observed in Phase 1 studies, with a summary for BID dosing shown below.

Table 35: Frequency of Treatment-emergent Adverse Events (All Causalities) for Part 3 of Protocol EIDD-2801-1001-UK (Multiple Ascending Doses)

Preferred Term	Placebo capsule BID (fasted) (N = 14)	EIDD-2801 capsule BID (fasted) 50 mg (N = 6)	100 mg (N = 6)	200 mg (N = 6)	300 mg (N = 6)	400 mg (N = 6)	600 mg (N = 6)	800 mg (N = 6)
Overall	7 (50.0%)	2 (33.3%)	3 (50.0%)	3 (50.0%)	2 (33.3%)	3 (50.0%)	2 (33.3%)	3 (50.0%)
Diarrhoea	1 (7.1%)	---	---	1 (16.7%)	---	---	1 (16.7%)	1 (16.7%)
Back pain	---	---	2 (33.3%)	---	1 (16.7%)	---	---	---
Headache	---	---	1 (16.7%)	---	2 (33.3%)	---	---	---
Somnolence	2 (14.3%)	---	---	---	---	1 (16.7%)	---	---
Abdominal pain upper	---	1 (16.7%)	---	---	---	---	---	---
Abnormal dreams	---	---	---	---	---	1 (16.7%)	---	---
Abnormal sensation in eye	---	---	---	1 (16.7%)	---	---	---	---
Agnosia	---	---	---	1 (16.7%)	---	---	---	---
Arthropod bite	---	1 (16.7%)	---	---	---	---	---	---
Catheter site dryness	1 (7.1%)	---	---	---	---	---	---	---
Catheter site pain	1 (7.1%)	---	---	---	---	---	---	---
Catheter site rash	---	---	---	---	---	1 (16.7%)	---	---
Claustrophobia	---	---	---	---	---	---	---	1 (16.7%)
Dizziness postural	---	---	---	1 (16.7%)	---	---	---	---
Eosinopenia	---	---	---	---	---	1 (16.7%)	---	---
Gastrointestinal sounds abnormal	---	---	---	1 (16.7%)	---	---	---	---
Hot flush	1 (7.1%)	---	---	---	---	---	---	---
Hypervolaemia	1 (7.1%)	---	---	---	---	---	---	---
Hypoaesthesia	1 (7.1%)	---	---	---	---	---	---	---
Influenza like illness	---	---	---	1 (16.7%)	---	---	---	---
Insomnia	---	---	---	---	---	---	1 (16.7%)	---
Medical device site reaction	---	---	---	---	---	---	---	1 (16.7%)
Nausea	1 (7.1%)	---	---	---	---	---	---	---
Ocular hyperaemia	1 (7.1%)	---	---	---	---	---	---	---
Oropharyngeal pain	---	---	---	1 (16.7%)	---	---	---	---

With the exception of one subject with Grade 2 TEAEs (pain in extremity, oropharyngeal pain and influenza-like illness) after 200 mg BID, all TEAEs were Grade 1 in severity. The majority was not considered by the investigator to be treatment related. While 16.7% of subjects who received EIDD-2801 BID and 21.4% who received placebo reported at least 1 treatment-related TEAE, these were all Grade 1 in severity.

Because of the thrombocytopenia observed in animal studies, effects on haematological parameters received special attention. There were no definitive or consistent indications of bone marrow suppression in any cohort and none of the decreases in platelets was clinically significant. One subject who received 600 mg in Part 1 had a decrease in platelets to <150 × 10^9/L on Days -1 and 9 (188 ×

10^9/L, 150 × 10^9/L and 147 × 10^9/L at screening, Day -1 and 9, respectively) but platelets were 178 × 10^9/L by the end of study visit. One subject who received 300 mg BID had decreases in platelets from 171 × 10^9 at screening to 130 × 10^9/L by Day 9. Platelets increased to 144 × 10^9/L by the EOS visit.

There were no trends in mean or individual subject 12-lead ECG parameters and no clinically significant findings. A few out-of-range parameters were noted, including:

- A maximum increase from baseline in QTcF of 41 msec at the EOS visit, 22 days after a 1600 mg dose. This subject had QTcF intervals of 410, 366, 377, and 407 msec at screening, Day 1, Day 4 and EOS, respectively.
- A maximum QTcF of 453 msec at the EOS visit, 14 days after 200 mg in the fed state. This subject had QTcF intervals of 441 msec at screening; 449 and 445 msec on Days 1 and 4, respectively, in Period 1 (fasted); and 445 and 436 msec on Days 1 and 4, respectively, in Period 2 (fed).
- A maximum QTcF of 451 msec at 2 h after 50 mg on Day 1. This subject had QTcF intervals of 436 msec at screening; 441 and 451 msec at pre-dose and 2 h, respectively, on Day 1; 433 and 441 msec at pre-dose and 2 h, respectively, on Day 6; 450 msec on Day 9 (72 h); and 425 msec at the EOS visit.

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The table below summarises the safety profile.

Table 14 Overall Summary of Treatment Emergent Adverse Events (Full Safety Population)

	Molnupiravir 200 mg		Molnupiravir 400 mg		Molnupiravir 800 mg		All Molnupiravir		Placebo	
	(N=23)		(N=62)		(N=55)		(N=140)		(N=62)	
Category	n	(%) E	n	(%) E	n	(%) E	n	(%) E	n	(%) E
Any Adverse Event	11	(47.8) 16	20	(32.3) 42	11	(20.0) 21	42	(30.0) 79	18	(29.0) 31
Any Adverse Event Related to Study Drug	4	(17.4) 4	13	(21.0) 21	1	(1.8) 4	18	(12.9) 29	8	(12.9) 10
Any Adverse Event Grade 2 or Higher	5	(21.7) 6	7	(11.3) 9	6	(10.9) 8	18	(12.9) 23	9	(14.5) 12
Any Adverse Event Grade 3 or Higher	1	(4.3) 1	2	(3.2) 2	4	(7.3) 4	7	(5.0) 7	5	(8.1) 5
Any Adverse Event Grade 3 or Higher Related to Study Drug	0		0		0		0		0	
Any Adverse Event Leading to Discontinuation from Study Drug	0		1	(1.6) 1	1	(1.8) 1	2	(1.4) 2	1	(1.6) 1
Any Related Adverse Event Leading to Discontinuation from Study Drug	0		0		0		0		0	
Any Serious Adverse Event	0		2	(3.2) 2	1	(1.8) 1	3	(2.1) 3	1	(1.6) 1
Any Serious Adverse Event Related to Study Drug	0		0		0		0		0	
Any Adverse Event Leading to Death	0		0		0		0		0	

Abbreviations: E = number of events; n = number of participants with an event; N = number of participants.

The only AE reported in more than 5% of participants in any group was insomnia (6.5% placebo and 2.9% combined molnupiravir group). AEs reported >3% in any group were headache (4.3% combined molnupiravir group and 4.8% placebo), ALT increased (2.9% and 3.2%) and abdominal pain (0.7% and 3.2%). Nine subjects had an AE with onset from Day 14 onwards but none of these occurred in the 800 mg BID group.

There were 12 severe AEs reported as shown in the table. None was considered treatment related.

Table 17 Brief Listing of Severe Treatment-Emergent Adverse Events by Treatment Group (Safety Population)

Molnupiravir 200-mg	Molnupiravir 400-mg	Molnupiravir 800-mg	Placebo
N=23	N=62	N=55	N=62
n=1 (4.3%)	n=2 (3.2%)	n=4 (7.3%)	n = 5 (8.1%)
Creatinine renal clearance decreased	Cerebrovascular accident Oxygen saturation decreased	Headache Acute respiratory failure Supraventricular tachycardia Anaemia	Blood glucose decreased Blood pressure increased Migraine Hypoxia Musculoskeletal chest pain

The majority of AEs was not considered related to treatment. There was no relationship between related AE rates and molnupiravir dose and rates were mostly similar between the combined molnupiravir and placebo groups. None of the treatment-related AEs was graded as severe and none was serious.

Table 15 Brief Summary of Treatment-Emergent Adverse Events Related to Study Drug by Treatment Group (Safety Population)

	Molnupiravir 200 mg	Molnupiravir 400 mg	Molnupiravir 800 mg	All Molnupiravir	Placebo
System Organ Class	(N=23)	(N=62)	(N=55)	(N=140)	(N=62)
Preferred Term	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E
Subjects with at Least 1 Treatment-Related Adverse Event	4 (17.4) 4	13 (21.0) 21	1 (1.8) 4	18 (12.9) 29	8 (12.9) 10
Gastrointestinal disorders	1 (4.3) 1	5 (8.1) 5	0	6 (4.3) 6	2 (3.2) 3
Nausea	1 (4.3) 1	2 (3.2) 2	0	3 (2.1) 3	1 (1.6) 1
Abdominal pain upper	0	1 (1.6) 1	0	1 (0.7) 1	1 (1.6) 1
Gastrooesophageal reflux disease	0	1 (1.6) 1	0	1 (0.7) 1	0
Oral mucosal exfoliation	0	1 (1.6) 1	0	1 (0.7) 1	0
Abdominal pain	0	0	0	0	1 (1.6) 1
Investigations	0	4 (6.5) 7	1 (1.8) 3	5 (3.6) 10	2 (3.2) 3
Alanine aminotransferase increased	0	2 (3.2) 2	1 (1.8) 1	3 (2.1) 3	2 (3.2) 2
Blood creatinine increased	0	3 (4.8) 3	0	3 (2.1) 3	0
Aspartate aminotransferase increased	0	1 (1.6) 1	1 (1.8) 1	2 (1.4) 2	1 (1.6) 1
Blood alkaline phosphatase increased	0	0	1 (1.8) 1	1 (0.7) 1	0
Haemoglobin decreased	0	1 (1.6) 1	0	1 (0.7) 1	0
Nervous system disorders	1 (4.3) 1	2 (3.2) 3	0	3 (2.1) 4	0
Headache	0	2 (3.2) 3	0	2 (1.4) 3	0
Dizziness	1 (4.3) 1	0	0	1 (0.7) 1	0
Psychiatric disorders	2 (8.7) 2	1 (1.6) 1	0	3 (2.1) 3	3 (4.8) 3
Insomnia	2 (8.7) 2	1 (1.6) 1	0	3 (2.1) 3	3 (4.8) 3

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Skin and subcutaneous tissue disorders	0	2 (3.2) 2	1 (1.8) 1	3 (2.1) 3	1 (1.6) 1
Pruritus	0	1 (1.6) 1	0	1 (0.7) 1	1 (1.6) 1
Rash	0	0	1 (1.8) 1	1 (0.7) 1	0
Skin burning sensation	0	1 (1.6) 1	0	1 (0.7) 1	0
Cardiac disorders	0	1 (1.6) 1	0	1 (0.7) 1	0
Cardiac flutter	0	1 (1.6) 1	0	1 (0.7) 1	0
General disorders and administration site conditions	0	1 (1.6) 1	0	1 (0.7) 1	0
Chest discomfort	0	1 (1.6) 1	0	1 (0.7) 1	0
Metabolism and nutrition disorders	0	1 (1.6) 1	0	1 (0.7) 1	0
Hyponatraemia	0	1 (1.6) 1	0	1 (0.7) 1	0

Overall, 13 participants reported 23 TEAEs related to an abnormal clinical laboratory value (6 placebo, 3 200 mg, 8 400 mg and 6 800 mg). There were no dose- or treatment-related trends in the incidence or types of laboratory TEAEs. No participant in a molnupiravir group had a platelet value <120,000/µL at any time after baseline. See also section 4.5.

MK4482-002 Part 1

The observed safety profile is summarised in the table.

Adverse Event Summary
During Treatment and 14-Day Follow-Up Period
All Participants as Treated Population
MK-4482-002 1A2

	MK-4482 200 mg		MK-4482 400 mg		MK-4482 800 mg		MK-4482 Combined		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	74		77		74		225		74		299	
with one or more adverse events	25	(33.8)	19	(24.7)	29	(39.2)	73	(32.4)	28	(37.8)	101	(33.8)
with no adverse event	49	(66.2)	58	(75.3)	45	(60.8)	152	(67.6)	46	(62.2)	198	(66.2)
with drug-related* adverse events	4	(5.4)	6	(7.8)	4	(5.4)	14	(6.2)	5	(6.8)	19	(6.4)
with serious adverse events	1	(1.4)	3	(3.9)	4	(5.4)	8	(3.6)	4	(5.4)	12	(4.0)
with serious drug related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.3)
discontinued drug due to an adverse event	0	(0.0)	0	(0.0)	3	(4.1)	3	(1.3)	1	(1.4)	4	(1.3)
discontinued drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.3)
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)	2	(2.7)	2	(0.9)	0	(0.0)	2	(0.7)
discontinued drug due to a serious drug related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

* Determined by the investigator to be related to the drug.

The incidence and type of AEs were comparable across the intervention groups. The most frequently reported (≥5% in any group) AEs during the treatment period through the 14-day follow-up were COVID-19 pneumonia (5.4%) in the 800 mg group and diarrhoea (5.4%) and COVID-19 (6.8%) in the placebo group. There were no clear trends in AEs by molnupiravir dose. The table below summarises AEs considered by investigators to be treatment related.

Participants With Drug-Related Adverse Events During Treatment and 14-Day Follow-Up Period
(Incidence > 0% in One or More Treatment Groups)
All Participants as Treated Population
MK-4482-002 1A2

	MK-4482 200 mg		MK-4482 400 mg		MK-4482 800 mg		MK-4482 Combined		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	74		77		74		225		74		299	
with one or more drug-related adverse events	4	(5.4)	6	(7.8)	4	(5.4)	14	(6.2)	5	(6.8)	19	(6.4)
with no drug-related adverse events	70	(94.6)	71	(92.2)	70	(94.6)	211	(93.8)	69	(93.2)	280	(93.6)
Blood and lymphatic system disorders	**0**	**(0.0)**	**2**	**(2.6)**	**0**	**(0.0)**	**2**	**(0.9)**	**0**	**(0.0)**	**2**	**(0.7)**
Leukocytosis	0	(0.0)	1	(1.3)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.3)
Lymphopenia	0	(0.0)	1	(1.3)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.3)
Neutrophilia	0	(0.0)	1	(1.3)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.3)
Cardiac disorders	**0**	**(0.0)**	**1**	**(1.3)**	**0**	**(0.0)**	**1**	**(0.4)**	**0**	**(0.0)**	**1**	**(0.3)**
Tachycardia	0	(0.0)	1	(1.3)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.3)
Gastrointestinal disorders	**3**	**(4.1)**	**2**	**(2.6)**	**3**	**(4.1)**	**8**	**(3.6)**	**4**	**(5.4)**	**12**	**(4.0)**
Abdominal pain	1	(1.4)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.3)
Abdominal pain upper	0	(0.0)	1	(1.3)	1	(1.4)	2	(0.9)	1	(1.4)	3	(1.0)
Diarrhoea	2	(2.7)	2	(2.6)	1	(1.4)	5	(2.2)	2	(2.7)	7	(2.3)
Epigastric discomfort	1	(1.4)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.3)
Gastrointestinal disorders	**3**	**(4.1)**	**2**	**(2.6)**	**3**	**(4.1)**	**8**	**(3.6)**	**4**	**(5.4)**	**12**	**(4.0)**
Nausea	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.4)	1	(1.4)	2	(0.7)
General disorders and administration site conditions	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.4)**	**1**	**(0.4)**	**0**	**(0.0)**	**1**	**(0.3)**
Chest pain	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.4)	0	(0.0)	1	(0.3)
Investigations	**0**	**(0.0)**	**1**	**(1.3)**	**0**	**(0.0)**	**1**	**(0.4)**	**0**	**(0.0)**	**1**	**(0.3)**
Alanine aminotransferase increased	0	(0.0)	1	(1.3)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.3)
Musculoskeletal and connective tissue disorders	**1**	**(1.4)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.4)**	**0**	**(0.0)**	**1**	**(0.3)**
Back pain	1	(1.4)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.3)
Nervous system disorders	**0**	**(0.0)**	**1**	**(1.3)**	**0**	**(0.0)**	**1**	**(0.4)**	**0**	**(0.0)**	**1**	**(0.3)**
Headache	0	(0.0)	1	(1.3)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.3)
Renal and urinary disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.4)**	**1**	**(0.3)**
Renal and urinary disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.4)**	**1**	**(0.3)**
Pollakiuria	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.3)

Every participant is counted a single time for each applicable row and column.
Adverse event terms are from MedDRA Version 23.1.

The most commonly (>2%) reported drug-related AE was diarrhoea, reported by 5 (2.2%) in the combined molnupiravir groups (none led to discontinuation) and 2 (2.7%) in the placebo group (one of which led to discontinuation). All drug-related AEs were Grade 1 or Grade 2. There were no AEs that met the criteria for an event of clinical interest (ECI), which included liver transaminase increases suggestive of liver injury, platelets <50,000/µL and amylase or lipase >3xULN.

MK4482-002 Part 2

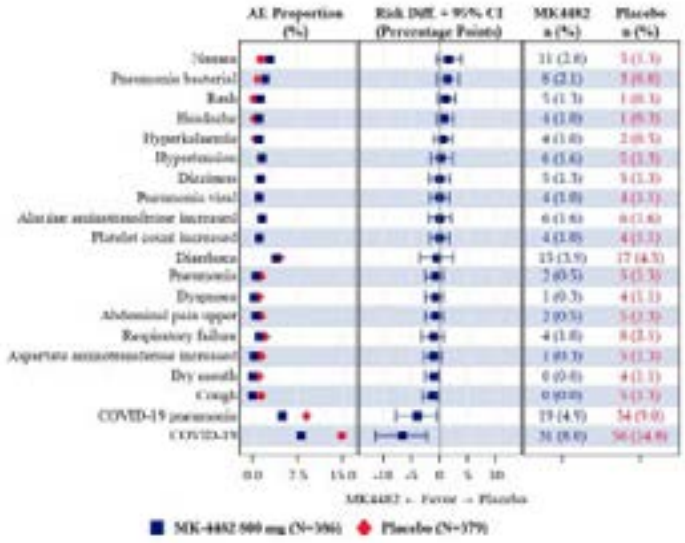
The table summarises the safety profile as reported at the time of the cut-off date applied to IA4.

Analysis of Adverse Event Summary
During Treatment and 14-Day Follow-Up Period
All Participants as Treated Population
MK-4482-002 Combined IA3/IA4

	MK-4482 800 mg		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[a]
Participants in population	386		379		
with one or more adverse events	135	(35.0)	150	(39.6)	-4.6 (-11.4, 2.3)
with no adverse event	251	(65.0)	229	(60.4)	4.6 (-2.3, 11.4)
with drug-related[b] adverse events	48	(12.4)	42	(11.1)	1.4 (-3.3, 6.0)
with serious adverse events	28	(7.3)	53	(14.0)	-6.7 (-11.2, -2.4)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0.0 (-1.0, 1.0)
who died	0	(0.0)	10	(2.6)	-2.6 (-4.8, -1.4)
discontinued drug due to an adverse event	5	(1.3)	13	(3.4)	-2.1 (-4.6, 0.0)
discontinued drug due to a drug-related adverse event	3	(0.8)	3	(0.8)	-0.0 (-1.6, 1.6)
discontinued drug due to a serious adverse event	1	(0.3)	9	(2.4)	-2.1 (-4.2, -0.6)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0.0 (-1.0, 1.0)

[a] Based on Miettinen & Nurminen method.
[b] Determined by the investigator to be related to the drug.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

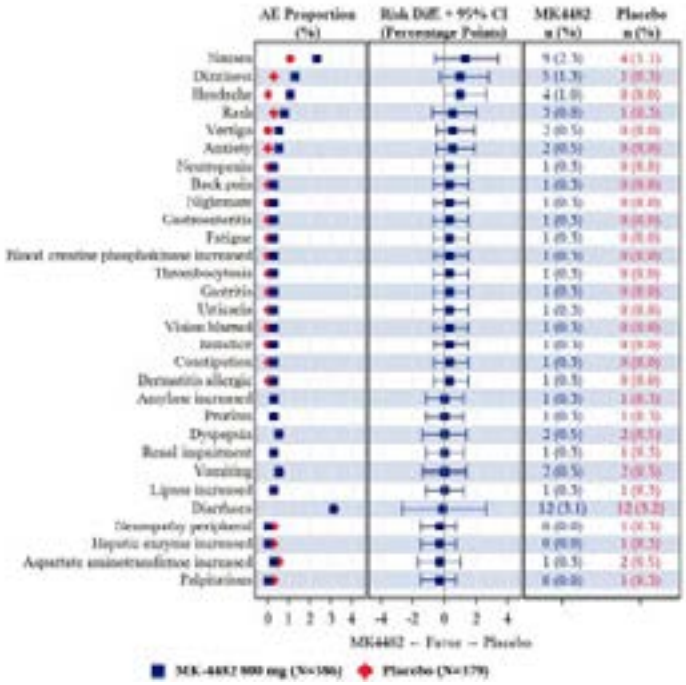
Rainfall Plot of Participants with Adverse Events During Treatment and 14-Day Follow-Up Period
(Incidence ≥ 4 Participants in One or More Treatment Groups)
All Participants as Treated Population
MK-4482-002 Combined IA3/IA4



The most frequently reported AEs (≥5% in either group) were COVID-19 (molnupiravir 8.0%, placebo 14.8%) and COVID-19 pneumonia (4.9%, 9.0%). The percentages with at least 1 AE were generally comparable in the age subgroups of ≥65 years and <65 years. The majority was Grade 1 or Grade 2, with Grade 3 AEs reported in 6.7% and 7.4% and Grade 4 AEs in 1.0% and 5.3%, respectively.

The percentages with drug-related AEs were comparable (12.4% vs. 11.1%).

Rainfall Plot of Participants with Drug-related Adverse Events During Treatment and 14-Day Follow-Up Period
(Incidence > 0% in One or More Treatment Groups)
All Participants as Treated Population
MK-4482-002 Combined 1A3/1A4



The most frequently reported drug-related AEs (≥2%) were diarrhoea (3.1%) and nausea (2.3%) in the molnupiravir group and diarrhoea (3.2%) in the placebo group. Most drug-related AEs were Grade 1 or Grade 2, with Grade 3 AEs in 0.3% per group.

Participants With Drug-Related Adverse Events During Treatment and 14-Day Follow-Up Period
(Incidence > 0% in One or More Treatment Groups)
All Participants as Treated Population
MK-4482-002 Combined 1A3/1A4

	MK-4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	386		379		765	
with one or more drug-related adverse events	48	(12.4)	42	(11.1)	90	(11.8)
with no drug-related adverse events	338	(87.6)	337	(88.9)	675	(88.2)
Blood and lymphatic system disorders	**2**	**(0.5)**	**1**	**(0.3)**	**3**	**(0.4)**
Leukopenia	0	(0.0)	1	(0.3)	1	(0.1)
Neutropenia	1	(0.3)	0	(0.0)	1	(0.1)
Thrombocytosis	1	(0.3)	0	(0.0)	1	(0.1)
Cardiac disorders	**0**	**(0.0)**	**1**	**(0.3)**	**1**	**(0.1)**
Palpitations	0	(0.0)	1	(0.3)	1	(0.1)
Ear and labyrinth disorders	**2**	**(0.5)**	**0**	**(0.0)**	**2**	**(0.3)**
Vertigo	2	(0.5)	0	(0.0)	2	(0.3)
Eye disorders	**1**	**(0.3)**	**0**	**(0.0)**	**1**	**(0.1)**
Vision blurred	1	(0.3)	0	(0.0)	1	(0.1)
Gastrointestinal disorders	**26**	**(6.7)**	**22**	**(5.8)**	**48**	**(6.3)**

	MK-4482 800mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Gastrointestinal disorders	**26**	**(6.7)**	**22**	**(5.8)**	**48**	**(6.3)**
Abdominal pain	0	(0.0)	1	(0.3)	1	(0.1)
Abdominal pain upper	2	(0.5)	4	(1.1)	6	(0.8)
Constipation	1	(0.3)	0	(0.0)	1	(0.1)
Diarrhoea	12	(3.1)	12	(3.2)	24	(3.1)
Dry mouth	0	(0.0)	3	(0.8)	3	(0.4)
Dyspepsia	2	(0.5)	2	(0.5)	4	(0.5)
Gastritis	1	(0.3)	0	(0.0)	1	(0.1)
Nausea	9	(2.3)	4	(1.1)	13	(1.7)
Vomiting	2	(0.5)	2	(0.5)	4	(0.5)
General disorders and administration site conditions	**1**	**(0.3)**	**2**	**(0.5)**	**3**	**(0.4)**
Chest discomfort	0	(0.0)	1	(0.3)	1	(0.1)
Fatigue	1	(0.3)	0	(0.0)	1	(0.1)
Pyrexia	0	(0.0)	1	(0.3)	1	(0.1)
Hepatobiliary disorders	**1**	**(0.3)**	**0**	**(0.0)**	**1**	**(0.1)**
Jaundice	1	(0.3)	0	(0.0)	1	(0.1)
Infections and infestations	**1**	**(0.3)**	**0**	**(0.0)**	**1**	**(0.1)**
Gastroenteritis	1	(0.3)	0	(0.0)	1	(0.1)
Investigations	**6**	**(1.6)**	**10**	**(2.6)**	**16**	**(2.1)**
Alanine aminotransferase increased	3	(0.8)	4	(1.1)	7	(0.9)
Amylase increased	1	(0.3)	1	(0.3)	2	(0.3)
Aspartate aminotransferase increased	1	(0.3)	2	(0.5)	3	(0.4)
Blood creatine phosphokinase increased	1	(0.3)	0	(0.0)	1	(0.1)
Blood lactate dehydrogenase increased	0	(0.0)	1	(0.3)	1	(0.1)
Hepatic enzyme increased	0	(0.0)	1	(0.3)	1	(0.1)
Lipase increased	1	(0.3)	1	(0.3)	2	(0.3)
Liver function test abnormal	0	(0.0)	1	(0.3)	1	(0.1)
Platelet count decreased	0	(0.0)	1	(0.3)	1	(0.1)
Transaminases increased	0	(0.0)	1	(0.3)	1	(0.1)
Metabolism and nutrition disorders	**0**	**(0.0)**	**1**	**(0.3)**	**1**	**(0.1)**
Diabetes mellitus	0	(0.0)	1	(0.3)	1	(0.1)
Musculoskeletal and connective tissue disorders	**1**	**(0.3)**	**2**	**(0.5)**	**3**	**(0.4)**
Musculoskeletal and connective tissue disorders	**1**	**(0.3)**	**2**	**(0.5)**	**3**	**(0.4)**
Back pain	1	(0.3)	0	(0.0)	1	(0.1)
Myalgia	0	(0.0)	1	(0.3)	1	(0.1)
Myositis	0	(0.0)	1	(0.3)	1	(0.1)
Nervous system disorders	**9**	**(2.3)**	**2**	**(0.5)**	**11**	**(1.4)**
Dizziness	5	(1.3)	1	(0.3)	6	(0.8)
Headache	4	(1.0)	0	(0.0)	4	(0.5)
Neuropathy peripheral	0	(0.0)	1	(0.3)	1	(0.1)
Psychiatric disorders	**4**	**(1.0)**	**3**	**(0.8)**	**7**	**(0.9)**
Anxiety	2	(0.5)	0	(0.0)	2	(0.3)
Insomnia	1	(0.3)	3	(0.8)	4	(0.5)
Nightmare	1	(0.3)	0	(0.0)	1	(0.1)
Renal and urinary disorders	**1**	**(0.3)**	**1**	**(0.3)**	**2**	**(0.3)**
Renal impairment	1	(0.3)	1	(0.3)	2	(0.3)
Skin and subcutaneous tissue disorders	**6**	**(1.6)**	**3**	**(0.8)**	**9**	**(1.2)**
Skin and subcutaneous tissue disorders	**6**	**(1.6)**	**3**	**(0.8)**	**9**	**(1.2)**
Angioedema	0	(0.0)	1	(0.3)	1	(0.1)
Dermatitis allergic	1	(0.3)	0	(0.0)	1	(0.1)
Pruritus	1	(0.3)	1	(0.3)	2	(0.3)
Rash	3	(0.8)	1	(0.3)	4	(0.5)
Urticaria	1	(0.3)	0	(0.0)	1	(0.1)

Every participant is counted a single time for each applicable row and column.
Adverse event terms are from MedDRA Version 24.0.

	MK-4482 800mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	386		379		765	
with one or more drug-related adverse events	48	(12.4)	42	(11.1)	90	(11.8)
Grade 1	34	(8.8)	33	(8.7)	65	(8.5)
Grade 2	13	(3.4)	10	(2.6)	23	(3.0)
Grade 3	1	(0.3)	1	(0.3)	2	(0.3)
with no drug-related adverse events	338	(87.6)	337	(88.9)	675	(88.2)

MK4482-001 Part 1

The table summarises the safety profile observed over 29 days in this study in hospitalised subjects.

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Adverse Event Summary
During Treatment and 14-Day Follow-Up Period
All Participants as Treated Population
MK-4482-001 1A2

	MK-4482 200 mg		MK-4482 400 mg		MK-4482 800 mg		MK-4482 Combined		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	73		73		72		218		75		293	
with one or more adverse events	40	(54.8)	36	(49.3)	45	(62.5)	121	(55.5)	46	(61.3)	167	(57.0)
with no adverse event	33	(45.2)	37	(50.7)	27	(37.5)	97	(44.5)	29	(38.7)	126	(43.0)
with drug-related* adverse events	8	(11.0)	6	(8.2)	10	(13.9)	24	(11.0)	16	(21.3)	40	(13.7)
with serious adverse events	11	(15.1)	9	(12.3)	13	(18.1)	33	(15.1)	12	(16.0)	45	(15.4)
with serious drug-related adverse events	1	(1.4)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.3)
who died	6	(8.2)	4	(5.5)	4	(5.6)	14	(6.4)	2	(2.7)	16	(5.5)
discontinued drug due to an adverse event	0	(0.0)	1	(1.4)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.3)
discontinued drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)	1	(1.4)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.3)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

* Determined by the investigator to be related to the drug.

The most frequently reported AEs (>5%) in the molnupiravir groups were COVID-19, AST/ALT elevation, constipation, bacterial pneumonia, hyperglycaemia and respiratory failure. The most frequently reported AEs (>5%) in the placebo group were constipation, COVID-19, COVID-19 pneumonia, ALT increased and respiratory failure.

AEs considered treatment-related by investigators were reported less often with molnupiravir (8.2% to 13.9%) compared with placebo (21.3%). The most common (>2%) treatment-related AE in the combined molnupiravir groups was ALT increased (2.3%) but this was also reported for 4% in the placebo group. Urticaria considered treatment-related was reported for 4 subjects who received molnupiravir and no placebo subjects. Treatment was not discontinued due to these AEs.

Two participants had laboratory values that met the predefined criteria for an ECI. One received molnupiravir 800 mg BID and had post-baseline elevated AST or ALT ≥3x ULN and elevated total bilirubin ≥2x ULN and alkaline phosphatase <2x ULN (thus satisfying the criteria for potential DILI) on Day 14. These criteria were no longer satisfied on Day 15 when alkaline phosphatase became >2x ULN, secondary to fatal septic shock and cholestasis; thus, the event was not considered DILI. The other received placebo and had platelets <50,000 µL on Day 10 with fatal septic shock due to bacterial pneumonia on Day 11.

Serious adverse events and deaths

MK4482-006

One participant in the placebo group died 31 days after discontinuation from the study after a SAE.

Four subjects had SAEs, of which 3 received molnupiravir as summarised in the table below. The SAE in the placebo patient resulted in death 31 days after discontinuation from the study. Two SAEs in participants randomised to 400 mg and 800 mg resulted in discontinuation from the study. None of the four SAEs was considered treatment related.

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Table 16 Brief Tabular Summary of Serious Adverse Events

ID	Event Preferred Term	Treatment	No. of Doses Taken	Baseline Antibody Status[a]	Baseline Viral Load (Log_{10} copies/mL)	TSSO to First Dose (Days)	Risk factors for Severe COVID-19 Disease	Seriousness Criteria	Severity	Causality	Outcome
[redacted]	Oxygen saturation decreased	MOL 400 mg	8	Negative	8.71	5.0	No. of risk factors = 2 BMI ≥30 Diabetes	Hospitalization	Severe	Not related	Recovered
	Acute respiratory failure	MOL 800 mg	2	Positive	7.14	4.6	No. of risk factors = 3 BMI ≥35 Diabetes Age ≥55 and hypertension	Hospitalization	Severe	Not related	Recovered
	[redacted]	Placebo	2	[redacted]				Hospitalization, death	Severe	Not related	Died after discontinuation from the study
	Cerebrovascular accident	MOL 400 mg	9	Negative	4.87	4.8	No. of risk factors = 2 Diabetes Age ≥55 and hypertension	Hospitalization	Severe	Not related	Recovered

MK4482-002 Part 1

There was one death in a placebo subject at Day 36 due to COVID-19 pneumonia and mesenteric thrombosis.

SAEs were reported by 4% of subjects, with COVID-19 pneumonia in 2.7% combined molnupiravir subjects and 2.7% placebo subjects. No SAE was considered treatment related.

Participants With Serious Adverse Events During Treatment and 14-Day Follow-Up Period
(Incidence > 0% in One or More Treatment Groups)
All Participants as Treated Population
MK-4482-002 1A2

	MK-4482 200 mg		MK-4482 400 mg		MK-4482 800 mg		MK-4482 Combined		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	74		77		74		225		74		299	
with one or more serious adverse events	1	(1.4)	3	(3.9)	4	(5.4)	8	(3.6)	4	(5.4)	12	(4.0)
with no serious adverse events	73	(98.6)	74	(96.1)	70	(94.6)	217	(96.4)	70	(94.6)	287	(96.0)
Infections and infestations	**1**	**(1.4)**	**2**	**(2.6)**	**4**	**(5.4)**	**7**	**(3.1)**	**2**	**(2.7)**	**9**	**(3.0)**
COVID-19	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.3)
COVID-19 pneumonia	1	(1.4)	2	(2.6)	3	(4.1)	6	(2.7)	2	(2.7)	8	(2.7)
Pneumonia	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.4)	0	(0.0)	1	(0.3)
Metabolism and nutrition disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.4)**	**1**	**(0.3)**
Diabetic metabolic decompensation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.3)
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**1**	**(1.3)**	**0**	**(0.0)**	**1**	**(0.4)**	**0**	**(0.0)**	**1**	**(0.3)**
Pulmonary embolism	0	(0.0)	1	(1.3)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.3)
Vascular disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.4)**	**1**	**(0.3)**

MK4482-002 Part 2

AEs leading to death were reported for 0 (0.0%) participants in the molnupiravir group and 10 (2.6%) in the placebo group.

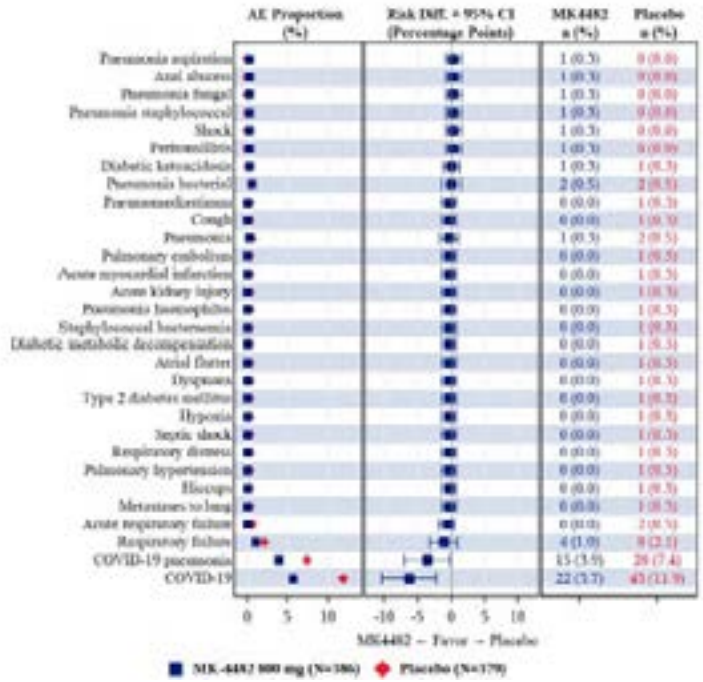
Participants With Adverse Events Resulting in Death During Treatment and 14-Day Follow-Up Period
(Incidence > 0% in One or More Treatment Groups)
All Participants as Treated Population
MK-4482-002 Combined IA3/IA4

	MK-4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	386		379		765	
with one or more adverse events resulting in death	0	(0.0)	10	(2.6)	10	(1.3)
with no adverse events resulting in death	386	(100.0)	369	(97.4)	755	(98.7)
Infections and infestations	**0**	**(0.0)**	**8**	**(2.1)**	**8**	**(1.0)**
COVID-19	0	(0.0)	7	(1.8)	7	(0.9)
COVID-19 pneumonia	0	(0.0)	3	(0.8)	3	(0.4)
Septic shock	0	(0.0)	1	(0.3)	1	(0.1)
Staphylococcal bacteraemia	0	(0.0)	1	(0.3)	1	(0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**(0.0)**	**1**	**(0.3)**	**1**	**(0.1)**
Metastases to lung	0	(0.0)	1	(0.3)	1	(0.1)
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**3**	**(0.8)**	**3**	**(0.4)**
Acute respiratory failure	0	(0.0)	1	(0.3)	1	(0.1)
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**3**	**(0.8)**	**3**	**(0.4)**
Respiratory failure	0	(0.0)	2	(0.5)	2	(0.3)

Every participant is counted a single time for each applicable row and column.
Adverse event terms are from MedDRA Version 24.0.

The percentage with SAEs was 7.3% in the molnupiravir group (7.3%) compared with 14% in the placebo group.

Rainfall Plot of Participants with Serious Adverse Events During Treatment and 14-Day Follow-Up Period
(Incidence > 0% in One or More Treatment Groups)
All Participants as Treated Population
MK-4482-002 Combined IA3/IA4



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No SAEs were considered drug-related by the investigators. One SAE of pulmonary embolism (molnupiravir group; unrelated) was reported after database lock so it is not included in the safety summary tables. The most frequently reported SAEs (≥5% in either group) were COVID-19 in (5.7% vs. 11.9%) and COVID-19 pneumonia (3.9% vs. 7.4%) and discontinuations due to AEs occurred in 0.3% vs. 2.4%.

MK4484-001 Part 1

The number with AEs resulting in a fatal outcome differs from the number of deaths in the efficacy analyses because the safety analysis counted AEs that led to death with onset during treatment and the 14-day follow up period regardless of the timing of the death. There were 16 participants who had AEs resulting in death (6 in the 200 mg group, 4 400 mg, 4 800 mg and 2 placebo). Most deaths occurred in participants who had severe COVID-19 at baseline (12/16), were >60 years of age (13/16), had underlying comorbidities (14/16) and/or had duration of COVID-19 symptoms >5 days before randomisation (12/16). None of the deaths was considered treatment-related by investigators.

The proportions with SAEs were comparable across groups. COVID-19 (7.5%) and respiratory failure (4.4%) were the most frequently reported SAEs. One participant in the 200 mg had an SAE of Grade 3 urticaria considered to be treatment related. The subject withdrew consent after the first dose of molnupiravir and the urticaria had onset the following day. It lasted for 2 days and was reported as resolved. One participant in the 400 mg group discontinued treatment due to an SAE of respiratory failure, which resolved after 2 months.

Laboratory findings

MK4482-006

Mean change from Baseline values for platelet count showed increases for all groups at all post-baseline time points.

There were no important treatment- or dose-related trends in mean clinical chemistry data over time during the study. Mean ALT decreased from baseline to Day 28 in all groups and AST was lower at many post-baseline time points and on Day 28 was lower in all groups. Mean creatinine clearance was slightly lower post-baseline in the placebo group and slightly higher in the molnupiravir 800 mg group. Few participants experienced treatment-emergent laboratory abnormalities. No participant met the criteria for Hy's law.

One participant in the 400 mg group had a treatment-emergent Grade 3 ALT value by Day 5 and a Grade 2 AST value on Days 3 and 5. The participant had no relevant medical history or concomitant medications during the study. Baseline viral load was 31,595 copies/mL and the participant had antibodies to SARS-CoV-2 at that time. By Day 7, no SARS-CoV-2 RNA was detectable. The participant took all 10 doses of study drug and completed the study. The Grade 3 ALT value was not reported as an AE.

MK4482-002 Part 1

The proportions with laboratory values that met predefined limits of change (worsening Grade 3 or 4) were comparable between intervention groups. There was no evidence of haematologic, pancreatic, or hepatic toxicity as a function of either dose or treatment. No subject had a change in platelets that met the criteria.

Analysis of Participants With Laboratory Findings that Met Predetermined Criteria
Worsening Grade 3 or 4
All Participants as Treated Population
MK-4482-002 1A2

Test Name (Unit)	Criterion	Treatment	N	n/m (%)	Difference in % vs Placebo Estimate (95% CI)[a]
Chemistry					
Alanine Aminotransferase (IU/L)	Grade 3: 5.0 - <10.0 x ULN or Grade 4: >=10.0 x ULN	MK-4482 200 mg	74	1/54 (1.9)	0.1
		MK-4482 400 mg	77	1/60 (1.7)	-0.1
		MK-4482 800 mg	74	0/58 (0.0)	-1.7
		Placebo	74	1/58 (1.7)	
Aspartate Aminotransferase (IU/L)	Grade 3: 5.0 - <10.0 x ULN or Grade 4: >=10.0 x ULN	MK-4482 200 mg	74	1/66 (1.5)	-0.0
		MK-4482 400 mg	77	0/68 (0.0)	-1.6
		MK-4482 800 mg	74	0/64 (0.0)	-1.6
		Placebo	74	1/64 (1.6)	
Creatinine (mg/dL)	Grade 3: >1.8 - <3.5 x ULN or Increase to 1.5 to <2.0 x above baseline	MK-4482 200 mg	74	2/64 (3.1)	3.1
		MK-4482 400 mg	77	1/65 (1.5)	1.5
		MK-4482 800 mg	74	1/65 (1.5)	1.5
		Placebo	74	0/66 (0.0)	
GFR from Creatinine Adjusted for BSA (mL/min/1.73m2)	Grade 3: 30 - <60 or 30% - <50% decrease from participant's baseline or Grade 4: <30 or >=50% decrease from participant's baseline	MK-4482 200 mg	74	8/64 (12.5)	4.9 (-5.9, 16.3)
		MK-4482 400 mg	77	4/65 (6.2)	-1.4 (-11.3, 8.3)
		MK-4482 800 mg	74	4/65 (6.2)	-1.4 (-11.3, 8.3)
		Placebo	74	5/66 (7.6)	

MK4482-002 Part 2

No molnupiravir subject had laboratory values that met the predefined ECI criteria for potential DILI, for platelet count of <50,000 cells/µL or had a >50% drop in platelets. Percentages with any Grade 1 laboratory findings were 1.9% for molnupiravir and 3.4% for placebo with Grade 2 in 0.6% and 0.9%. Grade 1 absolute neutrophil counts occurred in 1.2% and 3.2% and Grade 2 in 1.2% and 0.4% with no Grade 3 or 4 results. Grade 3 or Grade 4 ALT increases occurred in 1.6% and 2.5% and abnormal lipase (>3× ULN) occurred in 0.0% and 1.7%, respectively.

Participants With Laboratory Findings That Met Predetermined Criteria
All Participants as Treated Population
MK-4482-002 Combined IA3/IA4

Criteriona	MK-4482 800 mg		Placebo		Total	
	n/m	(%)	n/m	(%)	n/m	(%)
Participants in population	386		379		765	
CHEMISTRY						
Albumin (g/dL)						
Grade 1: 3.0 - <LLN	12/359	(3.3)	15/354	(4.2)	27/713	(3.8)
Grade 2: ≥2.0 - <3.0	7/359	(1.9)	6/354	(1.7)	13/713	(1.8)
Grade 3: <2.0	0/359	(0.0)	0/354	(0.0)	0/713	(0.0)
Alkaline Phosphatase (IU/L)						
Grade 1: 1.25 - <2.5 x ULN	12/356	(3.4)	9/353	(2.5)	21/709	(3.0)
Grade 2: 2.5 - <5.0 x ULN	0/356	(0.0)	1/353	(0.3)	1/709	(0.1)
Grade 3: 5.0 - <10.0 x ULN	0/356	(0.0)	0/353	(0.0)	0/709	(0.0)
Grade 4: ≥10.0 x ULN	0/356	(0.0)	0/353	(0.0)	0/709	(0.0)
Alanine Aminotransferase (IU/L)						
Grade 1: 1.25 - <2.5 x ULN	56/316	(17.7)	58/323	(18.0)	114/639	(17.8)
Grade 2: 2.5 - <5.0 x ULN	9/316	(2.8)	31/323	(9.6)	40/639	(6.3)
Grade 3: 5.0 - <10.0 x ULN	4/316	(1.3)	8/323	(2.5)	12/639	(1.9)
Grade 4: ≥10.0 x ULN	1/316	(0.3)	0/323	(0.0)	1/639	(0.2)
Amylase (IU/L)						
Grade 1: 1.1 - <1.5 x ULN	19/357	(5.3)	31/353	(8.8)	50/710	(7.0)
Grade 2: 1.5 - <3.0 x ULN	6/357	(1.7)	16/353	(4.5)	22/710	(3.1)
Grade 3: 3.0 - <5.0 x ULN	1/357	(0.3)	1/353	(0.3)	2/710	(0.3)
Grade 4: ≥ 5.0 x ULN	0/357	(0.0)	1/353	(0.3)	1/710	(0.1)
Aspartate Aminotransferase (IU/L)						
Grade 1: 1.25 - <2.5 x ULN	33/359	(9.2)	55/350	(15.7)	88/709	(12.4)
Grade 2: 2.5 - <5.0 x ULN	6/359	(1.7)	17/350	(4.9)	23/709	(3.2)
Grade 3: 5.0 - <10.0 x ULN	4/359	(1.1)	2/350	(0.6)	6/709	(0.8)
Grade 4: ≥10.0 x ULN	0/359	(0.0)	0/350	(0.0)	0/709	(0.0)
Bicarbonate (mEq/L)						
Grade 1: 16.0 - <LLN	55/302	(18.2)	52/299	(17.4)	107/601	(17.8)
Grade 2: 11.0 - <16.0	2/302	(0.7)	6/299	(2.0)	8/601	(1.3)
Grade 3: 8.0 - <11.0	0/302	(0.0)	0/299	(0.0)	0/601	(0.0)
Grade 4: <8.0	0/302	(0.0)	0/299	(0.0)	0/601	(0.0)
Bilirubin (mg/dL)						

Grade 1: 1.1 - <1.6 x ULN	10/359	(2.8)	9/354	(2.5)	19/713	(2.7)
Grade 2: 1.6 - <2.6 x ULN	2/359	(0.6)	0/354	(0.0)	2/713	(0.3)
Grade 3: 2.6 - <5.0 x ULN	0/359	(0.0)	0/354	(0.0)	0/713	(0.0)
Grade 4: ≥5.0 x ULN	0/359	(0.0)	0/354	(0.0)	0/713	(0.0)
Calcium, High (mg/dL)						
Grade 1: 10.6 - <11.5	2/358	(0.6)	2/354	(0.6)	4/712	(0.6)
Grade 2: 11.5 - <12.5	0/358	(0.0)	0/354	(0.0)	0/712	(0.0)
Grade 3: 12.5 - <13.5	0/358	(0.0)	0/354	(0.0)	0/712	(0.0)
Grade 4: ≥13.5	0/358	(0.0)	0/354	(0.0)	0/712	(0.0)
Calcium, Low (mg/dL)						
Grade 1: 7.8 - <8.4	21/358	(5.9)	33/354	(9.3)	54/712	(7.6)
Grade 2: 7.0 - <7.8	8/358	(2.2)	9/354	(2.5)	17/712	(2.4)
Grade 3: 6.1 - <7.0	4/358	(1.1)	8/354	(2.3)	12/712	(1.7)
Grade 4: <6.1	4/358	(1.1)	3/354	(0.8)	7/712	(1.0)
Creatine Kinase (IU/L)						
Grade 1: 3.0 - <6.0 x ULN	7/354	(2.0)	2/345	(0.6)	9/699	(1.3)
Grade 2: 6.0 - <10.0 x ULN	3/354	(0.8)	4/345	(1.2)	7/699	(1.0)
Grade 3: 10.0 - <20.0 x ULN	1/354	(0.3)	2/345	(0.6)	3/699	(0.4)
Grade 4: ≥ 20.0 x ULN	0/354	(0.0)	1/345	(0.3)	1/699	(0.1)
Creatinine (mg/dL)						
Grade 1: 1.1 - 1.3 x ULN	1/359	(0.3)	3/356	(0.8)	4/715	(0.6)
Grade 2: >1.3 - 1.8 x ULN or Increase to 1.3 to < 1.5 x baseline	23/359	(6.4)	17/356	(4.8)	40/715	(5.6)
Grade 3: >1.8 - <3.5 x ULN or Increase to 1.5 to <2.0 x above baseline	6/359	(1.7)	7/356	(2.0)	13/715	(1.8)
Grade 4: ≥3.5 x ULN or Increase of ≥2.0 x above baseline	1/359	(0.3)	2/356	(0.6)	3/715	(0.4)
GFR from Creatinine Adjusted for BSA (mL/min/1.73m2)						
Grade 2: 60 - <90 or 10% - <30% decrease from participant's baseline	62/295	(21.0)	77/288	(26.7)	139/583	(23.8)
Grade 3: 30 - <60 or 30% - <50% decrease from participant's baseline	16/295	(5.4)	20/288	(6.9)	36/583	(6.2)
Lipase (IU/L)						
Grade 1: 1.1 - <1.5 x ULN	19/357	(5.3)	12/353	(3.4)	31/710	(4.4)
Grade 2: 1.5 - <3.0 x ULN	6/357	(1.7)	19/353	(5.4)	25/710	(3.5)
Grade 3: 3.0 - <5.0 x ULN	0/357	(0.0)	3/353	(0.8)	3/710	(0.4)
Grade 4: ≥5.0 x ULN	0/357	(0.0)	3/353	(0.8)	3/710	(0.4)

MK4482-001 Part 1

While the CSR states that there were no clinically meaningful findings in the laboratory values that met pre-determined criteria, section 4.3 reports the ECI resulting from a subject who received molnupiravir 800 mg BID and had post-baseline elevated AST or ALT ≥3x ULN and elevated total bilirubin ≥2x ULN and alkaline phosphatase <2x ULN (thus satisfying the criteria for potential DILI) on Day 14. These criteria were no longer satisfied on Day 15 when alkaline phosphatase became >2x ULN, secondary to fatal septic shock and cholestasis; thus, the event was not considered DILI.

Discontinuation due to AES

In MK-4482-004, one subject had pruritus and rash with 800 mg BID that was considered treatment-related and discontinued drug on Day 4.

In MK4482-006, three of the four SAEs led to study drug discontinuation and all of these participants also discontinued from the study (see section 3.4) but none was considered treatment-related.

MK4482-002 Part 1

AEs leading to study intervention discontinuation were reported for 4 (1.3%) participants. In the molnupiravir groups, 3/225 discontinued due to an AE (2 due to COVID-19 pneumonia, 1 due to hypoaesthesia and insomnia) but none was considered treatment-related. One placebo subject discontinued due to drug-related diarrhoea.

MK4482-002 Part 2

AEs leading to discontinuation of study drug occurred in 1.3% in the molnupiravir group and 3.4% in the placebo group (see table below). Drug-related AEs leading to discontinuation of study drug were reported for 0.8% in each group.

Participants With Adverse Events Leading to Discontinuation of Treatment
(Incidence > 0% in One or More Treatment Groups)
All Participants as Treated Population
MK-4482-002 Combined 1A3/1A4

	MK-4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	386		379		765	
with one or more adverse events leading to discontinuation	5	(1.3)	13	(3.4)	18	(2.4)
with no adverse events leading to discontinuation	381	(98.7)	366	(96.6)	747	(97.6)
Eye disorders	**1**	**(0.3)**	**0**	**(0.0)**	**1**	**(0.1)**
Vision blurred	1	(0.3)	0	(0.0)	1	(0.1)
Gastrointestinal disorders	**2**	**(0.5)**	**2**	**(0.5)**	**4**	**(0.5)**
Abdominal pain upper	0	(0.0)	2	(0.5)	2	(0.3)
Diarrhoea	0	(0.0)	2	(0.5)	2	(0.3)
Nausea	2	(0.5)	0	(0.0)	2	(0.3)
Vomiting	2	(0.5)	0	(0.0)	2	(0.3)
General disorders and administration site conditions	**1**	**(0.3)**	**1**	**(0.3)**	**2**	**(0.3)**
Chest discomfort	0	(0.0)	1	(0.3)	1	(0.1)
Fatigue	1	(0.3)	0	(0.0)	1	(0.1)
Infections and infestations	**1**	**(0.3)**	**8**	**(2.1)**	**9**	**(1.2)**
COVID-19	0	(0.0)	7	(1.8)	7	(0.9)
Infections and infestations	**1**	**(0.3)**	**8**	**(2.1)**	**9**	**(1.2)**
COVID-19 pneumonia	0	(0.0)	3	(0.8)	3	(0.4)
Peritonsillitis	1	(0.3)	0	(0.0)	1	(0.1)
Tonsillitis	1	(0.3)	0	(0.0)	1	(0.1)
Metabolism and nutrition disorders	**0**	**(0.0)**	**1**	**(0.3)**	**1**	**(0.1)**
Diabetic metabolic decompensation	0	(0.0)	1	(0.3)	1	(0.1)
Musculoskeletal and connective tissue disorders	**0**	**(0.0)**	**1**	**(0.3)**	**1**	**(0.1)**
Myalgia	0	(0.0)	1	(0.3)	1	(0.1)
Nervous system disorders	**2**	**(0.5)**	**0**	**(0.0)**	**2**	**(0.3)**
Dizziness	1	(0.3)	0	(0.0)	1	(0.1)
Headache	1	(0.3)	0	(0.0)	1	(0.1)
Psychiatric disorders	**0**	**(0.0)**	**1**	**(0.3)**	**1**	**(0.1)**
Insomnia	0	(0.0)	1	(0.3)	1	(0.1)
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**1**	**(0.3)**	**1**	**(0.1)**
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**1**	**(0.3)**	**1**	**(0.1)**
Hiccups	0	(0.0)	1	(0.3)	1	(0.1)

Every participant is counted a single time for each applicable row and column.
Adverse event terms are from MedDRA Version 24.0.

MK4482-001 Part 1

One participant in the 400 mg group discontinued treatment due to an SAE of respiratory failure, which resolved after 2 months. This was not considered to be treatment related.

2.4.3.1. Discussion on Safety

Demonstrated risks

Of the 1069 subjects, mostly infected with COVID-19, who have been exposed to molnupiravir, 593 have received 800 mg BID for up to 5 days and 587 of this number had COVID-19. The vast majority of these 587 were enrolled into MK4482-002 so they provide safety data for the target population. This total is considered to be appropriate in light of the intended emergency use of molnupiravir.

For all AEs and for drug-related AEs there was no clear trend for a major effect of molnupiravir dose on the safety profile. For the most part the overall rates and rates for individual PTs have overlapped between molnupiravir and placebo groups. Relatively few AEs have been Grade 3 or 4 and there has been no excess of these in molnupiravir-treated subjects.

There was a subject in MK8842-004 with pruritus and rash who discontinued. No SAEs likely to represent hypersensitivity were reported, however in MK4482-002 5 (1.3%) in the molnupiravir 800 mg BID group and 1 in the placebo group had a rash, regardless of relatedness, and this is adequately addressed in the conditions for use.

The company did not conduct a TQT studybut did collect ECGs in MK4482-004, which did not suggest any clinically important effect on cardiac conduction.

Based on the non-clinical findings, the company has paid close attention to any possible effects of molnupiravir on bone marrow in the clinical studies, including any events of thrombocytopenia. Thus far, the clinical data do not point to an issue arising from a 5-day treatment course.

With the exception of MK4482-001 Part 1, in which molnupiravir failed to show a clinical benefit (see discussion on efficacy), there were no deaths in molnupiravir-treated subjects. It should also be noted that in MK4482-001 Part 1 the number of deaths differs from the number in the efficacy analyses because the safety analysis counted AEs that led to death with onset during treatment and the 14-day follow up period regardless of the timing of the death. Thus, 16 subjects had AEs resulting in death (6 in the 200 mg group, 4 in the 400 mg, 4 in the 800 mg group and 2 in the placebo group). Most deaths occurred in participants who had severe COVID-19 at baseline (12/16), were >60 years of age (13/16), had underlying comorbidities (14/16) and/or had duration of COVID-19 symptoms >5 days before randomisation (12/16). None of the deaths was considered treatment-related by investigators.

With small groups and with no dose-related trend, it seems unlikely that molnupiravir contributed to these deaths and the distribution may have arisen by chance.

Rates for SAEs have not been higher with molnupiravir and much of the difference vs. placebo in MK4482-002 was driven by the rate of worsening of COVID-19 in the placebo group.

The safety data was translated into Section 6 of the conditions for use, and below table is considered to be appropriate:

Table 1: Tabulated list of adverse reactions

Frequency	**Adverse Reaction**
Nervous sytem disorders	
Common	dizziness, headache
Gastrointestinal disorders	

Common	diarrhoea, nausea
Uncommon	vomiting
Skin and subcutaneous tissue disorders	
Uncommon	rash, urticaria

Uncertainty about risks

Whilst the available data do not point to major concerns for use of 800 mg BID for 5 days, the safety database remains somewhat limited. There is also some concern that molnupiravir may be used off label and for longer durations in individuals who present with more severe COVID-19 despite the fact that MK4482-001 Part 1 showed no clinical benefit based on time to sustained recovery through Day 29.

2.4.3.2. Conclusions on clinical safety

In light of the nonclinical findings, noting that the target population is confined to adults at this time, it is concluded that molnupiravir is not recommended during pregnancy or breastfeeding with a 4-day post-treatment window for use of contraception and avoidance of breastfeeding. However, the Member States and the company should consider putting in place pharmacovigilance activities to capture all instances of use of molnupiravir in pregnant women, so that when a registry to monitor the pregnancy outcomes is established all relevant cases are captured.

The potential concerns regarding effects of molnupiravir on bone marrow do not appear to be clinical concerns when treatment is restricted to 800 mg BID for up to 5 days.

An excess of deaths with molnupiravir vs. placebo was seen only in MK4482-001 Part 1 and there is no evidence of a relationship to dose. With relatively small denominators, the differences in numbers may have arisen by chance. The data from treated outpatients do not show any deaths in the molnupiravir groups.

The Committee further 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. Healthcare professionals will be asked to report any suspected adverse reactions.

3. Overall Conclusions

Based on the available quality, non-clinical and clinical data, a harmonised scientific opinion at EU level could be reached on currently available information on molnupiravir and on potential conditions for use with a view to supporting national decisions.

Quality aspects

Considering the data provided by the company on the manufacture, characterisation, pharmaceutical development, control and stability of the active substances and finished products, the overall quality of molnupiravir is acceptable in the context of this procedure, when used in accordance with the conditions for use.

Non-clinical aspects

The mechanism of action of molnupiravir has been established, as well as its antiviral action against tested Sars-Cov-2 strains. Pharmacokinetic parameters indicate dose proportional exposure. The most important concern affects the advice on use in women of childbearing potential, pregnancy and

breastfeeding, based on studies in animals that have shown reproductive and maternal toxicity at similar dose levels, which is reflected in the conditions for use.

Overall, the non-clinical data provided support the proposed use of molnupiravir in the conditions for use.

Clinical aspects

The trial considered pivotal for the purpose of this procedure showed that Molnupiravir 800 mg BID started within 5 days of symptom onset provided a statistically significant reduction in the rate of hospitalisation or death in the population enrolled into MK4482-002 Part 2.

The population in which efficacy was demonstrated in this study was not receiving supplemental oxygen at baseline and all subjects had at least one protocol-listed risk factor for progression of COVID-19. Therefore, the data are considered to support the below indication:

"Lagevrio is indicated 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 (see section 6.)".

The CHMP however highlighted that patients receiving oxygen for other diseases than COVID-19 should not be prevented from being treated with molnupiravir.

CHMP further noted, that efficacy could not be established in a subgroup that was seropositive at baseline. The implications of this finding are still unclear considering the low number of cases, however, would warrant further assessment as part of the full MA procedure.

In addition, an increased mutation rate of SARS-COV-2 has been observed in molnupiravir-treated subjects compared with those given placebo, in terms of nucleotide changes in the viral RNA and their translation into amino acid changes. While this effect is expected based on the mechanism of action of this class of medicines the clinical relevance of this finding is so far not known and may require further follow-up as part of the MA.

In view of clinical safety aspects, noting that the target population is confined to adults at this time in light of the no-nclinical findings, it is also appropriate that Section 5.5 of the conditions for use advises that use of molnupiravir is not recommended during pregnancy or breastfeeding with a 4-day post-treatment window for use of effective contraception and interruption of breastfeeding.

Based on the current data in the clinical studies, the potential concerns regarding effects of molnupiravir on bone marrow do not appear to be clinical concerns when treatment is restricted to 800 mg twice daily for 5 days.

An excess of deaths with molnupiravir vs. placebo was seen only in MK4482-001 Part 1 and there is no evidence of a relationship to dose. With relatively small denominators, the differences in numbers may have arisen by chance. The data from treated outpatients does not show any deaths in the molnupiravir groups. In the other studies, the safety profile of molnupiravir did not deviate largely from placebo.

Overall conclusion

Considering the data provided by the company on quality aspects, preclinical aspects and the clinical dataset provided, Lagevrio (molnupiravir) might provide clinical benefit for the treatment of confirmed COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of progression to severe COVID-19.

In view of safety reporting for product distribution of molnupiravir 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

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EudraVigilance Post-Authorisation Module (EVPM) any individual case safety reports (serious non-EEA; serious and non-serious EEA) related to molnupiravir and reported directly to them by patients and healthcare professionals.

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Document 3A.5

EMA Conditions of Use, Conditions for Distribution and Patients Targeted and Conditions for Safety Monitoring Addressed to Member States for Unauthorized Product Lagevrio (molnupiravir) Available for Use

Document URL

https://www.ema.europa.eu/en/documents/referral/lagevrio-also-known-molnupiravir-mk-4482-covid-19-article-53-procedure-conditions-use-conditions_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-lagevrio-(also-known-as-molnupiravir-or-mk-4482)-for-treating-covid-19-section

License

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ANNEX I

CONDITIONS OF USE, CONDITIONS FOR DISTRIBUTION AND PATIENTS TARGETED AND CONDITIONS FOR SAFETY MONITORING ADRESSED TO MEMBER STATES

FOR

UNAUTHORISED PRODUCT
Lagevrio (molnupiravir)

AVAILABLE FOR USE

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1. MEDICINAL PRODUCT FOR USE

- **Name of the medicinal product for use: Lagevrio**
- **Active substance(s): molnupiravir**
- **Pharmaceutical form: Capsule**
- **Route of administration: Oral Use**
- **Strength: 200 mg**

2. NAME AND CONTACT DETAILS OF THE COMPANY

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

[Contact details will be added at the National level]

3. TARGET POPULATION

Lagevrio is indicated 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. See section 6.

4. CONDITIONS FOR DISTRIBUTION

Medicinal product subject to medical prescription.

5. CONDITIONS OF USE

5.1 Posology

- **Dosing recommendations and treatment duration**

The recommended dose of Lagevrio is 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days.

Lagevrio 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 Lagevrio in patients below 18 years of age have not yet been established. No data are available.

Elderly
No dose adjustment of Lagevrio is required.

Renal impairment
No dose adjustment of Lagevrio is required. See section 5.3.

Hepatic impairment
No dose adjustment of Lagevrio is required. See section 5.3.

- **Method of administration**

For oral use.
Lagevrio 200 mg capsules can be taken with or without food.

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Patients should be advised to swallow the capsules whole and not to open, break, or crush the capsule.

5.2 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 5.11).

5.3 Special warnings and precautions for use

Renal and hepatic impairment

Patients with severe renal impairment were excluded from clinical trials. There is limited experience of the use of molnupiravir in persons with any degree of hepatic impairment.

Sodium
This medicinal product contains 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

No clinical interaction studies have been performed with molnupiravir. No substantial risks for clinically important drug interactions when dosing with molnupiravir 800 mg every 12 hours for 5 days have been identified based on the limited available in-vitro data.

5.5 Pregnancy and lactation

- **Women of childbearing potential**

Women of childbearing potential must use effective contraception for the duration of treatment and for 4 days after the last dose of Lagevrio.

- **Pregnancy**

There are no data from the use of Lagevrio in pregnant women. Studies in animals have shown reproductive toxicity. Oral administration of molnupiravir to pregnant rats during the period of organogenesis resulted in embryofetal lethality and teratogenicity at 7.5 times the human NHC exposures at the recommended human dose (RHD) and reduced foetal growth at ≥ 2.9 times the human N-hydroxycytidine (NHC) exposure at the RHD.

Oral administration of molnupiravir to rabbits during the period of organogenesis resulted in reduced foetal body weights at 18 times the human NHC exposure at the RHD. The safety margin at the NOAEL to human NHC exposure is 0.8 times and 6.5 times at the RHD in rats and rabbits, respectively. Although maternal toxicity was observed in both rats and rabbits at all dose levels in which developmental toxicity occurred, a substance-related effect cannot be excluded.

Lagevrio is not recommended during pregnancy and in women of childbearing potential not using effective contraception.

- **Breast-feeding**

It is unknown whether Lagevrio or any of the components of Lagevrio are present in human milk, affect human milk production, or have effects on the breastfed infant. Animal lactation studies with molnupiravir have not been conducted.

Based on the potential for adverse reactions on the breastfeeding infant from Lagevrio, breast-feeding should be interrupted during treatment and for 4 days after the last dose of Lagevrio.

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- **Fertility**

No human data on the effect of molnupiravir on fertility are available. There were no effects on female or male fertility in rats at approximately 2 and 6 times the human NHC exposure at the RHD respectively.

5.6 Incompatibilities

Not applicable.

5.7 Overdose

There is no human experience of overdosage with Lagevrio. Treatment of overdose with Lagevrio should consist of general supportive measures including the monitoring of the clinical status of the patient. Haemodialysis is not expected to result in effective elimination of NHC.

5.8 Shelf life

18 months

5.9 Storage conditions

This medicinal product does not require any special storage conditions. Store in the original package.

5.10 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

5.11 List of excipients

Capsule content:
Croscarmellose sodium
Hydroxypropyl cellulose
Magnesium stearate
Microcrystalline cellulose
Purified water

Capsule shell:
Hypromellose
Titanium dioxide
Red iron oxide

Printing ink:
Potassium hydroxide
Shellac
Titanium dioxide

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6. OTHER INFORMATION

- **Undesirable effects**

Summary of the safety profile

The most common adverse reactions reported during treatment with 800 mg every 12 hours for 5 days and during 14 days after the last dose were diarrhoea (3%), nausea (2%), dizziness (1%) and headache (1%) all of which were Grade 1 (mild) or Grade 2 (moderate).

Tabulated list of adverse reactions
The adverse reactions 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 (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000).

Table 1: Tabulated list of adverse reactions

Frequency	**Adverse Reaction**
Nervous sytem disorders	
Common	dizziness, headache
Gastrointestinal disorders	
Common	diarrhoea, nausea
Uncommon	vomiting
Skin and subcutaneous tissue disorders	
Uncommon	rash, urticaria

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
Molnupiravir is a prodrug that is metabolised to the ribonucleoside analogue N - hydroxycytidine (NHC). NHC distributes into cells where it is phosphorylated to form the pharmacologically active ribonucleoside triphosphate (NHC-TP). NHC-TP incorporation into viral RNA by the viral RNA polymerase results in an accumulation of errors in the viral genome leading to inhibition of replication. This mechanism of action is referred to as viral error catastrophe.

Antiviral Activity
NHC was active in cell culture assays against SARS-CoV-2 with 50% effective concentrations (EC_{50}) ranging between 0.67 to 2.66 µM in A-549 cells and 0.32 to 2.03 µM in Vero E6 cells. NHC had similar activity against SARS-CoV-2 variants B.1.1.7 (Alpha), B.1351 (Beta), P.1 (Gamma) and B.1.617.2 (Delta) with EC_{50} values of 1.59, 1.77 and 1.32 and 1.68 µM, respectively.

Resistance

Studies to evaluate resistance to NHC with SARS-CoV-2 in cell culture and in clinical studies have not been completed. In-vitro resistance selection studies with other coronaviruses (Murine Hepatitis Virus and MERS-CoV) showed a low likelihood of resistance development to NHC. Following 30 passages in cell culture only a 2-fold decrease in susceptibility was observed and no NHC resistance-associated amino acid substitutions were identified. NHC retained activity *in vitro* against SARS-CoV-2 and recombinant mouse hepatitis virus with polymerase substitutions (e.g. F480L, V557L and E802D) associated with decreased remdesivir sensitivity, indicating a lack of cross-resistance.

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- **Summary of relevant Clinical properties**

Clinical efficacy and safety

Clinical data are based on an interim analysis of data from 775 randomised subjects in the Phase 3 MOVe-OUT trial. MOVe-OUT was a randomised, double blind and placebo-controlled trial in non-hospitalised adult patients with laboratory-confirmed COVID-19.

Eligible patients had not been vaccinated against SARS-CoV-2 and had symptom onset within 5 days of enrolment. At study entry, patients were not receiving supplemental oxygen and had at least one of the protocol-listed risk factors for progression to severe COVID-19 (60 years of age or older, diabetes, obesity [BMI >30], chronic kidney disease, serious heart conditions, chronic obstructive pulmonary disease or active cancer). Subjects were randomised 1:1 to receive 800 mg of Lagevrio or placebo orally every 12 hours for 5 days.

At baseline the median age was 44 years (range: 18 to 88 years); 14% of patients were 60 years of age or older and 3% were over 75 years of age; 52% were male; 52% were White, 6% Black or African American and 2% Asian; 58% were Hispanic or Latino. Forty-nine percent of subjects received Lagevrio or placebo within 3 days of COVID-19 symptom onset. The most common risk factors were obesity (77%), 60 years of age or older (14%) and diabetes (14%). Overall, baseline demographic and disease characteristics were well balanced between the treatment arms.

Table 2 provides the results of the primary endpoint (the percentage of subjects who were hospitalised or died through Day 29 due to any cause).

Table 2: Interim Efficacy Results in Non-Hospitalised Adults with COVID-19

	Lagevrio (N=385) n (%)	**Placebo (N=377) n (%)**	**Risk difference* (95% CI)**	**p-value†**
All-cause hospitalisation or death through Day 29‡	28 (7.3%)	53 (14.1%)	-6.8 (-11.3, -2.4)	0.0012
Hospitalisation	28 (7.3%)	52 (13.8%)		
Death	0 (0%)	8 (2.1%)		
Unknown§	0 (0%)	1 (0.3%)		

* Risk difference of molnupiravir-placebo based on Miettinen and Nurminen method stratified by time of COVID-19 symptom onset (≤3 days vs. >3 [4-5] days). Relative risk reduction of molnupiravir compared to placebo is 52% (95% CI: 33%, 80%) based on the Cochran-Mantel-Haenszel method stratified by time of COVID-19 symptom onset (≤3 days vs. >3 [4-5] days).
† 1-sided p-value
‡ Defined as ≥24 hours of acute care in a hospital or an acute care facility (e.g., emergency room).
§ Subjects with unknown status at Day 29 are counted as having an outcome of all-cause hospitalization or death in the efficacy analysis.
Note: All subjects who died through Day 29 were hospitalised prior to death.

Efficacy results were consistent across sub-groups including age (>60 years), at risk medical conditions (e.g., obesity, diabetes) and SARS-CoV-2 variants. In the subgroup of subjects positive for SARS-CoV-2 antibodies at baseline (approximately 18%; reflecting current or prior infection), there was no difference for the primary endpoint between the molnupiravir and placebo groups.

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7. CONDITIONS FOR SAFETY MONITORING

This medicine is subject to additional monitoring. This enables new safety information to be identified quickly. Healthcare Professionals are asked to report any suspected adverse reactions. For information on reporting side effects, see section 6.

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Document 3A.6

U.S. FDA Emergency Use Authorization (EUA) for Molnupiravir 200 mg Capsules Center for Drug Evaluation and Research (CDER) Review (December 23, 2021)

Document URL

https://www.fda.gov/media/155241/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

Non applicable

SEE ATTACHED ADDENDUM

Emergency Use Authorization for Molnupiravir 200 mg Capsules

Center for Drug Evaluation and Research Review

Table 1. 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]	000108
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	Merck Sharp & Dohme., a subsidiary of Merck & Co., Inc. 1 Merck Drive PO Box 100 Whitehouse Station, NJ 08889-0100 908-423-1000 POC: Sushma Kumar, PhD, PMP Director, Global Regulatory Affairs and Clinical Safety Merck Sharp & Dohme Corp. (b) (6) (b) (6)
Submission Date(s)	October 8, 2021
Receipt Date(s)	October 8, 2021
OND Division / Office	Division of Antivirals/Office of Infectious Diseases

[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.

Reviewer Name(s)/Discipline(s)		
	Discipline Review Team	
	Discipline Reviewer	**Team Lead**
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	Nonclinical: Mark Seaton	Laine Peyton Myers
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	Associate Director for Therapeutic Review, Division of Infectious Disease Pharmacology	Vikram Arya
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	OND Policy: Andrew LeBoeuf, Acting Associate Director for Policy	OSE RPM: Danyal Chaudhry and Oyinlola Fashina OSE CDTL: Neha Gada

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Integrated Review Completion Date	December 23, 2021
Proprietary Name	n/a
Established Name/Other names used during development	Molnupiravir (MK-4482; MOV; EIDD-2801)
Dosage Forms/Strengths	Oral capsule, 200 mg
Therapeutic Class	SARS-CoV2 antiviral
Intended Use or Need for EUA	Treatment of mild-to-moderate coronavirus disease 2019 (COVID-19)
Intended Population(s)	Adults who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.
Product in the Strategic National Stockpile (SNS)	No
Distributor, if other than Sponsor	AmerisourceBergen Corporation

Abbreviations: ATL, application technical lead; CDTL, cross-disciplinary team leader; DD, division director; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DPMH, Division of Pediatric and Maternal Health; DPV, Division of Pharmacovigilance; DRM, Division of Risk Management; EUA, Emergency Use Authorization; MHT, Maternal Health Team; MO, medical officer; MOV, molnupiravir; OMQ, Office of Manufacturing Quality; OND, Office of New Drugs; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OPRO, Office of Program and Regulatory Operations; OSE, Office of Surveillance and Epidemiology; PLT, patient labeling team; RBPM, regulatory business process manager; RPM, regulatory project manager; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SE, safety evaluator; TL, team lead; USG,

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Glossary

A	adenosine
AE	adverse event
ALT	alanine aminotransferase
API	Active Pharmaceutical Ingredient
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice daily
BMI	body mass index
C	cytidine
CBRN	chemical, biological, radiological, or nuclear
CC_{50}	50% cytotoxicity concentration
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CNT	concentrative nucleoside transporter
COVID-19	coronavirus disease 2019
CYP	cytochrome p450
DNA	deoxyribonucleic acid
EC_{50}	50% effective concentration
ECI	events of clinical interest
EFD	embryo-fetal development
ENT	equilibrative nucleoside transporter
EOT	end of treatment
EUA	Emergency Use Authorization
FDA	U.S. Food and Drug Administration
G	guanosine
GD	gestation day
GSc	Genotoxicity Subcommittee
HHS	U.S. Department of Health and Human Services
IC_{50}	50% inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	investigational new drug
IR	information request
MERS	Middle East respiratory syndrome
MHV	mouse hepatitis virus
mITT	modified intent-to-treat
MOV	molnupiravir
MUT-RTC	mutant reticulocyte
MUT-RBC	mutant red blood cell
nCoV	novel (new) coronavirus
NGS	next generation sequencing
NHC	N3-hydroxycytidine
NHC-MP	N3-hydroxycytidine monophosphate
NHC-TP	N3-hydroxycytidine triphosphate
NOAEL	no-observed adverse effect level
NOEL	no observed effect level
NP	nasopharyngeal
nsp	nonstructural protein

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NTD	N-terminal domain
OP	oropharyngeal
OSI	Office of Scientific Investigations
PBMC	peripheral blood mononuclear cell
PK	pharmacokinetic
PPND	pre- and postnatal development
PT	preferred term
Q12H	every 12 hours
RdRp	RNA-dependent RNA polymerase
RNA	ribonucleic acid
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	system organ class
U	uridine
WHO	World Health Organization

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I. Emergency Use Authorization Determination/Declaration

On February 4, 2020, the U.S. Secretary of Health and Human Services (HHS) determined pursuant to section 564 of the federal Food, Drug, and Cosmetic Act that there is a significant potential for a public health emergency that has a significant potential to affect national security or the health and security of U.S. 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 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes the illness coronavirus disease 2019 (COVID-19).

On the basis of this determination, the U.S. Secretary of HHS declared that circumstances exist justifying the authorization of emergency use of drugs and biologics during the COVID-19 outbreak, pursuant to section 564 of the Food, Drug, and Cosmetic Act, subject to the terms of any authorization issued under that section.

II. Recommendations

1. Emergency Use Authorization Issuance

The Division of Antivirals (the Division) and Office of Infectious Diseases, Office of New Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration (FDA or the Agency) recommends an Emergency Use Authorization (EUA) issuance.

We recommend that molnupiravir (MOV) be authorized for the treatment of mild-to-moderate COVID-19 in adults

- 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 (refer to the Centers for Disease Control and Prevention (CDC) website[2] for additional details), and
- for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.

LIMITATIONS OF AUTHORIZED USE

- Molnupiravir is not authorized for use in patients who are less than 18 years of age
- Molnupiravir is not authorized for initiation of treatment in patients hospitalized due to COVID-19[3]. Benefit of treatment with molnupiravir has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19
- Molnupiravir is not authorized for use for longer than 5 consecutive days.
- Molnupiravir is not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

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[2] 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.

[3] Should a patient require hospitalization after starting treatment with molnupiravir, the patient may complete the full 5 day treatment course per the healthcare provider's discretion.

MOV use requires a complex benefit/risk assessment and extensive counseling and documentation on the part of the prescriber. Therefore, the review team has determined that the prescribing of MOV is not appropriate for pharmacists at this time. MOV 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 molnupiravir belongs (i.e., anti-infectives).

2. Eligibility of the Product for an EUA

- COVID-19 is a serious or life-threatening disease or condition caused by the chemical, biological, radiological, or nuclear (CBRN) agent specified in the declaration of emergency.
- Based on the totality of the scientific evidence available to FDA, it is reasonable to believe that this product may be effective in (1) diagnosing, preventing, or treating the serious or life-threatening disease or condition, or (2) diagnosing, treating, or preventing a disease or condition caused by an EUA product or an FDA-approved product used to diagnose, treat, or prevent the specified disease or condition caused by the CBRN agent.[4]
- Based on the totality of the scientific evidence available to FDA, it is reasonable to believe that the known and potential benefits outweigh the known and potential risks of the product when used to diagnose, treat, or prevent the serious or life-threatening disease or condition.
- There are no adequate, approved, and available alternatives to the emergency use of MOV for the treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing. MOV is a SARS-CoV-2 viral mutagenic nucleoside analogue replication inhibitor. Remdesivir (Veklury®) is the only drug approved by FDA to treat COVID-19 at the time of FDA's review of MOV. Remdesivir is a nucleotide analog ribonucleic acid (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

1. Proposed Use(s) Under the EUA

Treatment of mild-to-moderate COVID-19 in adults

- with positive results of direct SARS-CoV-2 viral testing, and

[4] A medical countermeasure may produce an adverse effect for which medical management might include other products that could be the subject of an EUA.

- who are at high risk for progression to severe COVID-19, including hospitalization or death (refer to CDC website for additional details), and for
- whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate

LIMITATIONS OF AUTHORIZED USE

- Molnupiravir is not authorized for use in patients who are less than 18 years of age
- Molnupiravir is not authorized for initiation of treatment in patients hospitalized due to COVID-19[5]. Benefit of treatment with molnupiravir has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19
- Molnupiravir is not authorized for use for longer than 5 consecutive days.
- Molnupiravir is not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

MOV use requires a complex benefit/risk assessment and extensive counseling and documentation on the part of the prescriber. Therefore, at this time, MOV 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 molnupiravir belongs (i.e., anti-infectives).

2. Proposed Dosing Regimen(s) for Use Under the EUA

2.1. Adult Patients

- 800 mg (four 200 mg capsules) taken orally every 12 hours (Q12H) for 5 days, with or without food.
- MOV should be administered as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.
- As was done in the clinical trials and also confirmed by population pharmacokinetic (PK) analysis, if the patient misses a dose of MOV within 10 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 10 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.

[5] Should a patient require hospitalization after starting treatment with molnupiravir, the patient may complete the full 5 day treatment course per the healthcare provider's discretion.

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2.2. Other Specific Populations (e.g., Geriatric Patients, Patients With Renal or Hepatic Impairment, and Pregnant Women)

Geriatric Patients

No dosage adjustment is recommended in geriatric patients. Clinical trials of MOV included patients aged 65 years and over (N=95 out of 549 patients). The PK of the ribonucleoside analog N3-hydroxycytidine (NHC) is similar in geriatric patients compared with younger patients based on population PK analysis (see Section XXVII.8). Age is not identified as a significant covariate in the population PK analysis of NHC.

Patients With Renal Impairment

No dosage adjustment is recommended in patients with any degree of renal impairment. Clinical trials of MOV included patients with mild (estimated glomerular filtration rate (eGFR) 60-79 mL/min/1.73 m^2, N=256) or moderate (eGFR 30-59 mL/min/1.73 m^2, N=43) renal impairment, and there is no clinically meaningful difference in NHC PK in patients with mild-to-moderate renal impairment compared to those with normal renal function (N=250) based on the population PK analysis (see Section XXVII.8). No patients with end-stage renal disease or severe renal impairment (eGFR less than 30 mL/min/1.73m^2) were enrolled in the clinical trials. Renal elimination does not contribute significantly to the elimination of MOV or NHC; and while renal impairment can alter hepatic cytochrome p450 (CYP) enzymes and drug transporters (adenosine triphosphate-binding cassette and solute carrier transporters), these enzymes and transporters are not involved in the elimination of MOV and NHC. As such, severe renal impairment and end-stage renal disease are not expected to have a significant effect on the PK of MOV and NHC.

Patients With Hepatic Impairment

No dosage adjustment is recommended in patients with any degree of hepatic impairment. Population PK analysis showed that mild hepatic impairment is not expected to significantly alter the PK of NHC (see Section XXVII.8). The hydrolysis of MOV to NHC is mediated by high-capacity carboxylesterases widely distributed not only in the liver, but also in the intestinal epithelial cells and other tissues. Hepatic elimination is not expected to be a major route of elimination for NHC based on preclinical data. Also, drug absorption of MOV is not likely to be altered due to reduction in bile flow in the intestine caused by hepatic impairment considering the high solubility of MOV in buffers with and without bile acids. Therefore, moderate or severe hepatic impairment is not expected to have a significant effect on the PK of MOV or NHC.

Pregnant Women

If a decision is made to use MOV in pregnancy, no dose adjustments are recommended. No pregnant women were enrolled in the clinical trials, therefore, no data in pregnant women are available to determine if MOV dose adjustment is warranted.

3. Rationale for Dosing Regimen

- The dosing and duration of treatment (800 mg Q12H, for 5 days, without regard to food) was chosen based on the totality of the virologic data from Trials MK-4482-001 (also

referred to as P001 and MOVe-IN), MK-4482-002 (also referred to as P002 or MOVe-OUT), and MK-4482-006, trends in the clinical efficacy in MK-4482-002, and safety data from all clinical studies (MK-4482-001, MK-4482-002, MK-4482-004,and MK-4482-0006).

- Food (Part 2 of MK-4482-004) did not significantly impact the area under the curve (AUC), AUC_{last} and $AUC_{0\text{-}inf}$, of NHC, but decreased the geometric mean C_{max} of NHC by 36% and delayed median T_{max} by 2 hours. Decrease in the geometric mean C_{max} of NHC is not expected to be clinically relevant, hence, MOV can be given with or without food.
- The 800 mg Q12H dose is the highest dose evaluated clinically. The dose-response and exposure-response analysis results indicate that the 800 mg Q12H dose appears to yield the greatest virologic response of the studied treatments (see Section XXVII.8).
- The administration of MOV at the proposed dosing regimen (800 mg, Q12H, 5 days) is not associated with a significant QTc prolongation effect.

IV. Product Information (Dose Preparation and Administration)

Not applicable. MOV is supplied in a 40-capsule-count bottle and should be stored at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) (see United States Pharmacopeial Convention's controlled room temperature).

V. Background Information on the Disease/Condition and Available Therapeutic Alternatives

1. Background Information on the Condition

There are many types of human coronaviruses including some that commonly cause mild upper-respiratory-tract illness. 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 WHO, approximately 262.9 million confirmed cases of COVID-19 caused by the 2019 novel coronavirus (SARS-CoV-2) have been reported as of December 2, 2021, including an estimated 5.2 million deaths. In the United States, according to the CDC, as of December 3, 2021, approximately 48.6 million cases of COVID-19 had been reported with over 780,000 deaths.

SARS-CoV-2 variants have emerged over time and continue to emerge. According to the CDC's national surveillance report for the period of October 10, 2021, to October 16, 2021, the most common Variant of Concern in the United States was the Delta (B.1.617.2) variant. On November 24, 2021, a new variant of SARS-CoV-2, B.1.1.529, was reported to the WHO. On November 26, 2021, the WHO designated this variant as Omicron and classified it as a Variant of Concern. The first confirmed U.S. case of Omicron was identified on December 1, 2021. At

present, there is uncertainty regarding the true prevalence of the Omicron variant. On December 20, 2021, CDC posted surveillance data stating that Omicron accounted for 0.7% of the SARS-CoV-2 sequences for the week ending December 4, 2021. Nowcast modeling predicted that the frequency of the Omicron variant was 73.2% of the total circulating variants in the US for the week ending December 18, 2021, with a wide confidence interval (95% CI 34.0-94.9%). SARS-CoV-2 variants of concern have primarily been characterized as having certain changes in the viral spike protein that could impact virus transmissibility or susceptibility to antibody-based therapeutics or vaccine-induced immune responses.

Patients with symptomatic SARS-CoV-2 infection, or COVID-19, can experience a wide range of clinical manifestations. Mild illness is defined by the presence of symptoms without shortness of breath, dyspnea, 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 and critical illness are defined as worsening pulmonary status requiring hospitalization, supplemental oxygen, noninvasive ventilation, high-flow oxygen devices, invasive mechanical ventilation, or extracorporeal membrane oxygenation.

The progression of SARS-CoV-2 infection to severe COVID-19 can occur in adults of any age, but the risk increases with age. Per the CDC, more than 80% of 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, including but not limited to cancer, chronic kidney disease, chronic lung disease, obesity, diabetes, pregnancy, and immunocompromised states, increase the risk for 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 (CDC 2021b).

2. Therapeutic Alternatives for the Disease

There is no adequate, approved, and available alternative to the emergency use of MOV for the treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing who are at high risk for progression to severe COVID-19, including hospitalization or death.

There is an approved drug for more severe COVID-19. Remdesivir (Veklury®) is a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor approved for use in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization. This medication was initially authorized for emergency use on May 1, 2020, and was ultimately approved on October 22, 2020, under new drug application 214787. At the time of this review, remdesivir 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.

Several monoclonal antibodies are currently authorized for emergency use 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 and/or hospitalization. Casirivimab 1200 mg and imdevimab 1200 mg were authorized to be administered together on November 21, 2020. Bamlanivimab 700 mg and etesevimab 1400 mg were authorized to be administered together on February 9, 2021. Bamlanivimab and etesevimab also includes authorized use in pediatric

patients, including neonates. Of note, bamlanivimab 700 mg as monotherapy was authorized for emergency use on November 9, 2020, and was subsequently revoked on April 16, 2021, due to a sustained increase in variants resistant to bamlanivimab alone resulting in the increased risk for treatment failure. Sotrovimab was authorized on May 26, 2021.On December 22, 2021, FDA authorized Pfizer's PAXLOVID for emergency use as treatment for 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.

There are currently no approved therapies for the treatment of COVID-19 in outpatients. Additional information on COVID-19 treatments can be found on the CDC website (CDC 2021a).

VI. Related Regulatory Submission(s)

MOV 800 mg, administered orally, is being studied under investigational new drug (IND) 147734 (Table 2) for the treatment of COVID-19 and under IND 155588 for the prevention of COVID-19. In addition, MOV is planned to be studied under IND 147122 for the treatment of uncomplicated influenza. However, no trials for the treatment of influenza have been initiated to date. Merck Sharp and Dohme Corp is the Sponsor for all three INDs. However, MOV is being developed jointly by Merck Sharp and Dohme Corp and Ridgeback Biotherapeutics.

1. Related Master Files

No drug master files were referenced for this EUA.

VII. Summary of Clinical Data

Table 2. All Clinical Trials

Study Number	IND, NDA, or Literature Reference	Type of Study	Population (Planned N)	Study Design and Type of Control	Test Product(s); Dosing Regimens; Dosage Forms; Routes of Administration; Duration	Study Status
MK-4482-002 (MOVe-OUT, P002) NCT04575597	IND 147734	Efficacy, Safety, PK	Part 1: N=300 Part 2: N=1550 Outpatient adults with COVID-19 and with an increased risk of severe illness from COVID-19	Phase 2/3 randomized, double-blind, placebo-controlled trial Part 1 (Phase 2): 1:1:1:1 randomization to three MOV doses or placebo Part 2 (Phase 3): 1:1 randomization to MOV or placebo	Part 1: MOV 200 mg PO Q12H x 5 d MOV 400 mg PO Q12H x 5 d MOV 800 mg PO Q12H x 5 d Placebo PO Q12H x 5 d Part 2: MOV 800 mg PO Q12H x 5 d Placebo PO Q12H x 5 d	Enrollment complete Part 1: MOV 200 mg: 74 MOV 400 mg: 77 MOV 800 mg: 74 Placebo: 74 Part 2 IA3/IA4b: MOV 800 mg: 387 Placebo: 388 Full population: MOV 800 mg:716 Placebo: 717 Total participants enrolled in Part 2=1433[1]
MK-4482-001 (MOVe-IN, P001) NCT04575584	IND 147734	Efficacy, Safety, PK	Part 1: N=300 Part 2: N=1000 Hospitalized adults with COVID-19	Phase 2/3 randomized, double-blind, placebo-controlled trial Part 1 (Phase 2): 1:1:1:1 randomization to three MOV doses or placebo Part 2 (Phase 3): 1:1 randomization to MOV or placebo	Part 1: MOV 200 mg PO Q12H x 5 d MOV 400 mg PO Q12H x 5 d MOV 800 mg PO Q12H x 5 d Placebo PO Q12H x 5 d Part 2: Never initiated	Enrollment complete Part 1: MOV 200 mg: 73 MOV 400 mg: 73 MOV 800 mg: 72 Placebo: 75 Part 2: Will not be conducted

Study Number	IND, NDA, or Literature Reference	Type of Study	Population (Planned N)	Study Design and Type of Control	Test Product(s); Dosing Regimens; Dosage Forms; Routes of Administration; Duration	Study Status
MK-4482-006 (EIDD-2801-2003, P006) NCT04405570	IND 147734	Efficacy, Safety	N = up to 204 Symptomatic adult outpatients with COVID-19 (all-comers)	Phase 2a randomized, double-blind, placebo-controlled trial Part 1: 1:1 randomization to MOV or placebo Parts 2 to 9: 3:1 randomization to MOV or placebo	Part 1: MOV 200 mg BID x 5 d Placebo BID x 5 d Parts 2 to 9: MOV up to 800 mg BID x 5 d Placebo BID x 5 d	Enrollment Complete Part 1: MOV 200 mg: 23 Placebo: 23 Parts 2 to 9: MOV 400 mg: 62 MOV 800 mg: 55 Placebo: 39
MK-4482-007 (EIDD-2801-2004, P007) NCT04405739	IND 147734	Efficacy, Safety	N=80 Hospitalized adults with COVID-19	A Phase 2a randomized, double-blind, placebo-controlled trial Part 1: 1:1:1 randomization to two MOV doses or placebo Parts 2 to 4: 2:1 randomization to MOV or placebo	Part 1: MOV 200 mg PO BID x 5 d MOV 400 mg PO BID x 5 d Placebo PO BID x 5 d Part 2: MOV 400 mg PO BID x 5 d Placebo PO BID x 5 d Part 3: MOV 800 mg PO BID x 5 d Placebo PO BID x 5 d Part 4: (optional) MOV up to 800 mg PO BID x 5 d Placebo PO BID x 5 d	Ongoing As of September 24, 2021, 65 participants enrolled
MK-4482-005 (AGILE CST-2, P005) NCT04746183	Non-IND	Efficacy, Safety	N=198 Outpatient adults with COVID-19 who are either ≥60 years of age, or ≥50 years of age with at least 1 well-controlled comorbidity	A Phase 1/2 randomized, seamless, adaptive platform trial Phase 1: 1:1 randomization to MOV or standard of care (open-label) Phase 2: 1:1 randomization to MOV or placebo (blinded)	Phase 1: MOV 300 mg PO BID x 10 doses MOV 600 mg PO BID x 10 doses, MOV 800 mg PO BID × 10 doses Standard of care Phase 2: MOV 800 mg PO BID x 10 doses Placebo PO BID × 10 doses	Ongoing As of September 24, 2021, 18 participants enrolled in Phase 1 and 114 participants enrolled in Phase 2

Study Number	IND, NDA, or Literature Reference	Type of Study	Population (Planned N)	Study Design and Type of Control	Test Product(s); Dosing Regimens; Dosage Forms; Routes of Administration; Duration	Study Status
MK-4482-004 (EIDD-2801-1001, P004) NCT04392219	IND 147734	Safety, PK	N = up to 130 Healthy volunteers	A Phase 1, first in human, double-blind, placebo-controlled trial <u>Part 1</u>: 3:1 randomization to MOV or placebo (single dose) <u>Part 2</u>: Open-label, randomized, 2-period crossover food-effect study <u>Part 3</u>: 3:1 randomization to MOV or placebo (multiple dose)	<u>Part 1</u>: MOV 50 mg PO x 1 dose MOV 100 mg PO x 1 dose MOV 200 mg PO x 1 dose MOV 400 mg PO x 1 dose MOV 600 mg PO x 1 dose MOV 800 mg PO x 1 dose MOV 1200 mg PO x 1 dose MOV 1600 mg PO x 1 dose Placebo PO x 1 dose <u>Part 2</u>: MOV 200 mg single dose <u>Part 3</u>: MOV 50 mg PO Q12H x 5.5 d MOV 100 mg PO Q12H x 5.5 d MOV 200 mg PO Q12H x 5.5 d MOV 400 mg PO Q12H x 5.5 d MOV 600 mg PO Q12H x 5.5 d MOV 800 mg POxQ12H x 5.5 d Placebo PO Q12H x 5.5 d	Completed <u>Part 1</u>: MOV 50 mg: 6 MOV 100 mg: 6 MOV 200 mg: 6 MOV 400 mg: 6 MOV 600 mg: 6 MOV 800 mg: 6 MOV 1200 mg: 6 MOV 1600 mg: 6 Placebo: 16 <u>Part 2</u>: MOV 200 mg: 10 <u>Part 3</u>: MOV 50 mg: 6 MOV 100 mg: 6 MOV 200 mg: 6 MOV 300 mg: 6 MOV 400 mg: 6 MOV 600 mg: 6 MOV 800 mg: 6 Placebo: 14

[1]Upon review of the IA3/IA4 data, the study was closed to enrollment on October 2, 2021, at the recommendation of the eDMC
Abbreviations: BID, twice daily; d, days; IND, investigational new drug; MOV, molnupiravir; PK, pharmacokinetics; PO, orally; Q12H, administered once every 12 hours; NDA, new drug application

In addition, there is an ongoing trial of MOV 800 mg orally Q12H for 5 days for post-exposure prophylaxis for COVID-19 in adults residing with a person with COVID-19, though no data are currently available from this trial.

VIII. Human Clinical Efficacy: Assessment of Potential Benefit

The main source of clinical efficacy data to support this EUA request is the Phase 2/3 trial, MK-4482-002, with the bulk of clinical data coming from Part 2 (Phase 3). Results from the Phase 2/3 trial in hospitalized participants will also be briefly summarized.

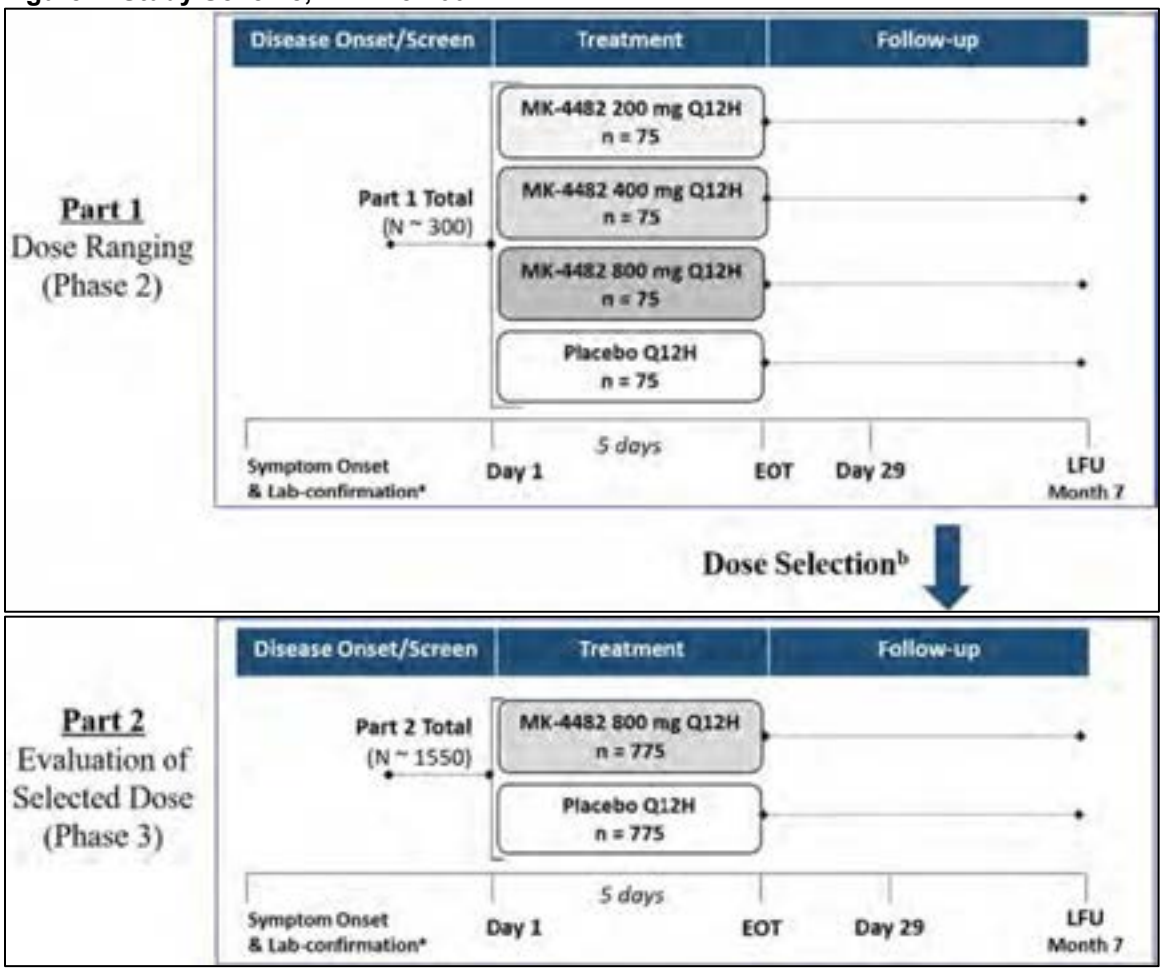
1. Trial Design, MK-4482-002

MK-4482-002 is a Phase 2/3, randomized, placebo-controlled, double-blind trial to evaluate the efficacy, safety, and pharmacokinetics of MOV in outpatient adults with COVID-19. MK-4482-002 is a two-part trial. Part 1 (Phase 2) is a dose-finding trial in which 302 participants were randomized 1:1:1:1 to MOV 200 mg Q12H x 5 days, MOV 400 mg Q12H x 5 days, MOV 800 mg Q12H x 5 days, or placebo Q12H x 5 days. The results for Part 1 (Phase 2) are included in Section XXVII.1. Based on data from Part 1 of MK-4482-002, Part 1 of the Phase 2/3 trial in hospitalized patients (MK-4482-001), and data from the Phase 2 trial, MK-4482-006, a MOV dose of 800 mg Q12H x 5 days was chosen for Part 2 (Phase 3).

In Part 2, a total of 1550 participants was to be randomized 1:1 to MOV 800 mg Q12H x 5 days or placebo Q12H x 5 days. A single interim analysis was planned at approximately 50% of participants enrolled and completed through Day 29 to potentially stop for efficacy or futility. In addition, a sample size re-estimation based on conditional power was to be conducted when 30% to 50% of the planned Part 2 (Phase 3) participants were followed through Day 29. Both the interim analysis and the sample size re-estimation were conducted simultaneously when 50% of Part 2 enrollment (775 participants of 1550 planned) were followed through the Day 29 visit. At the planned interim analysis (N=775 for efficacy and N=765 for safety), the external data-monitoring committee recommended that due to efficacy on the primary endpoint of reducing hospitalization $\geqslant$24 hours for acute care of illness or death due to any cause by Day 29, the study met the criteria for stopping enrollment. On October 2, 2021, the trial stopped enrollment, and all the randomized participants (N=1433) will continue to be followed until their Month 7 visit (end of study) or early withdrawal.

The Sponsor's initial EUA request included combined data from interim analysis 3 and interim analysis 4 (interim analyses 3/4) of Part 2 of MK-4482-002 as the primary source of support for the EUA. However, the participants who had been enrolled at the time the trial was stopped but had not yet reached Day 29 at the time of interim analyses 3/4, subsequently reached Day 29 while the EUA was still under review. Therefore, given the relatively small number of participants included in interim analyses 3/4, the Agency requested that the Sponsor submit topline safety and efficacy data for the full randomized population to provide further support for the EUA request. On November 22, 2021, the Agency received a high-level summary of the safety and efficacy findings for the full population (N=1433).

Figure 1. Study Scheme, MK-4482-002



Source: MK-4482-002 Protocol
Abbreviations: EOT, end of treatment; LFU, late follow-up visit; N, total number of planned participants in each study part; n, number of participants per group; Q12H, administered once every 12 hours

2. Eligibility Criteria, MK-4482-002

Inclusion criteria for enrollment in MK-4482-002 specified that participants be at least 18 years of age and have laboratory-confirmed SARS-CoV-2 infection with associated signs/symptoms of mild-to-moderate COVID-19. Originally, the time from diagnosis of SARS-CoV-2 infection to randomization and the time from COVID-19 symptom onset to randomization was ≤7 days. However, based on the findings in Part 1 of MK-4482-002, this was changed to ≤5 days in Protocol Amendment #2. Additionally, the original protocol specified that participants with mild COVID-19 had to have at least one baseline characteristic/underlying condition that is associated with an increased risk of severe illness from COVID-19[6]; and that at least 75% of

[6] Participants with any of the following were considered to be at increased risk for severe illness from COVID-19 and were eligible for enrollment in MK-4482-002: Age >60 years, active cancer, chronic kidney disease, chronic obstructive pulmonary disease, obesity (body mass index ≥30), serious heart conditions such as heart failure, coronary artery disease, or cardiomyopathies, and diabetes mellitus. This list of high-risk characteristics differs from the list used for COVID-19 therapeutics authorized for use in patients at high risk for progression to severe COVID-19 and/or hospitalization.

participants enrolled must have at least one characteristic or underlying medical condition associated with being at increased risk for severe illness from COVID-19. Based on the findings in Part 1 of MK-4482-002, Amendment #2 required that all participants in Part 2 of the trial must have at least one characteristic or underlying medical condition associated with being at increased risk for severe illness from COVID-19.

Pregnant women were excluded from MK-4482-002 and all heterosexually active male and female participants of reproductive potential were required to agree to use contraception. Originally contraception use was required for 90 days and 28 days for male and female participants, respectively. In Amendment #2, the required duration of contraception use was shortened to 4 days after the last dose of study drug for both males and females (to cover 5 times the half-life of the metabolite).

Patients were excluded if they were hospitalized, were on dialysis, or had an eGFR <30 mL/min/1.73 m^2, were severely immunosuppressed, had a platelet count <100,000/µL, had an active diagnosis of hepatitis B virus or hepatitis C virus infection, or had a history of acute pancreatitis within 3 months prior to randomization.

Lastly, SARS-CoV-2 vaccines were prohibited any time prior to randomization and through Day 29. Sponsor-designated standard of care for treatment for COVID-19 (e.g., remdesivir, dexamethasone, etc.) was generally permitted as indicated. However, use of anti-SARS-CoV-2 monoclonal antibodies were prohibited.

3. Analysis Populations, MK-4482-002

The trial included the following analysis populations:

Part 1

All Randomized Participants

- N=302; MOV 200 mg: 75; MOV 400 mg: 77; 800 mg: 76; placebo: 74

All Participants as Treated (Safety)

- All randomized participants who received at least one dose of study treatment
- N=299; MOV 200 mg: 74; MOV 400 mg: 77; 800 mg: 74; placebo: 74

Modified Intent-to-Treat

- All randomized participants who received at least one dose of study intervention and were not hospitalized prior to their first dose
- N=299; MOV 200 mg: 74; MOV 400 mg: 77; 800 mg: 74; placebo: 74

Part 2

Interim Analysis Population

All Randomized Participants

- N=775; MOV 800 mg: 387; placebo: 388

All Participants as Treated (Safety)

- All randomized participants who received at least one dose of study treatment
- N=765; MOV 800 mg: 386; placebo: 379

Modified Intent-to-Treat

- All randomized participants who received at least one dose of study intervention and were not hospitalized prior to their first dose
- N=762; MOV 800 mg; 385; placebo: 377

Post-Interim Analysis Population

All Randomized Participants

- N=658; MOV 800 mg: 329; placebo: 329

All Participants as Treated (Safety)

- All randomized participants who received at least one dose of study treatment
- N=646; MOV 800 mg: 324; placebo: 322

Modified Intent-to-Treat

- All randomized participants who received at least one dose of study intervention and were not hospitalized prior to their first dose
- N=646; MOV 800 mg; 324; placebo: 322

Full Analysis Population

All Randomized Participants

- N=1433; MOV 800 mg: 716; placebo: 717

All Participants as Treated (Safety)

- All randomized participants who received at least one dose of study treatment
- N=1411; MOV 800 mg: 710; placebo: 701

Modified Intent-to-Treat

- All randomized participants who received at least one dose of study intervention and were not hospitalized prior to their first dose
- N=1408; MOV 800 mg; 709; placebo: 699

4. Interim Efficacy Results, MK-4482-002, Part 2

At baseline, in all randomized participants, the median age was 41 years (range:18 to 88); 14% of participants were over 60 years of age and 3% were 75 years of age or older; 52% of participants were male; 52% were White, 6% Black or African American, 2% Asian, 58% Hispanic or Latino. Only 5% of participants were enrolled from sites in North America; the majority of participants were enrolled from sites in Latin America (56%) and Europe (23%).

Forty-nine percent of participants received MOV or placebo within 3 days of COVID-19 symptom onset. The most common risk factors were obesity (77%), over 60 years of age (14%), and diabetes (14%). The most common SARS-CoV-2 genotype clades at baseline were 21A/I/J (Delta; 46.1%), 21H (Mu; 26.3%), and 20J (Gamma; 14.5%), based on the SARS-CoV-2 viral sequence data that were available for 74% (574/775) of trial participants. Overall, baseline demographic and disease characteristics were well balanced between the treatment arms (Table 3).

Table 3. Demographics and Baseline Characteristics in All Randomized Participants, MK-4482-002, Part 2, IA Population

Parameter	MK-4482 800 mg (N=387) n (%)	Placebo (N=388) n (%)
Female	200 (52)	171 (44)
Race/ethnicity		
American Indian or Alaska Native	20 (5)	9 (2)
Asian	7 (2)	11 (3)
Black or African American	27 (7)	20 (5)
White	194 (50)	209 (54)
Multiple	139 (36)	139 (36)
Hispanic Or Latino	224 (58)	228 (59)
Geographic region		
North America	15 (4)	22 (6)
Latin America	216 (56)	214 (55)
Europe	89 (23)	90 (23)
Asia Pacific	5 (1)	6 (2)
Africa	62 (16)	56 (14)
Age (years), median (min, max)	41 (18, 87)	43 (18, 88)
Age ≥65 years	31 (8)	37 (10)
Age ≥75 years	7 (2)	13 (3)
At least one risk factor	385 (100)	384 (99)
Age >60 years	51 (13)	55 (14)
Active cancer	6 (2)	11 (3)
Chronic kidney disease	14 (4)	20 (5)
Chronic obstructive pulmonary disease	7 (2)	22 (6)
Obesity (BMI ≥30)	306 (79)	287 (74)
Serious heart condition	42 (11)	36 (9)
Diabetes mellitus	48 (12)	57 (15)
Time from COVID-19 symptom onset ≤3 days	188 (49)	184 (47)
Mild baseline COVID-19 severity	222 (57)	212 (55)
Moderate baseline COVID-19 severity	162 (42)	174 (45)
Severe baseline COVID-19 severity	2 (1)	0 (0)
Positive SARS-CoV-2 baseline antibody	71 (18)	70 (18)
Negative SARS-CoV-2 baseline antibody	299 (77)	288 (74)
Unknown SARS-CoV-2 baseline antibody[a]	17 (4)	30 (8)

Parameter	MK-4482 800 mg (N=387) n (%)	Placebo (N=388) n (%)
SARS-CoV-2 viral clade at baseline		
Participants with evaluable sequence data available[b]	281 (72.6)	288 (74.2)
19B	1 (0.4)	1 (0.3)
20A	3 (1.1)	2 (0.7)
20B	4 (1.4)	4 (1.4)
20C	0 (0)	1 (0.3)
20D	2 (0.7)	1 (0.3)
20H (Beta)	5 (1.8)	6 (2.1)
20I (Alpha)	12 (4.3)	9 (3.1)
20J (Gamma)	35 (12.5)	48 (16.7)
21A (Delta)	99 (35.2)	95 (33.0)
21G (Lambda)	13 (4.6)	7 (2.4)
21H (Mu)	70 (24.9)	81 (28.1)
21I (Delta)	7 (2.5)	3 (1.0)
21J (Delta)	30 (10.7)	30 (10.4)
Sequence data not available or could not be classified	106 (27.4)	100 (25.8)
SARS-CoV-2 RNA at baseline in nasopharyngeal sample (qualitative assay)		
Detectable	332 (85.8)	331 (85.3)
Undetectable	28 (7.2)	29 (7.5)
Unknown [b]	27 (7.0)	28 (7.2)

Source: Sponsor's response to FDA November 5, 2021, information request, Table 1
[a] Missing data, invalid sample, tests not done, or results reported as "Unknown" are categorized as Unknown, excluding those that could not be classified.
[b] Percentage is based on the number of participants with evaluable sequence data available
Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; IA, interim analysis; N, total number of participants; n, number of participants with a given characteristic; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Primary Efficacy Analysis

In the modified intent-to-treat (mITT) population, which was comprised of almost all randomized participants (98.3%, 762/775), the primary endpoint, percentage of participants who were hospitalized for ≥24 hours for acute care or died from any cause through Day 29, in the MOV group, (7.3%) was statistically significantly lower than in the placebo group (14.1%); treatment difference (MOV – placebo) -6.8% with 95% confidence interval (CI) of (-11.3%, -2.4%). The treatment effect was driven by the subcomponent of hospitalization ≥24 hours for acute care of any disease, as it constituted the preponderance of the clinical events and all participants who died by Day 29 were hospitalized prior to death.

All eight deaths by Day 29 occurred in the placebo arm. The relative risk reduction of MOV compared to placebo was 48% (95% CI: 20%, 67%) based on the Cochran-Mantel-Haenszel method stratified by time of COVID-19 symptom onset (≤3 days versus >3 [4 to 5] days). A supportive analysis of COVID-related (as assessed by the investigator) hospitalizations or deaths was consistent with the results of the primary analysis (risk difference: -6.8% [95% CI: -11.1, -2.6]; Table 4).

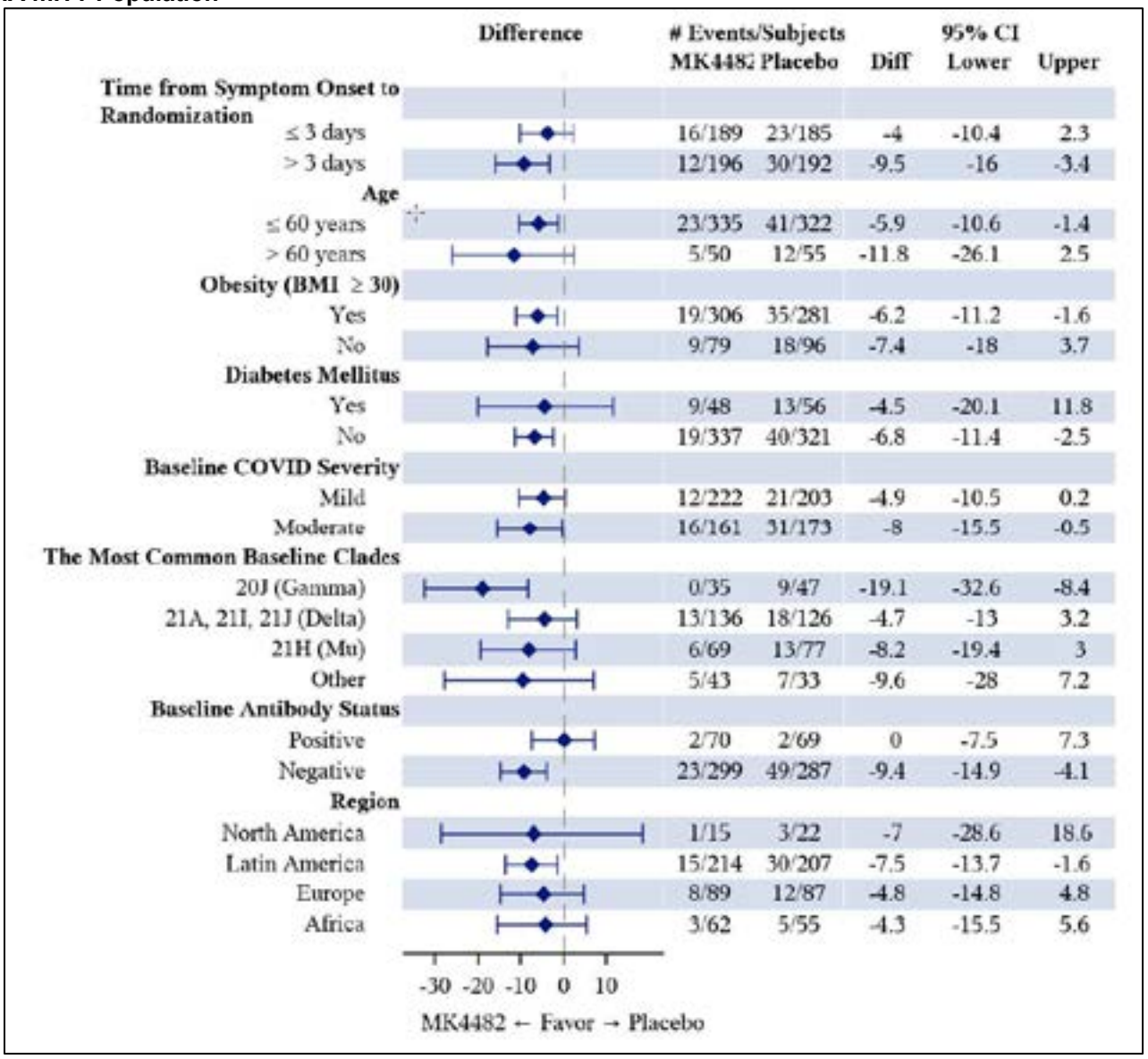
Table 4. Incidence of COVID-Related Hospitalization or Death Through Day 29, IA mITT Population

Parameter	MOV (N=385) n (%)	Placebo (N=377) n (%)	Risk Difference[a] (95% CI)	1-Sided P-Value
All-cause hospitalization or death through Day 29[b]	28 (7.3%)	53 (14.1%)	-6.8 (-11.3, -2.4)	0.0012
Hospitalization	28 (7.3%)	52 (13.8%)		
Death	0 (0%)	8 (2.1%)		
Unknown[c]	0 (0%)	1 (0.3%)		

Source: Modified from EUA request, Tables 74 and 75
[a] Risk difference of molnupiravir-placebo based on Miettinen and Nurminen method stratified by time of COVID-19 symptom onset (≤3 days vs. >3 [4 to 5] days).
[b] Defined as ≥24 hours of acute care in a hospital or an acute care facility (e.g., emergency room).
[c] Participants with unknown status at Day 29 are counted as having an outcome of all-cause hospitalization or death in the efficacy analysis.
Note: All participants who died through Day 29 were hospitalized prior to death. Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.
The 1-sided p-value boundary for early efficacy is 0.0092 using the Gamma family spending function with y = -1 based on the final evaluable sample size at the interim analysis (n=762 in the mITT population out of a total of 1550 planned;)
Abbreviations: CI, confidence interval; COVID, coronavirus disease; IA, interim analysis; mITT, modified intent-to-treat; N, total number of participants; n, number of participants who experienced all-cause hospitalization or death through Day 29; MOV, molnupiravir; EUA, Emergency Use Authorization

The exploratory subgroup analyses findings by various baseline characteristics, shown in Figure 2 below, were generally consistent with the primary analysis, with exception of the baseline antibody status, which will be discussed in Section VIII.7.

Figure 2. Incidence of Hospitalization or Death Through Day 29 by Subgroup, MK-4482-002, Part 2, IA mITT Population



Source: Efficacy amendment received December 13, 2021, Figure 1
Cis are based on Miettinen & Nurminen method.
Time from symptom onset to randomization is based on the value of the stratification factor collected at randomization.
The findings of these subgroup analyses are considered exploratory.
Abbreviations: BMI, body mass index; CI, confidence interval; COVID, coronavirus disease; IA, interim analysis; mITT, modified intent-to-treat

Analysis of SARS-CoV-2 Variants

The subgroup analyses of the primary endpoint by SARS-CoV-2 variants/clades need to be interpreted carefully because there were limited sequence analysis data available (68% [527/775] of trial participants) and should be further evaluated once additional data are available. The subgroup analyses by baseline variant/clade are presented in Figure 2 above.

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Secondary Efficacy Analysis

Secondary endpoints included in the trial were:

- Time to sustained resolution or improvement of each targeted self-reported sign/symptom present at randomization (i.e., Day 1), defined as the number of days from randomization to the first of 3 consecutive days when resolution or improvement is demonstrated for each targeted self-reported sign/symptom. Participants who meet criteria for sustained resolution or improvement after 3 consecutive days must not relapse by Day 29 (i.e., have 2 or more consecutive days of each self-reported sign/symptom returning to the baseline severity or worse than baseline severity after the criteria for sustained resolution or improvement are met). The 3 consecutive days of resolution or improvement can be out of the Day 29 range as long as the first day is on or before Day 29. Resolution or improvement is defined as follows:
  - A symptom reported at randomization as Mild and is subsequently reported as None
  - A symptom reported at randomization as Moderate and is subsequently reported as Mild or None
  - A symptom reported at randomization as Severe and is subsequently reported as Moderate, Mild, or None
  - A symptom reported at randomization as Yes and is subsequently reported as No
- Time to progression of the targeted self-reported signs/symptoms present at randomization, defined as the number of days from randomization to the first of 2 consecutive days when the targeted self-reported signs/symptoms worsen. The 2 consecutive days of worsening can be out of the Day 29 range as long as the first day is on or before Day 29. Worsening is defined as follows:
  - A symptom reported at randomization as None or No and is subsequently reported as Mild/Moderate/Severe or Yes, respectively
  - A symptom reported as Mild at randomization and is subsequently reported as Moderate or Severe
  - A symptom reported as Moderate at randomization and is subsequently reported as Severe
- Odds of a more favorable response on the ordinal WHO 11-point for Clinical Progression Scale on Day 3, end-of-treatment (EOT), Day 10, Day 15, and Day 29. This scale provides a measure of illness severity across a range from 0 (not infected) to 10 (dead).

Analyses of the time to sustained resolution or improvement of each targeted self-reported sign/symptom present at randomization will not be discussed because, at this time, we are not able to assess the durability of symptom improvement of resolution; characterize any symptom worsening after resolution or improvement in terms of frequency, magnitude, and timing; and quantify the amount of missing symptom data. In addition, we do not plan to include analyses for this endpoint in the Fact Sheet for Health Care Providers.

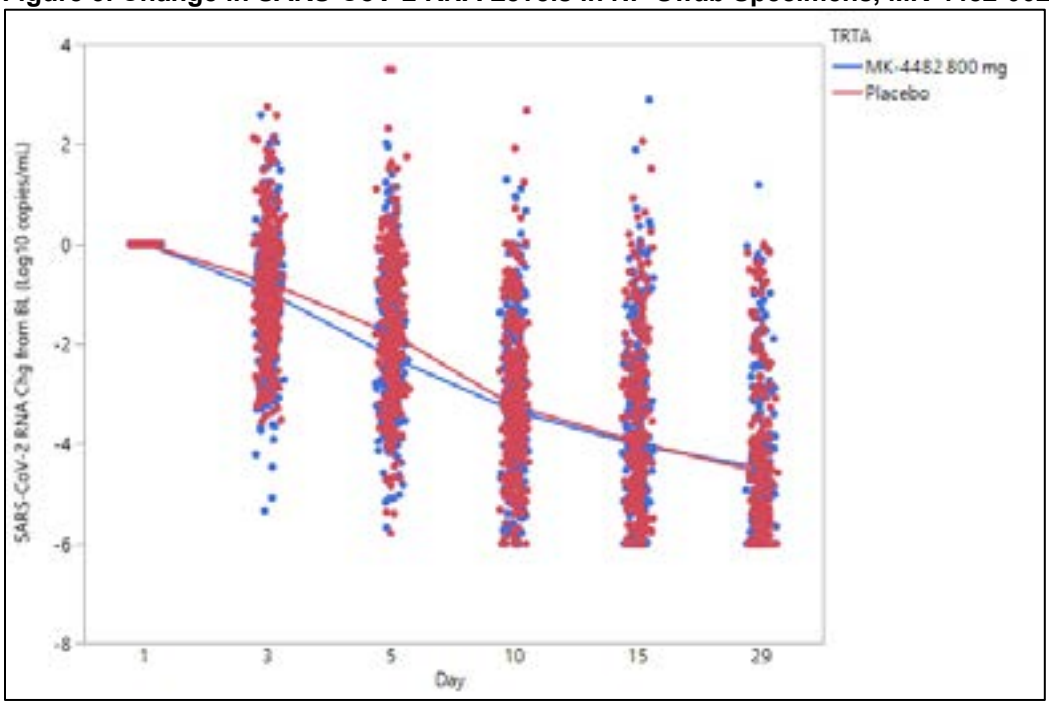
Analyses of the odds of a more favorable response on the ordinal WHO-11-point scale are not included, because the prespecified analyses were not included in the EUA request and the clinical meaningfulness of the analysis results is unclear. However, the primary endpoint includes progression to the categories of hospitalization and death included in the WHO-11-point scale.

Virologic Endpoint Analysis

Viral RNA levels in nasopharyngeal (NP) swab specimens were quantified in a central laboratory using the Q2 SARS-CoV-2 assay, which has a reported lower limit of quantification of 500 copies/mL and upper limit of quantification of 500,000,000 copies/mL.

MOV treatment was associated with modestly larger declines in SARS-CoV-2 RNA levels in NP swab samples at Day 3 and Day 5, with differences relative to placebo treatment in median SARS-CoV-2 declines from baseline of ~0.2 $\log_{10}$ copies/mL and ~0.5 $\log_{10}$ copies/mL, respectively ($p<0.05$, Wilcoxon test) (Figure 3). Of note, based on the mechanism of action of MOV related to viral genome mutagenesis, changes in SARS-CoV-2 RNA levels over time may underestimate the effect of MOV, as it does not have a direct impact on viral RNA production but rather is expected to lead to the accumulation of nucleotide mutations in viral RNA genomes leading to reduced replicative fitness and infectivity.

Figure 3. Change in SARS-CoV-2 RNA Levels in NP Swab Specimens, MK-4482-002, Part 2



Source: FDA analyses
Trendlines illustrate median values
Abbreviations: NP, nasopharyngeal; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Declines in viral RNA shedding were generally similar or slightly greater in MOV-treated participants relative to placebo-treated participants across key subgroups, including different SARS-CoV-2 variants, different times from symptom onset (> or ≤3 days), and mild versus moderate baseline disease severity.

5. Full Population Efficacy Results, MK-4482-002, Part 2

At baseline, in all randomized participants, the median age was 43 years (range: 18 to 90 years); 17% of participants were over 60 years of age and 3% were 75 years of age or older; 49% of participants were male; 57% were white, 5% black or African American, 3% Asian, and 50% Hispanic or Latino. Only 6% of participants were enrolled from sites in North America; the majority of participants were enrolled from sites in Latin America (46%) and Europe (33%). Forty-seven percent of participants received MOV or placebo within 3 days of COVID-19 symptom onset. The most common risk factors were obesity (74%), over 60 years of age (17%), and diabetes (16%). The most common SARS-CoV-2 genotype clades at baseline were 21A/I/J (Delta; 58.4%), 21H (Mu; 20.6%), and 20J (Gamma; 10.8%), based on the SARS-CoV-2 viral sequence data that were available for 55% (787/1433) of trial participants. Overall, baseline demographic and disease characteristics were well balanced between the treatment arms (Table 5).

Table 5. Demographics and Baseline Characteristics in All Randomized Participants, MK-4482-002, Part 2, Full Population

Parameter	MK-4482 800 mg (N=716) n (%)	Placebo (N=717) n (%)
Female	384 (53.6)	351 (49.0)
Race/ethnicity		
American Indian or Alaska Native	60 (8.4)	44 (6.1)
Asian	26 (3.6)	23 (3.2)
Black or African American	40 (5.6)	35 (4.9)
White	400 (55.9)	413 (57.6)
Multiple	190 (26.5)	202 (28.2)
Hispanic or Latino	355 (49.6)	356 (49.7)
Geographic region		
North America	45 (6.3)	46 (6.4)
Latin America	331 (46.2)	330 (46.0)
Europe	230 (32.1)	239 (33.3)
Asia Pacific	20 (2.8)	17 (2.4)
Africa	90 (12.6)	85 (11.9)
Age (years), median (min, max)	42 (18–90)	44 (18-88)
Age ≥65 years	73 (10.2)	82 (11.4)
Age ≥75 years	24 (3.4)	23 (3.2)
At least one risk factor	712 (99.4)	712 (99.3)
Age >60 years	119 (16.6)	127 (17.7)
Active cancer	13 (1.8)	16 (2.2)
Chronic kidney disease	38 (5.3)	46 (6.4)
Chronic obstructive pulmonary disease	22 (3.1)	35 (4.9)
Obesity (BMI ≥30)	538 (75.1)	518 (72.2)
Serious heart condition	86 (12.0)	81 (11.3)
Diabetes mellitus	107 (14.9)	121 (16.9)
Time from COVID-19 symptom onset ≤3 days	342 (47.8)	342 (47.7)
Mild baseline COVID-19 severity	395 (55.2)	390 (54.4)
Moderate baseline COVID-19 severity	315 (44.0)	323 (45.0)
Severe baseline COVID-19 severity	3 (0.4)	1 (0.1)
Unknown baseline COVID-19 severity	3 (0.4)	3 (0.4)
Positive SARS-CoV-2 baseline antibody	137 (19.1)	147 (20.5)
Negative SARS-CoV-2 baseline antibody	541 (75.6)	521 (72.7)
Unknown SARS-CoV-2 baseline antibody[a]	38 (5.3)	49 (6.8)

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Parameter	MK-4482 800 mg (N=716) n (%)	Placebo (N=717) n (%)
SARS-CoV-2 viral clade at baseline		
Participants with evaluable sequence data available[b]	394 (55.0)	393 (54.8)
19B	3 (0.8)	3 (0.8)
20A	4 (1.0)	3 (0.8)
20B	4 (1.0)	4 (1.0)
20C	0 (0.0)	1 (0.3)
20D	2 (0.5)	3 (0.8)
20H (Beta)	5 (1.3)	6 (1.5)
20I (Alpha)	12 (3.0)	9 (2.3)
20J (Gamma)	37 (9.4)	48 (12.2)
21G (Lambda)	14 (3.6)	7 (1.8)
21H (Mu)	76 (19.3)	86 (21.9)
21A (Delta), 21I (Delta), 21J (Delta)	237 (60.2)	223 (56.7)
Sequence data not available or could not be classified	322 (45.0)	324 (45.2)
SARS-CoV-2 RNA at baseline in nasopharyngeal sample (qualitative assay)		
Detectable	615 (85.9)	615 (85.8)
Undetectable	54 (7.5)	51 (7.1)
Unknown[a]	47 (6.6)	51 (7.1)

Source: Modified from the Sponsor's December 3, 2021, statistical report, Tables 3 and 4
[a] Missing data, invalid sample, tests not done, or results reported as "Unknown" are categorized as Unknown.
[b] Percentage is based on the number of participants with evaluable sequence data available, excluding those that could not be classified.
Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; N, total number of participants; n, number of participants with a given characteristic; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Primary Efficacy Analysis

In the mITT population, which was comprised of almost all randomized participants (98.3%, 1408/1433), the primary endpoint, percentage of participants who were hospitalized for ≥24 hours for acute care or died from any cause through Day 29 was 6.8% for the MOV group and 9.7% for the placebo group; adjusted treatment difference (MOV – placebo) = -3.0% with 95% CI of (-5.9%, -0.1%). The treatment effect was driven by the subcomponent of hospitalization ≥24 hours for acute care of any disease, as it constituted the preponderance of the clinical events and all participants, who died by Day 29 were hospitalized prior to death. Nine deaths by Day 29 occurred in the placebo group compared to only one death in the MOV group. The relative risk reduction of MOV compared to placebo was 30% (95% CI: 1%, 51%) based on the Cochran-Mantel-Haenszel method stratified by time of COVID-19 symptom onset (≤3 days versus >3 [4 to 5] days). A supportive analysis of COVID-related (as assessed by the investigator) hospitalizations or deaths was consistent with the results of the primary analysis (risk difference: -2.8% [95% CI: -5.7, -0.0]; Table 6).

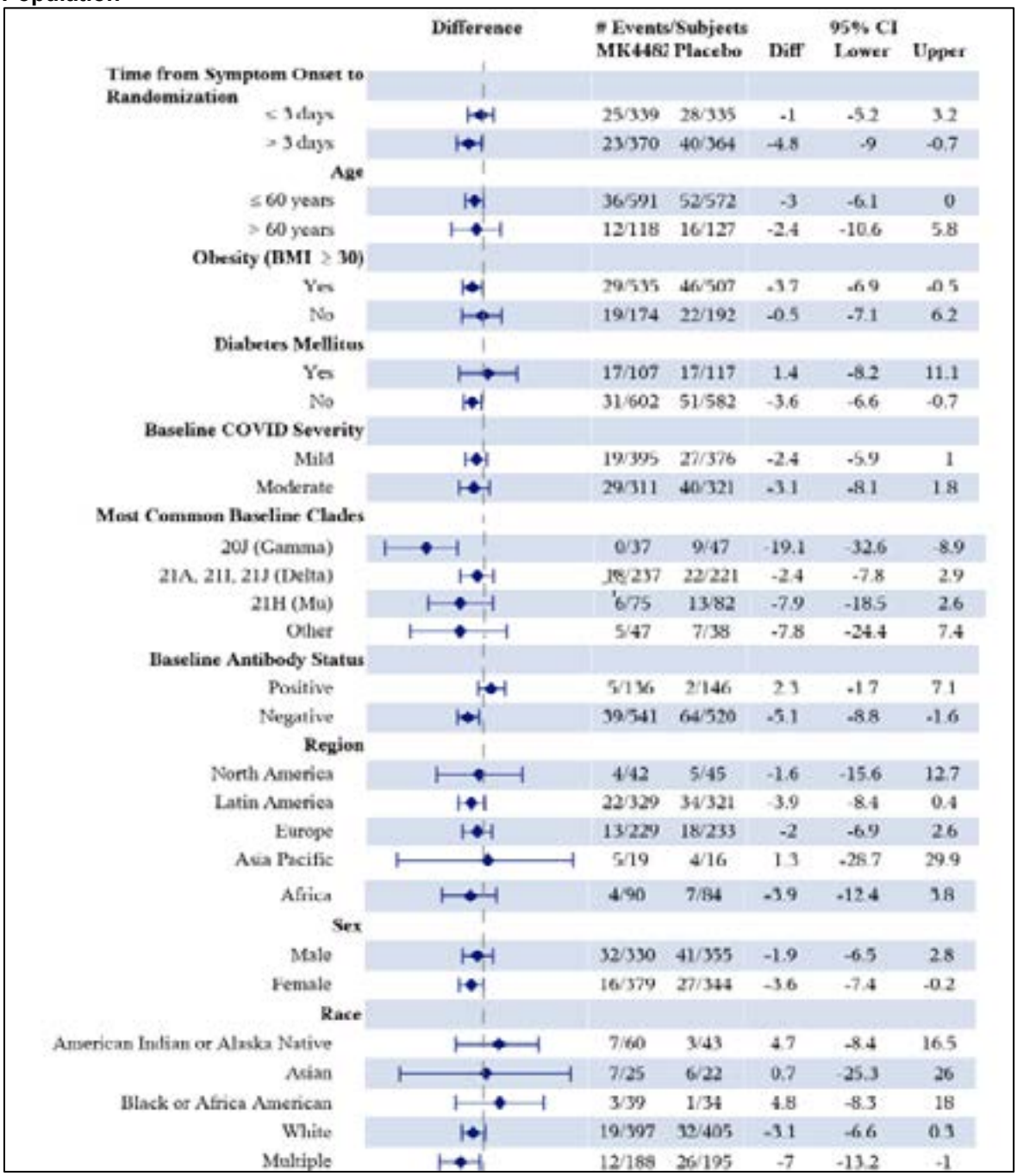
Table 6. Incidence of COVID-Related Hospitalization or Death Through Day 29, MK-4482-002, Part 2, Full mITT Population

Parameter	MOV (N=709) n (%)	Placebo (N=699) n (%)	Risk Difference[a] (95% CI)
All-cause hospitalization or death through Day 29[b]	48 (6.8%)	68 (9.7%)	-3.0 (-5.9, -0.1)
Hospitalization	48 (6.8%)	67 (9.6%)	
Death	1 (0.1%)	9 (1.3%)	
Unknown[c]	0 (0%)	1 (0.1%)	

Source: Modified from Efficacy information amendment received December 3, 2021, Tables 6 and 9
[a] Adjusted differences, the corresponding confidence intervals are based on Miettinen & Nurminen method stratified by time from symptom onset (≤3 days vs. >3 [4 to 5] days)
[b] Defined as ≥24 hours of acute care in a hospital or an acute care facility (e.g., emergency room).
[c] Participants with unknown status at Day 29 are counted as having an outcome of all-cause hospitalization or death in the efficacy analysis.
Note: All participants who died through Day 29 were hospitalized prior to death.
Abbreviations: CI, confidence interval; COVID, coronavirus disease; mITT, modified intent-to-treat; N, total number of participants; n, number of participants who experienced all-cause hospitalization or death through Day 29; MOV, molnupiravir

The exploratory subgroup analyses findings by various baseline characteristics, shown in Figure 4, were generally consistent with the primary analysis, with exception of the baseline antibody status and diabetes mellitus.

Figure 4. Incidence of Hospitalization or Death Through Day 29, MK-4482-002, Part 2, Full mITT Population



Source: Modified from December 3, 2021, efficacy amendment, Figure 2
The findings of these subgroup analyses are considered exploratory.
Abbreviations: BMI, body mass index; CI, confidence interval; COVID, coronavirus disease; mITT, modified intent-to-treat

As described above, the majority of participants enrolled in MK-4482-002 Part 2 were enrolled from sites in Latin America (46%) and Europe (33%) (predominantly from Ukraine and Russia). Only 6% of the population was enrolled from sites in North America (one participant was enrolled from Canada and the remaining North American participants were all enrolled from the United States).

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A subgroup analysis of the primary endpoint among those enrolled from sites in the United States revealed that the rate of hospitalization or death was similar across arms: 9.8% and 11.1% in MOV- and placebo-treated participants, respectively (risk difference, 95% CI: -1.4 (-15.5, 13.2)). Note, the number of participants enrolled in the United States is small and the subgroup analysis should be interpreted cautiously. Please see Section VIII.7.2 for additional discussion regarding obtaining additional data from the United States.

6. Hospitalized Treatment Trial, MK-4482-001

MK-4482-001 was a Phase 2/3 trial in hospitalized adults with laboratory-confirmed SARS-CoV-2 infection and symptom onset within 10 days prior to randomization. The primary efficacy endpoint was the rate of sustained recovery through Day 29. The Phase 2 part of MK-4482-001 was designed as a dose-ranging study in which 304 participants were randomized 1:1:1:1 to receive MOV 200, 400, or 800 mg or placebo Q12H for 5 days. Randomization was stratified according to time from symptom onset prior to the day of randomization (≤5 days, >5 days), age (≤60 years, >60 years), and remdesivir use for treatment of the index diagnosis of COVID-19 prior to or at the time of randomization (yes, no). Sponsor-designated standard of care treatment of COVID-19, which included remdesivir, systemic corticosteroids, and convalescent plasma, was permitted.

The primary endpoint was time-to-sustained recovery, with sustained recovery defined as either:

- Participant is alive and not hospitalized through Day 29 (including those rehospitalized and discharged again before Day 29). Includes those discharged to home, home with nursing care, a rehabilitation facility, a long-term care facility, or a nonhospital intermediate care facility.

  OR

- Participant is alive and medically ready for discharge through Day 29 as determined by the investigator. Includes those hospitalized or rehospitalized participants who no longer require ongoing medical care but remain hospitalized for infection-control reasons or due to delay in identifying living accommodation outside the hospital.

The primary analysis was conducted in the mITT population, which consisted of participants who received at least one dose of study medication. Failure to recover was censored at Day 29. Death before Day 29, including death following a prior recovery, will be censored at Day 29 to eliminate any bias that would be introduced by censoring at time of death. Lost to follow-up before Day 29, regardless of prior recovery, will not be considered a sustained recovery and will be censored at the day of last contact. Withdrawal (i.e., discontinuation from the study for reasons other than death or lost to follow-up) before Day 29, regardless of prior recovery, will not be considered a sustained recovery and will be censored at the day of discontinuation.

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The rate of sustained recovery was similar across treatment groups (Table 7).

Table 7. Time-to-Sustained Recovery, MK-4482-001, mITT Population

Treatment	N	Number of Events (%)	Median Time to Recovery[a] (Days) (95% CI)	Recovery Rate at Day 29 in %[a] (95% CI)
MK-4482 200 mg	73	56 (76.7)	9.0 (7.0, 10.0)	81.5 (71.4, 89.7)
MK-4482 400 mg	73	56 (76.7)	9.0 (8.0, 10.0)	85.2 (75.4, 92.6)
MK-4482 800 mg	72	59 (81.9)	9.0 (8.0, 11.0)	84.3 (74.8, 91.6)
Placebo	75	61 (81.3)	9.0 (8.0, 11.0)	84.7 (75.5, 91.9)

Source: Clinical study report, Table 11-1
[a] From product-limit (Kaplan-Meier) method for censored data
Abbreviations: CI, confidence interval; mITT, modified intent-to-treat; N, total number of participants

For the secondary endpoint of all-cause mortality through Day 29, a numerically higher proportion of participants died in each of the MOV groups (MOV 200 mg [four participants, 5.5%], MOV 400 mg [eight participants, 11.0%], and MOV 800 mg [three participants, 4.2%]) compared with placebo [two participants, 2.7%]). The prespecified efficacy analyses considered participants with unknown survival status through Day 29 to have died.

At the time of data unblinding, survival status was unknown for four participants in the MOV 800 mg group and one participant in the placebo group. Subsequent to data unblinding, the Sponsor determined that two participants in the MOV 800 mg arm and one participant in the placebo arm whose survival status was unknown were actually alive. Sensitivity analyses that accounted for this later finding still showed a numerically higher proportion of participants in each of the MOV groups to have died by Day 29 compared to placebo. In addition, sensitivity analyses that did not apply the missing data rule also had similar findings, additional details on the mortality imbalance can be found in Section IX.3.9.

The Sponsor determined that the Part 1 (Phase 2) results from both MK-4482-002 and MK-4482-001 indicated that treatment with MOV is likely to have a greater benefit if initiated earlier in the disease course during peak viral replication (≤5 days of symptom onset) compared with initiation during the later stages of disease when the host inflammatory response predominates. As patients who are hospitalized due to COVID-19 are likely to be later in the course of disease and early initiation of MOV treatment may be difficult in this population, the Sponsor decided to not initiate enrollment in Phase 3 (Part 2) of MK-4482-001. Based on the observed mortality imbalance in the MOV groups compared to placebo, MOV will not be authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19. Benefit of treatment with MOV has not been observed in participants when treatment was initiated after hospitalization due COVID-19.

7. Key Review Issues Relevant to Evaluation of Potential Benefit

7.1. Overall Key Review Issue Relevant to the Evaluation of Benefit: Modest Treatment Benefit and Implications for Patient Selection

The overall key review issues relevant to the evaluation of potential benefit are (1) modest treatment benefit and (2) implications of this modest treatment benefit for patient selection.

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Based on the totality of the available data, considering the modest treatment benefit and the numerous risks outline in Section IX.4, the review team recommends that MOV be authorized for second line use only. Specifically, the authorized use statement for MOV should before the treatment of mild-to-moderate COVID-19 in adults

- 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 (refer to CDC website for additional details), and
- for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.

Section VIII.7.2 explores potential explanations for a decrease in efficacy that was observed in the second half of the pivotal Phase 3 trial, MK-4482-002, compared to the first half of the trial. Section VIII.7.3 describes several important patient selection considerations to identify patients in whom the benefits of MOV are most likely to outweigh the risks of MOV. The information and discussion provided herein will provide the rationale for the previously noted authorized use statement.

7.2. Key Review Issue #1: Modest Treatment Benefit in MK-4482-002

Background

As previously described, MK-4482-002 was a Phase 2/3 clinical trial in outpatients with mild-to-moderate COVID-19. The data to support the EUA request come from the Phase 3/Part 2 portion of this trial. In the original EUA request submission, MOV was found to be associated with an adjusted risk difference (MOV – placebo) of -6.8% (95% CI: 2.4%, 11.3%; 2-sided p=0.0024) corresponding to a 48% relative risk reduction in the incidence of hospitalization or death through Day 29 among high-risk outpatients with mild-to-moderate COVID-19. This original analysis was based on an interim analysis conducted when 50% of the planned MK-4482-002, Part 2 participants reached study day 29.

Based on the findings of this interim analysis, enrollment in the trial was stopped, at which time a total of 1433 participants had been enrolled (participants who had not reached Day 29 at the time of the interim analysis remained blinded). Several weeks into the review of this EUA request, the remaining randomized participants reached Day 29, and on November 22, 2021, the Agency became aware of topline safety and efficacy results from the full MK-4482-002, Part 2 population. In the full population, MOV was associated with an adjusted risk difference (MOV – placebo) of -3.0% (95% CI: -5.9, -0.1); corresponding to a 30% relative risk reduction in hospitalization or death through Day 29.

Assessment

An analysis was conducted for the primary efficacy endpoint in the interim analysis population, the post-interim analysis population (defined as those participants who had not reached Day 29 by the interim analysis data cutoff) and the full population and is presented in Table 8. In the first half of the trial (i.e., the interim analysis population), MOV was associated with a 48% relative risk reduction in hospitalization or death through Day 29. Conversely, in the second half of the trial (i.e., the post-interim analysis population), the observed rate of hospitalization or death through Day 29 was higher in the MOV arm (6.2%) than the placebo arm (4.7%).

Table 8. Incidence of All Cause Hospitalization or Death Through Day 29 by Analysis Population, MK-4482-002, Part 2

	Interim Analysis Population Enrollment Dates: 5/7/2021–08/5/2021		Post-Interim Analysis Population[a] Enrollment Dates: 8/6/2021–10/2/2021		Full Population Enrollment Dates: 5/7/2021–10/2/2021	
Parameter	**MOV**	**PBO**	**MOV**	**PBO**	**MOV**	**PBO**
Hospitalization or death by Day 29	28/385 (7.3%)	53/377 (14.1%)	20/324 (6.2%)	15/322 (4.7%)	48/709 (6.8%)	68/699 (9.7%)
Death by Day 29	0 (0%)	8/377 (2.1%)	1/324 (<1%)	1/322 (<1%)	1/709 (<1%)	9/699 (1.3%)

Source: EUA request and Efficacy Information Amendment dated December 3, 2021.
[a] The Post-Interim Analysis Population includes those participants who had not reached Day 29 by the interim analysis data cutoff date of September 18, 2021.
Abbreviations: MOV, molnupiravir; PBO placebo

Review of Table 8 reveals the rate of hospitalization or death remained relatively constant in the MOV arm over the course of the trial. However, the rate of hospitalization or death fluctuated considerably in the placebo arm, from 14.1% in the first half of the trial to 4.7% in the second half of the trial. The reason for this decline in the incidence of hospitalization of death in the placebo arm over time (without a corresponding decline in the MOV arm) is not immediately apparent.

Table 9 below compares the baseline characteristics among the interim analysis and post-interim analysis populations. While there are no apparent major differences in the populations, the following shifts in baseline characteristics are noted; in the post-interim analysis population, a larger proportion of female participants, white participants, participants >60 years of age, and participants with a positive baseline SARS-CoV-2 antibody status and a smaller proportion of Hispanic or Latino participants were noted.

In addition, we observed a shift in the regions from which the participants were enrolled. Specifically, in the post-interim analysis population, a smaller proportion of participants were enrolled from sites in Latin America and a larger proportion were enrolled from sites in Europe (predominantly eastern Europe). However, according to subgroup analyses in the full randomized population (see Figure 4), treatment effect was similar across sexes, among participants ≤60 years and >60 years of age, Hispanic and non-Hispanic participants, and participants from Latin America and Europe, so none of these shifts are anticipated to have reduced efficacy in the second half of the trial. The treatment effect of MOV in white participants was greater than that in American Indian or Alaskan Native, Asian, and Black or African American races, making the increase in the proportion of white participants enrolled unlikely to have accounted for the decreased efficacy observed in the second half of the trial.

Baseline SARS-CoV-2 seropositivity was associated with decreased treatment effect and will be discussed later in this section. It is possible that the larger proportion of seropositive participants in the second half of the trial could have contributed to the observed decreased treatment effect. However, the increase in seropositive participants was modest making this unlikely to be the sole reason for the decreased efficacy in the second half of the trial.

Table 9. Baseline Characteristics of the Interim Analysis Population and the Post-Interim Analysis Population, MK-4482-002, Part 2

	Interim Analysis Population		Post-Interim Analysis Population	
Parameter	**MK-4482 800 mg (N=387) n (%)**	**Placebo (N=388) n (%)**	**MK-4482 800 mg (N=329) n (%)**	**Placebo (N=329) n (%)**
Female	200 (52)	171 (44)	184 (56)	180 (55)
Race/ethnicity				
American Indian or Alaska Native	20 (5)	9 (2)	40 (12)	35 (11)
Asian	7 (2)	11 (3)	19 (6)	12 (4)
Black or African American	27 (7)	20 (5)	13 (4)	15 (5)
White	194 (50)	209 (54)	206 (63)	204 (62)
Multiple	139 (36)	139 (36)	51 (16)	63 (19)
Hispanic or Latino	224 (58)	228 (59)	131 (40)	128 (39)
Geographic region				
North America	15 (4)	22 (6)	30 (9)	24 (7)
Latin America	216 (56)	214 (55)	115 (35)	116 (35)
Europe	89 (23)	90 (23)	141 (43)	149 (45)
Asia Pacific	5 (1)	6 (2)	15 (5)	11 (3)
Africa	62 (16)	56 (14)	28 (9)	29 (9)
Age (years), median (min, max)	41 (18, 87)	43 (18, 88)	45 (18, 90)	46 (18, 88)
Age ≥65 years	31 (8)	37 (10)	42 (13)	45 (14)
Age ≥75 years	7 (2)	13 (3)	17 (5)	10 (3)
At least one risk factor	385 (100)	384 (99)	327 (99)	328 (100)
Age >60 years	51 (13)	55 (14)	68 (21)	72 (22)
Active cancer	6 (2)	11 (3)	7 (2)	5 (2)
Chronic kidney disease	14 (4)	20 (5)	24 (7)	26 (8)
Chronic obstructive Pulmonary disease	7 (2)	22 (6)	15 (5)	13 (4)
Obesity (BMI ≥30)	306 (79)	287 (74)	232 (71)	231 (70)
Serious heart condition	42 (11)	36 (9)	44 (13)	44 (13)
Diabetes mellitus	48 (12)	57 (15)	58 (18)	64 (19)
Time from COVID-19 symptom onset ≤3 days	188 (49)	184 (47)	151 (46)	152 (46)
Mild baseline COVID-19 severity	222 (57)	212 (55)	172 (52)	178 (54)
Moderate baseline COVID-19 severity	162 (42)	174 (45)	153 (47)	149 (45)
Severe baseline COVID-19 severity	2 (1)	0 (0)	2 (1)	1 (<1)
Positive SARS-CoV-2 baseline antibody	71 (18)	70 (18)	65 (20)	77 (23)

Parameter	Interim Analysis Population MK-4482 800 mg (N=387) n (%)	Interim Analysis Population Placebo (N=388) n (%)	Post-Interim Analysis Population MK-4482 800 mg (N=329) n (%)	Post-Interim Analysis Population Placebo (N=329) n (%)
Negative SARS-CoV-2 baseline antibody	299 (77)	288 (74)	240 (73)	232 (71)
Unknown SARS-CoV-2 baseline antibody [a]	17 (4)	30 (8)	24 (7)	20 (6)

Source: Sponsor's response to FDA November 5, 2021, information request (Table 1) and Efficacy Information Amendment dated December 6, 2021 (Tables 1 and 2).
[a] Missing data, invalid sample, tests not done, or results reported as "Unknown" are categorized as Unknown.
Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 19; N, total number of participants; n, number of participants with a given characteristic; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Changes in baseline viral clade/variant over the course of the trial were also explored. A summary of baseline viral clade based on available sequencing data from nasopharyngeal samples is presented in Table 10. Based on a data cutoff of November 19, 2021, evaluable sequencing data were available from 73% of the interim analysis population and approximately 33% of the post-interim analysis population. Among participants with evaluable sequencing data at the time of this review, the proportion of participants enrolled who were infected with the Delta variant (combining 21A, 21I, and 21J) increased from 46% (264/569) in the first half of the trial to 90% (196/218) in the second half of the trial.

Table 10. Baseline Viral Clade in the Interim Analysis Population and the Post-Interim Analysis Population, All Randomized Participants, MK-4482-002, Part 2

Clade Designation[a]	Interim Analysis Population MK-4482 800 mg (N=387) n (%)[b]	Interim Analysis Population Placebo (N=388) n (%)[b]	Post-Interim Analysis Population MK-4482 800 mg (N=329) n (%)[b]	Post-Interim Analysis Population Placebo (N=329) n (%)[b]
No evaluable sequence data available[c]	106	100	216	224
Evaluable sequence data available	281	288	113	105
20H (Beta)	5 (2)	6 (2)	0	0
20I (Alpha)	12 (4)	9 (3)	0	0
20J (Gamma)	35 (12)	48 (17)	2 (2)	0
21G (Lambda)	13 (5)	7 (2)	1 (1)	0
21H (Mu)	70 (25)	81 (28)	6 (5)	5 (5)
21A, 21I, and 21J (Delta)	136 (48)	128 (44)	101 (89)	95 (90)

Source: Sponsor's response to FDA November 5, 2021, information request (Table 1) and Efficacy Information Amendment dated December 3, 2021 (Table 10)
[a] Clades 19B, 20A, 20B, 20C, 20D, 20H were rarely reported and are not included in the table.
[b] Reported as the percentage of participants infected with a given clade out of the participants with evaluable sequencing data available.
[c] Includes participants in which the viral clade could not be classified and participants in whom sequence data are not yet available.
Abbreviations: N, total number of participants; n, number of participants with the indicated viral clade

We determined that the larger proportion of participants infected with the Delta variant in the second half of the trial was unlikely to explain the observed decreased treatment effect in the second half of the trial. Notably, given MOV's mechanism of action and available nonclinical virology data, we would not anticipate that viral variant/clade would have a direct impact on efficacy. As shown in Table 11, the rate of hospitalization or death through Day 29 decreased markedly in participants infected with the Delta variant in both the MOV- and placebo-treated groups between the first and second half of the trial.

The treatment effect of MOV also diminished between the first and second half of the trial. Therefore, based on the currently available baseline viral clade data, it does not appear that the decrease in efficacy observed in the second half of the trial (i.e., the post-interim analysis population) can be attributed to the increased proportion of participants infected with the Delta variant. However, given the large proportion of participants awaiting sequencing/clade determination at the time of this review, these findings should be interpreted cautiously.

Table 11. Incidence of Hospitalization or Death Through Day 29 Among Participants With Infected With Delta Variant Across Populations, MK-4482-002, Part 2[a]

Population	MOV 800 n/m (%)	PBO n/m (%)
Interim analysis	13/136 (9.6%)	18/126 (14.3%)
Post interim analysis	5/101 (5.0%)	4/95 (4.2%)
Full	18/237 (7.6%)	22/221 (10.0%)

Source: Efficacy Information Amendments dated December 3, 2021, December 6, 2021, and December 10, 2021
[a] This table summarized efficacy among participants infected with Delta variant based on the subset of the trial population with available sequencing data as of November 19, 2021.
Abbreviations: m, number of participants in the modified intent-to-treat population with the corresponding group; MOV, molnupiravir; n, number of participants died or hospitalized through Day 29; PBO, placebo

Another hypothesis regarding the decreased clinical efficacy observed in the second half of MK-4482-002 is that despite prior COVID-19 vaccination being exclusionary, some participants were vaccinated and the subgroup of previously vaccinated individuals increased over time given increased availability of vaccines. Similarly, the proportion of participants with a prior SARS-CoV-2 infection could have increased over time and immunity conferred by the prior infection could have impacted the outcomes during the current infection.

These hypotheses could potentially explain a decreased rate of hospitalization and death among placebo-treated participants in the setting of a relatively stable event rate among MOV-treated participants. Approximately 20% of participants enrolled in MK-4482-002 were anti-SARS-CoV-2 antibody positive at baseline. This is based on an assay that detects serum antibody reactive to the SARS-CoV-2 nucleocapsid (N) protein (IgG, IgM, or IgA). Therefore, the assay may identify participants with previous SARS-CoV-2 infection, but it would not identify those with prior COVID-19 vaccination and without prior infection. To further explore the possibility that vaccinated individuals enrolled in the trial, as well as to better understand whether those with anti-N antibody at baseline may have had a prior SARS-CoV-2 infection or have antibodies from the current infection, the Sponsor has agreed to conduct additional serologic testing on baseline specimens to determine the baseline rate of anti-N IgM and IgG positivity as well as anti-spike antibody positivity.

Conclusions

Though the overall efficacy in Trial MK-4482-002, Part 2 was modest, the review team concludes that based on the data submitted the known and potential benefits outweigh the known and potential risks for the treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing, who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate. Please refer to Sections VIII.7.3, IX.4, and XXI for further details to support the EUA. Notably, neither the review team nor the Sponsor have thus far been able to explain the decreased effectiveness of MOV and the decreased rate of hospitalization or death among placebo-treated participants between the first and second half of the trial. Therefore, the Sponsor will be required to conduct a thorough

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investigation into the discrepancies between the first and second halves of MK-4482-002 as a condition of the EUA.

Importantly, the criteria for an EUA are not the same as for FDA approval or licensure. In issuing an EUA, FDA must determine, among other things, that based on the totality of scientific evidence available to the Agency, 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 a serious or life-threatening disease or condition caused by a CBRN agent; that the known and potential benefits, when used to treat, diagnose or prevent such disease or condition, outweigh the known and potential risks for the product; and that there are no adequate, approved, and available alternatives. From the review team perspective, the standard for an EUA has been met.

Given the unexplained difference in efficacy results from the interim and full analysis populations, coupled with the modest benefit overall, additional efficacy data may be needed to support a New Drug Application.

One area where additional data will likely be needed is from participants in the United States. Only 6% of the MK-4482-002 full population was enrolled from sites in North America. At the time the study was conducted the Delta variant was the predominant circulating SARS-CoV-2 strain in the United States and Delta variant is well represented in MK-4482-002, Part 2. However, the primary endpoint is the incidence of hospitalization or death, which may be impacted by varying standards of care in different regions or countries. Unfortunately, the subgroup of participants enrolled from sites in the United States is too small to ascertain efficacy in this population. Therefore, additional data from the United States are of interest and ensuring adequate representation of participants from U.S. sites should be a priority in any future studies.

7.3. Key Review Issue #2: Patient Selection for Authorized Use

Background

In addition to the modest efficacy of MOV observed in the full MK-4482-002 population, numerous potential safety concerns associated with MOV were identified, including embryofetal toxicity, bone and cartilage toxicity, mutagenicity, and the development of SARS-CoV-2 variants that may be resistant to vaccines or immune-based therapies (see Section IX.4 for an in depth discussion of these safety considerations). Although there are no FDA approved therapies for the treatment of mild-to-moderate COVID-19, there are several FDA authorized products for the treatment of COVID-19 that are not associated with these many potential safety concerns. Therefore, careful consideration was given to identifying the appropriate patient population for the MOV authorization and to the role of MOV amidst the currently available (FDA authorized) products for the treatment of outpatients with mild-to-moderate COVID-19. Several patient selection factors evaluated by the review team and discussed at the Advisory Committee meeting[7] are summarized below.

[7] The MOV EUA request was discussed at an Antimicrobial Drugs Advisory Committee Meeting on November 30, 2021. Please see Section XX for additional information.

Assessments

How To Define High Risk for Progression to Severe COVID-19

All participants in Part 2 of MK-4482-002 were required to have one or more of the following risk factors for severe illness from COVID-19: age >60 years, active cancer, chronic kidney disease, chronic obstructive pulmonary disease, obesity (body mass index (BMI) $\geqslant$30 kg/m^2), a serious heart condition, or diabetes mellitus. The anti-SARS-CoV-2 mAb therapies currently authorized for the treatment of mild-to-moderate COVID-19 are all authorized for use in patients at high risk for progression to severe COVID-19, as defined by the CDC (CDC 2021b). The fact sheets for these three mAb therapies provide examples of risk factors for progression to severe COVID-19 and refer prescribers to the CDC website for a complete listing of high-risk criteria to assess eligibility for treatment under the EUA. The criteria outlined by the CDC are broader than the criteria used to determine eligibility for participation in Part 2 of MK-4482-002 and are also broader than the eligibility criteria for the pivotal mAb clinical trials in participants with mild-to-moderate COVID-19, which supported the mAb EUAs.

Across the various high-risk subgroups enrolled in Part 2 of MK-4482-002, the MOV treatment effect was generally maintained. However, an exception is the diabetes mellitus subgroup (see Figure 4). In the full MK-4482-002, Part 2 population, among the subgroup of participants with diabetes mellitus, the observed rate of hospitalization or death through Day 29 was numerically higher among MOV-treated participants (17/107, 15.9%) compared to placebo-treated participants (17/117, 14.5%). The reason for the lack of treatment effect among those with diabetes is unclear. While these reasons for the findings in the subgroup of participants with diabetes are unclear, they raise concerns that not only was there modest efficacy in the overall population, but there may be subpopulations in which MOV efficacy is further reduced or absent.

The available data do not allow for a robust assessment of efficacy in all potential subgroups of patients at high-risk for progression to severe COVID-19. Therefore, because our recommendation to authorize MOV is limited to patients for whom alternative FDA-authorized therapies are not accessible or clinically appropriate, the review team concluded that prescribers should have flexibility to use the CDC's broad list of medical conditions to select patients who are at high risk for severe COVID-19 to assess eligibility for MOV use under the EUA.

COVID-19 Vaccination Status

In MK-4482-002, SARS-CoV-2 vaccines were prohibited any time prior to randomization and through Day 29, so no data exist regarding the efficacy of MOV among vaccinated individuals. However, as described above, approximately 20% of participants enrolled in Part 2 of the trial were anti-SARS-CoV-2 antibody positive at baseline. The Roche Elecsys® Anti-SARS-CoV-2 assay (Diagnostics 2021) was used to determine anti-SARS-CoV-2 serostatus at baseline. This is a qualitative assay that detects serum antibody (regardless of isotype) reactive to the SARS-CoV-2 nucleocapsid (N) protein (Chan et al. 2020). Therefore, the assay does not distinguish between antibodies that were generated from a prior infection (mostly expected to be IgG) versus those generated from a current infection (IgM or a combination of IgM + IgG). As described above, additional serologic testing (anti-N IgG, anti-N IgM, and anti-S IgG) of baseline samples from MK-4482-002, Part 2 participants are planned.

In MK-4482-002, MOV efficacy in the subgroups of participants who were anti-SARS-CoV-2 seropositive and seronegative at baseline was assessed to determine if there were differences

in efficacy by baseline antibody serostatus. As shown in Table 12, the observed rate of all cause hospitalization or death through Day 29 was higher in the MOV seropositive subgroup than the placebo seropositive subgroup. However, given the small number of events observed in these subgroups, these findings must be interpreted cautiously. In contrast, for the larger subgroup of participants who were anti-SARS-CoV-2 seronegative at baseline, more placebo-treated participants (12.3%) were hospitalized or died by Day 29 compared to MOV-treated participants (7.2%).

Table 12. Incidence of Hospitalization or Death Through Day 29 by Baseline Antibody Status, MK-4481-002, Part 2, Full mITT Population

SARS-CoV-2 Baseline Antibody Serostatus[a]	MOV 800 mg N=709 n/m (%)	Placebo N=699 n/m (%)	Difference (MOV – Placebo) % (95% CI)[b]
Positive	5/136 (3.7)	2/146 (1.4)	2.3 (-1.7, 7.1)
Negative	39/541 (7.2)	64/520 (12.3)	-5.1 (-8.8, -1.6)

Source: Clinical Information Amendment Dated December 2, 2021
[a] Participants with unknown baseline SARS-CoV-2 antibody status are not included in this analysis.
[b] The corresponding confidence interval is based on Miettinen & Nurminen method.
Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.
Abbreviations: CI, confidence interval; m, number of participants in the modified intent-to-treat population with the corresponding group; mITT, modified intent-to-treat; MOV, molnupiravir; n, number of participants died or hospitalized through Day 29; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

The subgroup analysis presented above suggests that there is no MOV treatment benefit among participants who are anti-SARS-CoV-2 antibody positive at baseline. Ascertainment of serostatus prior to the initiation of treatment for COVID-19 is not currently feasible in clinical practice given the available assays and the turnaround time for results. Therefore, it is not practical to consider baseline serostatus as a potential patient selection factor for a MOV. However, in the absence of data from vaccinated individuals, data from seropositive individuals may provide some insight into the potential efficacy of MOV in vaccinated individuals.

It is unclear how applicable the findings in patients with positive baseline anti-SARS-CoV-2 N antibodies from natural immunity are to patients who have immunity following COVID-19 vaccination. There are likely numerous variables that impact the protection conferred by immune responses from both natural infection and vaccination. Factors to consider include the recency of the prior COVID-19 illness or vaccination, whether a booster vaccine has been administered, the SARS-CoV-2 strain/variant causing the current and prior infections, and host factors that impact the immune response to a vaccine or natural infection.

To further explore the potential for MOV to reduce the rate of hospitalization or death among fully vaccinated individuals, a literature review was undertaken. Data suggest that among fully vaccinated adults with breakthrough COVID-19 (defined as COVID-19 occurring in fully vaccinated individuals), hospitalization and death are uncommon but do occur. Data regarding the frequency and risk factors for these outcomes in fully vaccinated individuals are still emerging. Data reflective of the Delta variant experience are limited. However, available literature suggests that most breakthrough infections leading to hospitalization or death occur in patients with advanced age and in those with medical comorbidities. The comorbidities reported in association with breakthrough infections leading to hospitalization or death appear to overlap with the CDC risk factors for severe COVID-19 (Bosch et al. 2021; Brosh-Nissimov et al. 2021; Green et al. 2021; Kim et al. 2021).

As was the case with MOV, vaccinated individuals were not represented in the trials supporting the authorizations of the monoclonal antibodies for similar authorized uses. However, the monoclonal antibodies are authorized for use in outpatients at high risk for progression to

severe COVID-19, regardless of vaccination status. There are data available from an outpatient clinical trial of the monoclonal antibody combination, REGEN-COV, showing clinical benefit in both participants with a positive and negative baseline SARS-CoV-2 antibody status. See the Advisory Committee meeting briefing document (FDA 2021) and Section XXVII.2 for additional details. In the case of MOV, there are no data supporting potential benefit in seropositive or vaccinated patients and there are additional safety concerns that must be taken into consideration.

Ultimately, the review team concluded that denying vaccinated or previously infected high-risk patients access to MOV is not appropriate or warranted, particularly given that MOV is recommended to be authorized as a second-line therapy. Irrespective of COVID-19 vaccination status, MOV may provide benefit in high risk patients with mild-to-moderate COVID-19 for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate. Therefore, the review team does not recommend that prior COVID-19 vaccination be included as a limitation of the authorized use.

Immunocompromised Patients

Immunocompromised patients were eligible for participation in Part 2 of MK-4482-002, however, they comprised a small subset of the overall population. The Sponsor identified 25 MOV-treated participants and 32 placebo-treated participants who met one of the following criteria for immune compromise:

- Prior use of systemic corticosteroids for at least 4 weeks prior to receipt of the first dose of study intervention
- Prior and/or concomitant use of immunosuppressants (with the exception of receipt for the acute SARS-CoV-2 infection)
- Medical history of other conditions, including human immunodeficiency virus and active cancer (excluding minor cancers not associated with immunosuppression or significant morbidity/mortality [e.g., basal cell carcinomas]).

These 57 immunocompromised patients represent 4.0% of the total randomized population. Given the small size of this subgroup, the ability to assess efficacy in this subgroup is very limited. However, a subgroup analysis revealed that among immunocompromised participants, the rate of hospitalization or death through Day 29 was 2/25 (8.0%) and 8/32 (25.0%) in the MOV- and placebo-treated groups, respectively. Comparatively, among nonimmunocompromised participants, the rate of hospitalization or death through Day 29 was 46/684 (6.7%) and 60/667 (9.0%) in the MOV- and placebo-treated groups, respectively. Based on viral RNA shedding data, prolonged viral replication did not appear to be more common in immunocompromised patients compared to nonimmunocompromised patients in MK-4482-002, Part 2.

As described in detail in Section IX.4.4 there is concern that MOV may be associated with changes to the SARS-CoV-2 spike protein and may enhance viral evolution. Given that prolonged viral shedding has been reported in some immunocompromised patients with SARS-CoV-2 infection, the potential for the emergence of MOV-associated changes in the spike protein may be enhanced in immunocompromised patients. On the other hand, these concerns may be offset by a more rapid decrease in viral shedding in patients receiving MOV (compared to patients not receiving antiviral therapy) which would limit transmission and naturally occurring viral evolution.

Consistent with discussions at the Advisory Committee meeting, the review team has concluded that there is a need for additional data in immunocompromised patients in order to better understand the safety, clinical efficacy, and potential virologic effects of MOV in this unique and vulnerable population. However, there are many challenges in conducting a clinical trial in this population and at the time of this review discussions regarding the optimal approach were ongoing. Immunocompromised patients are included in the CDC definition of high-risk participants and could receive MOV if other FDA-authorized products were inaccessible or not clinically appropriate.

Time From Symptom Onset

In Part 1 of MK-4482-002, participants were required to be within 7 days of symptom onset at randomization. Based on MOV's mechanism of action and findings in the Phase 2/Part 1 of the trial, it was concluded that individuals earlier in the course of their illness are more likely to benefit from MOV. Therefore, eligibility in Part 2 of MK-4482-002 was restricted to participants within 5 days of symptom onset. Randomization in Part 2 was stratified by less than or equal to 3 days from symptom onset versus 4 to 5 days from symptom onset. As presented in Figure 4, the treatment effect was relatively consistent in the less than or equal to 3 days from symptom onset subgroup and the 4 to 5 days from symptom onset subgroup.

The review team considers that while it is important that MOV be administered when it is most likely to be effective, it is also important to have a treatment window within which patients can feasibly access MOV. As a frame of reference, the authorized monoclonal antibodies all require that patients be within 10 days of symptom onset at time of treatment. In the case of MOV, there are no data demonstrating benefit in participants who are beyond 5 days from symptom onset. Therefore, the review team concludes that the authorization should be limited to participants within 5 days of symptom onset as this was how the drug was studied.

Conclusions

In conclusion, identifying patients for whom the known and potential benefits of MOV outweigh the known and potential risks of MOV requires careful consideration. For a summary of how the patient selection factors discussed in this section are reflected in the MOV authorization, please see the Overall Conclusions Relevant to the Evaluation of Benefit: Modest Treatment Benefit and Implications for Patient Selection section below and to the Benefit-Risk Assessment Section XXI.

Overall Conclusions Relevant to the Evaluation of Benefit: Modest Treatment Benefit and Implications for Patient Selection

In the full MK-4482-002, Part 2 population, MOV was associated with a 30% relative reduction in the risk of hospitalization or death compared to placebo among outpatients with mild-to-moderate COVID-19 and at high risk for progression to severe COVID-19. In some subgroups of patients, such as those with diabetes and those with anti-SARS-CoV-2 antibodies as baseline, the treatment effect did not appear to be preserved, noting the limited number of participants in these subgroups. In addition to the overall modest treatment benefit, several potential safety and public health concerns were identified based on findings in nonclinical studies and clinical virology assessments (Section IX.4). Therefore, the review team has concluded that the currently available data only support MOV use as a second line agent in patients for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate. Additionally, MOV must be prescribed within 5 days of symptom onset.

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Regarding how to define patients at high risk for progression to severe COVID-19, there was no consensus among Advisory Committee members as to whether the broader CDC criteria or the more restrictive MK-4482-002 eligibility criteria should be used. The review team acknowledges that efficacy data are not available in all subgroups of participants who are at high risk for progression to severe COVID-19 as defined by the CDC. This is also true for mAbs. However, given that MOV will only be used in cases where alternative COVID-19 treatments options are not accessible or clinically appropriate, the review team concluded that allowing some flexibility regarding other patient selection factors was appropriate. The review team therefore decided that prescribers should be referred to the CDC website and exercise clinical judgment to determine if a patient is considered high risk for progression to severe COVID-19.

Regarding COVID-19 vaccination status, the review team concluded that there may be scenarios in which vaccinated patients at high risk for progression to severe COVID-19 who have no alternative treatment options may benefit from MOV. Therefore, we recommend that be authorized for use as described above, regardless of vaccination status. Lastly, though there is a clear need for additional data regarding MOV use in immunocompromised patients, the review team determined that MOV should be available to immunocompromised patients for whom no other COVID-19 treatment options are accessible or clinically appropriate.

The fact sheet will make it clear to prescribers the specific groups of patients from which the available efficacy results are based on (i.e., unvaccinated adults who were 18 years of age and older and had one or more predefined risk factors for disease progression: over 60 years of age, diabetes, obesity (BMI ⩾30), chronic kidney disease, serious heart conditions, chronic obstructive pulmonary disease, or active cancer). The fact sheet will also present efficacy results for various subgroups included in MK-4482-002, such as time from symptom onset to randomization, age, sex, obesity, diabetes mellitus, baseline COVID-19 severity, common baseline clades and baseline SARS-CoV-2 antibody status. It is thought that this information may help inform the benefit risk assessment for individual patients.

IX. Human Clinical Safety: Assessment of Risk and Risk Management

1. Potential Risks or Safety Concerns Based on Nonclinical Data

Mutagenicity, bone growth and cartilage findings, embryo-fetal toxicity, effect of MOV on SARS-CoV-2 spike protein sequences, and potential MOV resistance or remdesivir cross-resistance in clinical trials were identified as key review issues relevant to the evaluation of risk and are discussed in detail in Section IX.4. In addition, significant bone marrow toxicity was reported in a 28-day toxicology study in dogs (see Section XII). This finding prompted a careful assessment of hematologic parameters across all MOV clinical trials. See Section IX.3.6 for additional details.

2. Adequacy of Clinical Safety Database

MOV 800 mg orally Q12H for 5 days is currently being evaluated in clinical trials in adults with confirmed COVID-19 in outpatients and evaluated in hospitalized participants. The safety database for this EUA request consists of 917 adults who have received MOV 800 mg orally

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Q12H for 5 days. This includes 839 outpatient adults with mild-to-moderate confirmed COVID-19 (i.e., the population for which the EUA is being requested). In addition, there is supportive safety data from 72 adults hospitalized with COVID-19 and six healthy volunteers who all received MOV 800 mg orally Q12H for 5 days. The minimum duration of follow-up available for participants in each of the trials is displayed in Table 13 below. Given the short half-lives of NHC and NHC-triphosphate (TP) (approximately 3.3 hours and 15.5 hours, respectively), this duration of follow-up is considered adequate to assess safety.

Table 13. Summary of MOV 800 mg by Mouth Q12H for 5 Days Safety Database

Study	Population	Duration of Follow-Up	Number of Participants Who Received MOV 800 mg Q12H x 5 days
Primary Safety Data			
MK-4482-002 (MOVe-OUT, P002) Part 2	Outpatient adults with COVID-19 and with an increased risk of severe illness from COVID-19	Through at least Day 29[1]	710
Supportive Safety Data			
MK-4482-002 (MOVe-OUT, P002) Part 1	Outpatient adults with COVID-19.	Through at least Day 29[1]	74
MK-4482-006 (EIDD-2801-2003, P006)	Outpatient adults with COVID-19	Through Day 28	55
MK-4482-001 (MOVe-IN, P001)	Hospitalized adults with COVID-19	Through at least Day 29[1]	72
MK-4482-004 (EIDD-2801-1001, P004)	Healthy volunteers	Through 14 days after last dose	6
Total			917

Source: EUA request, File EUA.pdf, Table 82 and Clinical Information Amendment dated December 2, 2021.
[1]The data submitted for this EUA request was based on data from when all participants reached Day 29. Participants are then followed through Month 7, but these data are not available.
Abbreviations: COVID-19, coronavirus disease 19; MOV, molnupiravir; Q12H, administered once every 12 hours

The MOV clinical safety database is comparable to the clinical safety databases for other products that the Division has authorized for the treatment of mild-to-moderate COVID-19. The safety databases for sotrovimab, bamlanivimab, and casirivimab/imdevimab at the time of their initial authorizations ranged from 700 to more than 2000 participants at the to be authorized dose or higher (Table 14). There are no apparent clinical safety signals in the currently available MOV safety database, and it is considered sufficient to assess risk.

Table 14. Summary of Safety Database Size for Other Products Authorized for Use in Outpatients With Mild-to-Moderate COVID-19

Authorized Product	Size of Safety Database at Time of Original Authorization
Bamlanivimab	>1350
Bamlanivimab and etesevimab	>1500
Casirivimab and imdevimab	>2100
Sotrovimab[a]	>700

[a] The sotrovimab EUA was supported by additional preliminary topline safety data
Abbreviations: COVID-19, coronavirus disease 19

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Exposure for Safety Analysis

The Sponsor originally submitted safety data from the interim analysis population of MK-4482-002, Part 2. However, the safety data for the full randomized MK-4482-002 Part 2 population was subsequently provided. The safety analysis in this review is based on the full randomized MK-4482-002, Part 2 population. Specifically, the safety analyses were conducted in the all participants as treated population (N=1411), which consists of all randomized participants who received at least one dose of study treatment and includes 716 MOV-treated participants and 717 placebo-treated participants. The duration of exposure to study intervention was similar between the two groups with a mean duration of 4.4 days in each group. The majority (>94%) of participants received nine or 10 doses of study intervention.

3. Safety Findings and Concerns Based on Review of Clinical Safety Database

3.1. Safety Overview

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017) was used to grade all adverse events (AEs) and laboratory abnormalities in MK-4482-002. From the time of intervention randomization through 14 days following cessation of treatment, all AEs, serious AEs (SAEs), and other reportable safety events were reported. prespecified events of clinical interest (ECIs) were (1) an elevated aspartate amino transferase (AST) or alanine aminotransferase (ALT) that is ≥3 times the upper limit of normal with an elevated total bilirubin that is ≥2 times the upper limit of normal and, at the same time, and alkaline phosphatase lab value that is <2 times the upper limit of normal and (2) any postbaseline platelet value <50,000/μL.

As shown in Table 15 below, the rates of SAEs, fatal AEs, and AEs leading to treatment discontinuation were all higher in the placebo arm than the MOV arm.

Table 15. Adverse Event Summary During Treatment and 14-Day Follow-Up Period, MK-4482-002, All Participants as Treated Population

Adverse Event Category	MOV 800 mg (N=710) n (%)	Placebo (N=701) n (%)
Any AE	216 (30)	231 (33)
AEs related[a] to study drug	57 (8)	59 (8)
AEs leading to discontinuation of study drug	10 (1)	20 (3)
Any SAE	49 (7)	67 (10)
SAEs related[a] to study drug	0 (0)	1 (<1)
SAEs leading to discontinuation of study drug	5 (1)	13 (2)
Fatal SAEs	2 (<1)	12 (2)

Source: Clinical Information Amendment submitted December 2, 2021
a Determined by the investigator to be related to the drug
Abbreviations: AE, adverse event; MOV, molnupiravir; N, total number of participants; n, number of participants who experienced an adverse event; SAE, serious adverse event

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3.2. Deaths

Two fatal AEs (<1%) were reported among MOV-treated participants and 13 (2%) fatal AEs were reported among placebo-treated participants. These fatal adverse events are summarized in Table 16 below. Both of the MOV-treated participants experiencing a fatal AE were over the age of 60 and one had active cancer. Both of the MOV-treated participants who died experienced pneumonia as a complication of COVID-19. The cause of death among placebo-treated participants was predominantly COVID-19 related (e.g., COVID-19 pneumonia, COVID-19 with respiratory failure, and COVID-19 with septic shock). None of the fatal AEs in either arm were assessed to be drug-related.

Table 16. Fatal Adverse Events, MK-4482-002, All Participants as Treated Population

Study Arm	Subject ID	Age	Sex	Study Day of Death	Fatal AE Preferred Term(s)	Comments
MOV	(b) (6)	63	M	32	COVID-19 COVID-19 pneumonia Pneumonia	Participant had a history of diabetes and hypertension. On Day 3 he was hospitalized. On Day 10 he was transferred to the ICU and intubated. He experienced thrombocytopenia[a] on Day 14 and on Day 15 was found to have cerebral hemorrhage. On Day 19, he had progressive pulmonary infiltrates and respiratory cultures grew various gram negative organisms.
MOV		81	M	26	Pneumonia	Participant had a history of liver cancer. He was hospitalized on Day 7 with decreased oxygen saturation and was diagnosed with pneumonia. He received broad spectrum antibiotics. His condition deteriorated and he died “due to multiple organ dysfunction syndrome” according to the narrative.
PBO		69	F	11	COVID-19 COVID-19 pneumonia	
PBO		67	F	56	COVID-19 COVID-19 pneumonia Pneumonia staphylococcal	Participant was hospitalized on Day 5 and based on the narrative it is not clear if she was discharged and readmitted or if she remained in the hospital for 50+ days prior to her death.
PBO		47	F	16	Staphylococcal sepsis[b]	
PBO		81	F	25	COVID-19 COVID-19 pneumonia	
PBO		20	M	41	Metastases to lung	Participant had a history of osteosarcoma with metastases to the lung.
PBO		71	M	57	Not applicable	At the last study visit, no ongoing AEs were present. He was then hospitalized on Day 53 for an unknown reason. According to the narrative he died due to congestive cardiac failure and COVID-19 did not contribute to his death.

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Study Arm	Subject ID	Age	Sex	Study Day of Death	Fatal AE Preferred Term(s)	Comments
PBO	(b) (6)	39	F	15	COVID-19 COVID-19 pneumonia	
PBO		60	M	34	COVID-19 Septic Shock	Participant had pneumonia due to *Pseudomonas aeruginosa* requiring inotropic and vasopressor support.
PBO		88	M	13	COVID-19 Respiratory failure	
PBO		38	F	16	Acute respiratory failure	
PBO		69	M	13	COVID-19 COVID-19 pneumonia	
PBO		59	M	14	COVID-19 Respiratory failure	
PBO		61	M	17	COVID-19	

Source: Narratives submitted in EUA request and in a Clinical Information Amendment dated December 3, 2021

[a] The participants platelet count remained around baseline (123 x 10^9/L) throughout his treatment with MOV. Then on Day 10 platelet count dropped to 80 x 10^9/L and reached a nadir of 46 x 10^9/L on Day 13. According to a hematology consultant, the thrombocytopenia was hemoperfusion-related. According to the Sponsor, the thrombocythemia was also confounded by fluid shifts, sepsis, and numerous medications.

[b] In the narrative submitted with the original EUA request this was reported as staphylococcal bacteremia and the SAE was subsequently recoded as staphylococcal sepsis.

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; F, female; ICU, intensive care unit; ID, identification; M, male; MOV, molnupiravir; PBO, placebo

3.3. Serious Adverse Events

SAEs were more common among placebo-treated participants (10%) compared to MOV-treated participants (7%). One placebo-treated participant and zero MOV-treated participants experienced an SAE that was assessed by the investigator to be drug-related (the drug-related SAE reported in the placebo-treated participant was pancreatitis). The SAEs reported in both arms are presented in Table 17 below by system organ class (SOC) and preferred term (PT). COVID-19, COVID-19 pneumonia, or respiratory failure PTs accounted for the majority of SAEs in both arms, and all occurred at a greater frequency in the placebo arm than the MOV arm.

Table 17. Participants With Serious Adverse Events During Treatment and 14-Day Follow-Up Period, MK-4482-002, All Participants as Treated Population

System Organ Class Preferred Term	MOV N=710 n (%)	Placebo N=701 n (%)
Participants with one or more SAE	49 (6.9)	67 (9.6)
Blood and lymphatic system disorders	1 (0.1)	0
Thrombocytopenia	1 (0.1)	0
Cardiac disorders	0	2 (0.3)
Acute myocardial infarction	0	1 (0.1)
Atrial flutter	0	1 (0.1)
Gastrointestinal disorders	1 (0.1)	1 (0.1)
Pancreatitis	0	1 (0.1)
Pancreatitis acute	1 (0.1)	0
General disorders and administration site conditions	1 (0.1)	0
Edema peripheral	1 (0.1)	0
Infections and infestations	43 (6.1%)	61 (8.7)
Anal abscess	1 (0.1)	0
COVID-19	35 (4.9)	54 (7.6)
COVID-19 pneumonia	27 (3.8)	42 (6.0)
Lung abscess	1 (0.1)	0
Peritonsillitis	1 (0.1)	0
Pneumonia	2 (0.3)	0
Pneumonia aspiration	1 (0.1)	0
Pneumonia bacterial	3 (0.4)	2 (0.3)
Pneumonia haemophilus	0	1 (0.1)
Septic shock	0	1 (0.1)
Staphylococcal sepsis	0	1 (0.1)
Metabolism and nutrition disorders	1 (0.1)	3 (0.4)
Diabetic ketoacidosis	1 (0.1)	1 (0.1)
Diabetic metabolic decompensation	0	1 (0.1)
Type 2 diabetes mellitus	0	1 (0.1)
Neoplasms benign, malignant, and unspecified	0	1 (0.1)
Metastases to lung	0	1 (0.1)
Nervous system disorders	1 (0.1)	0
Cerebral hemorrhage	1 (0.1)	0
Renal and urinary disorders	0	1 (0.1)
Acute kidney injury	0	1 (0.1)

System Organ Class Preferred Term	MOV N=710 n (%)	Placebo N=701 n (%)
Respiratory, thoracic, and mediastinal disorders	9 (1.3)	19 (2.7)
Acute respiratory failure	0	2 (0.3)
Cough	0	1 (0.1)
Dyspnea	0	1 (0.1)
Hiccups	0	1 (0.1)
Hypoxia	1 (0.1)	1 (0.1)
Pneumomediastinum	0	1 (0.1)
Pneumothorax	1 (0.1)	0
Pulmonary embolism	1 (0.1)	1 (0.1)
Pulmonary hypertension	0	1 (0.1)
Respiratory distress	0	1 (0.1)
Respiratory failure	6 (0.8)	9 (1.3)
Vascular disorders	1 (0.1)	0
Shock	1 (0.1)	0

Source: Clinical Information Amendment Dated December 3, 2021.
Abbreviations: COVID-19, coronavirus disease 2019; MOV, molnupiravir; SAE, serious adverse event

3.4. Dropouts and/or Discontinuations Due to Adverse Events

Treatment discontinuations due to AEs were more common among placebo-treated participants than MOV-treated participants. In total, there were 10 (1.4%) MOV-treated participants and 20 (2.9%) placebo-treated participants who experienced an AE leading to treatment discontinuation. The 10 AEs that lead to treatment discontinuation in MOV-treated participants were COVID-19 (n=3), nausea (n=2), vomiting (n=2), COVID-19 pneumonia, hypoxia, vision blurred, fatigue, peritonsillitis, tonsillitis, dizziness, headache, and urticaria (each reported in one participant unless otherwise noted). Of note, the tonsillitis and peritonsillitis AEs were reported in the same participant who had a reported history of chronic tonsillitis.

3.5. Common Adverse Events

AEs were reported in 216 (30.4%) and 231 (33.0%) of MOV- and placebo-treated participants, respectively. Table 18 displays AEs reported by SOC and PT, in at least 1% of participants in either treatment arm. The Gastrointestinal disorders SOC and Infections and infestations SOC contained the largest proportion of AEs reported among MOV-treated participants. COVID-19 was the most common PT reported in both arms. The only PT slightly more common among MOV-treated participants than among placebo-treated participants was nausea. In addition, at the SOC level, there was a slightly larger proportion of MOV-treated participants reporting AEs in the Metabolism and nutrition disorder SOC, Nervous system SOC, and Skin and subcutaneous tissue disorders SOC than placebo-treated participants.

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Table 18. Analysis of Participants With Adverse Events During Treatment and 14-Day Follow-Up Period (Incidence ≥1% of Participants in One or More Treatment Groups), MK-4482-002, All Participants as Treated Population

System Organ Class Preferred Term	MOV N=710 n (%)	Placebo N=701 n (%)
Participants with one or more AE	216 (30.4)	231 (33.0)
Gastrointestinal disorders	43 (6.1)	52 (7.4)
Diarrhea	16 (2.3)	21 (3.0)
Nausea	13 (1.8)	6 (0.9)
General disorders and administration site conditions	6 (0.8)	7 (1.0)
Infections and infestations	93 (13.1)	119 (17.0)
COVID-19	56 (7.9)	69 (9.8)
COVID-19 pneumonia	45 (6.3)	67 (9.6)
Pneumonia bacterial	14 (2.0)	11 (1.6)
Investigations	35 (4.9)	49 (7.0)
Alanine aminotransferase increased	12 (1.7)	12 (1.7)
Aspartate aminotransferase increased	2 (0.3)	8 (1.1)
Metabolism and nutrition disorders	16 (2.3)	12 (1.7)
Musculoskeletal and connective tissue disorders	7 (1.0)	11 (1.6)
Nervous system disorders	19 (2.7)	13 (1.9)
Dizziness	10 (1.4)	9 (1.3)
Psychiatric disorders	13 (1.8)	10 (1.4)
Respiratory, thoracic, and mediastinal disorders	12 (1.7)	28 (4.0)
Respiratory failure	6 (0.8)	9 (1.3)
Skin and subcutaneous tissue disorders	17 (2.4)	8 (1.1)
Vascular disorders	12 (1.7)	10 (1.4)
Hypertension	9 (1.3)	7 (1.0)

Source: Clinical Information Amendment Dated December 3, 2021
Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; MOV, molnupiravir

The majority of AEs were Grades 1 and 2 in severity. Grade 3 AEs were reported in 46 (6.5%) and 39 (5.6%) MOV- and placebo-treated participants, respectively. Grade 4 AEs were reported in 6 (0.8%) and 20 (2.9%) MOV- and placebo-treated participants, respectively. The majority of the Grades 3 and 4 AEs reported among MOV-treated participants were in the Infections SOC (specifically the PTs COVID-19 and COVID-19 pneumonia). The non-COVID-19 Grade 4 AEs reported among MOV-treated participants were lung abscess, pneumonia bacterial, diabetic ketoacidosis, pulmonary embolism, respiratory failure, and shock, each reported in one patient.

The majority of AEs were not assessed by the investigator to be drug-related. Only 8.0% and 8.4% of participants in the MOV and placebo arms, respectively, experienced a drug-related AE. Drug-related AEs occurring in at least 1% of participants in either arm are displayed in Table 19 below. As shown, the rates of the most common drug-related AEs all occurred at a similar rate in the MOV and placebo arms.

Table 19. Drug-Related Adverse Events Occurring in ≥1% of Participants in One or More Treatment Groups During Treatment and 14-Day Follow-Up Period, MK-4482-002, All Participants as Treated Population

Preferred Term	MOV N=710 n (%)	Placebo N=701 n (%)
Participants with one or more drug-related AEs	57 (8.0)	59 (8.4)
Diarrhea	12 (1.7)	15 (2.1)
Nausea	10 (1.4)	5 (0.7)
Dizziness	7 (1.0)	5 (0.7)

Source: Efficacy Information Amendment dated December 3, 2021.
Abbreviations: AE, adverse event; MOV, molnupiravir

3.6. Adverse Events of Special Interest

As noted previously, fulfillment of Hy's Law criteria and any postbaseline platelet value <50,000/μL were prespecified ECIs. Two participants had an ECI reported in the all participants as treated population; one participant in the MOV group and one participant in the placebo group, both of whom had confirmed platelet counts of <50,000 cells/μL. This section provides an expanded discussion of hepatic and hematologic events and laboratory abnormalities as adverse events of special interest.

Hepatic Events

The only AEs under the hepatobiliary disorders SOC reported among MOV-treated participants were hypertransaminasemia and jaundice, which occurred in one MOV-treated participant each. The jaundice AE was assessed as drug-related. No hepatobiliary AEs were serious or led to treatment discontinuation. Grade 3 abnormalities in liver function test parameters were uncommon and occurred at a similar rate across arms (see Table 20). There was one Grade 4 ALT elevation reported among an MOV-treated participant, and no participants in either arm experienced a Grade 4 AST or bilirubin abnormality. No participants in either arm met Hy's Law criteria.

Hematologic Events

Severe decreases in bone marrow cellularity with associated decreases in all hematopoietic cell lines was observed in dog studies. Therefore, all hematologic Aes are of interest.

- Two MOV-treated participants experienced clinical neutropenia AEs (under the Blood and lymphatic system disorders SOC). One clinical neutropenia event was Grade 2 and the other was Grade 3 in severity. The Grade 2 event, but not the Grade 3 event, was assessed to be drug-related. Neither event led to treatment discontinuation. No clinical neutropenia AEs were reported in placebo-treated participants.
- The following bleeding AEs were reported: heavy menstrual bleeding and epistaxis, which both occurred in one placebo-treated participant each, and gingival bleeding, vessel puncture site hemorrhage, and cerebral hemorrhage each reported in one MOV-treated participant. None of these bleeding adverse events were temporally associated with thrombocytopenia or anemia, with the exception of the cerebral hemorrhage event which occurred in a participant with thrombocytopenia. See Table 16 on fatal adverse events for additional details regarding this participant.

3.7. Laboratory Findings

As shown in Table 20 below, Grades 3 and 4 chemistry laboratory abnormalities were uncommon overall and were generally balanced across treatment groups. Although not shown, Grades 1 and 2 chemistry laboratory abnormalities either occurred at a similar rate in both groups or occurred more frequently in the placebo group, with the exception of Grade 2 creatinine abnormalities which occurred in 7.9% of MOV-treated participants and 4.9% of placebo-treated participants.

Table 20. Grades 3 and 4 Abnormalities in Select Chemistry Laboratory Parameters, MK-4482-002, All Participants as Treated Population

Laboratory Parameter	MOV N=710 n/m (%)	Placebo N=701 n (%)
Alanine Aminotransferase (IU/L)		
Grade 3	7/609 (1.1)	10/621 (1.6)
Grade 4	1/609 (0.2)	0/621 (0)
Aspartate Aminotransferase (IU/L)		
Grade 3	5/659 (0.8)	3/651 (0.5)
Grade 4	0/659 (0)	0/651 (0.0)
Bilirubin (mg/dL)		
Grade 3	0/661 (0)	0/657 (0)
Grade 4	0/661 (0)	0/657 (0)
Creatine Kinase (IU/L)		
Grade 3	3/655 (0.5)	3/646 (0.5)
Grade 4	1/655 (0.2)	2/646 (0.3)
Creatinine (mg/dL)		
Grade 3	11/659 (1.7)	13/658 (2.0)
Grade 4	2/659 (0.3)	4/658 (0.6)
Lipase (IU/L)		
Grade 3	3/659 (0.5)	3/655 (0.5)
Grade 4	0/659 (0)	4/655 (0.6)

Source: Clinical Information Amendment dated December 3, 2021.
Abbreviations: m, number of participants with a baseline and at least one postbaseline test result; MOV, molnupiravir; n, number of participants with on-treatment postbaseline test results that met the predetermined criterion and are worse in grade than at baseline

Given the early safety signal for bone marrow toxicity in dogs, careful evaluation of abnormalities in hematologic parameters in patients is warranted. Therefore, Table 21 includes all Grade hematology laboratory abnormalities. A slightly greater proportion of MOV-treated participants compared to placebo-treated participants experienced any grade hemoglobin abnormalities, though most of these were Grades 1 or 2 in severity and these abnormalities are not thought to be clinically meaningful. Grades 3 and 4 hematology laboratory abnormalities were rare and generally balanced across treatment groups (except for Grades 3 and 4 lymphocyte abnormalities which were more common in the placebo group and may have been confounded by COVID-19-associated lymphopenia). Please see Section IX.3.6 for a detailed discussion of hematologic adverse events and laboratory abnormalities.

Table 21. Abnormalities in Select Hematology Laboratory Parameters, MK-4482-002, All Participants as Treated Population

Laboratory Parameter	MOV N=710 n/m (%)	Placebo N=701 n (%)
Hemoglobin (g/dL)		
Any Grade	25/615 (4.1)	16/616 (2.6)
Grade 1	13/615 (2.1)	10/616 (1.6)
Grade 2	10/615 (1.6)	2/616 (0.3)
Grade 3	2/615 (0.3)	4/616 (0.6)
Grade 4	0/615 (0)	0/616 (0)
Lymphocytes (10^9/L)		
Any Grade	27/610 (4.4)	41/616 (6.7)
Grade 1	8/610 (1.3)	3/616 (0.5)
Grade 2	7/610 (1.1)	16/616 (2.6)
Grade 3	8/610 (1.3)	16/616 (2.6)
Grade 4	4/610 (0.7)	6/616 (1.0)
Neutrophils (10^9/L)		
Any Grade	8/446 (1.8)	12/435 (2.8)
Grade 1	5/446 (1.1)	10/435 (2.3)
Grade 2	3/446 (0.7)	2/435 (0.5)
Grade 3	0/446 (0)	0/435 (0)
Grade 4	0/446 (0)	0/435 (0)
Platelets (10^9/L)		
Any Grade	15/607 (2.5)	27/605 (4.5)
Grade 1	11/607 (1.8)	18 /605 (3.0)
Grade 2	4/607 (0.7)	8/605 (1.3)
Grade 3	0/607 (0)	0/605 (0)
Grade 4	0/607 (0)	1/605 (0.2)
Leukocytes (10^9/L)		
Any Grade	15/615 (2.4)	12/616 (1.9)
Grade 1	13/615 (2.1)	10/616 (1.6)
Grade 2	0/615 (0)	1/616 (0.2)
Grade 3	2/615 (0.3)	1/616 (0.2)
Grade 4	0/615 (0)	0/616 (0)

Source: Clinical Information Amendment dated December 3, 2021.
Abbreviations: m, number of participants with a baseline and at least one postbaseline test result; MOV, molnupiravir; n, number of participants with on-treatment postbaseline test results that met the predetermined criterion and are worse in grade than at baseline

3.8. Supporting Safety Data From Other Outpatient Trials

In Part 1 of MK-4482-002, 76 outpatients with mild-to-moderate COVID-19 were randomized to the MOV 800 mg arm and 74 participants were included in the MOV 800 mg safety population. There were no deaths in the MOV 800 mg arm and one (1.4%) death in the placebo arm. The proportion of participants experiencing an SAE was the same in the MOV 800 mg arm (4/74, 5.4%) and the placebo arm (4/74, 5.4%). The four SAEs reported among participants receiving MOV 800 mg were COVID-19 pneumonia (n=3) and pneumonia (n=1). None of the SAEs were assessed to be drug-related. Three (4.1%) participants in the MOV 800 mg arm and one (1.4%) participant in the placebo arm discontinued study drug due to an adverse event. The three discontinuations in the MOV 800 mg arm were due to the following four AEs: COVID-19 pneumonia (n=2), hypoesthesia, and insomnia. Lastly, no participants in the MOV 800 mg arm experienced any graded hemoglobin, lymphocyte, or platelet laboratory abnormalities.

In MK-4482-006, 55 outpatients with mild-to-moderate COVID-19 were randomized to receive MOV 800 mg, and all 55 participants were included in the safety analyses. There were no deaths reported in this trial. One (1.8%) MOV 800 mg–treated participant and one (1.6%) placebo-treated participant experienced an SAE (the SAE reported by the MOV-treated participant was acute respiratory failure that occurred on Day 2 of study drug and was not assessed to be treatment related but led to study-drug discontinuation). One (1.8%) MOV 800 mg–treated participant (see prior summary of the acute respiratory failure SAE) and one (1.6%) placebo-treated participant discontinued study drug due to an AE. Grades 1 and 2 hemoglobin laboratory abnormalities were more common among MOV 800 mg–treated participants (5.7%) than placebo-treated participants (1.6%). No graded lymphocyte or platelet abnormalities were reported among MOV 800 mg–treated participants. No Grades 3 or 4 abnormalities in any hematologic laboratory parameters were reported across the trial.

No new safety signals were identified in these supportive data from outpatient trials of adults with mild-to-moderate COVID-19.

3.9. Experience in Hospitalized Patients

MK-4482-001, was a Phase 2/3 trial of MOV in hospitalized adults with COVID-19. The overall trial design was very similar to that of MK-4482-002. Upon completion of interim analysis 2 (conducted when all of the participants in the Part 1/Phase 2 portion of the trial had reached study Day 29), the Sponsor decided not to initiate Part 2/Phase3 of the trial because data indicated that “MOV is unlikely to demonstrate a clinical benefit in hospitalized participants, who generally have a long duration of symptoms prior to study entry.”

In Part 1 of the trial 72 participants received MOV 800 mg orally Q12H for 5 days and will therefore contribute to the safety database for this EUA request. However, in addition, as there is an imbalance in fatal AEs in this study when all MOV dose cohorts are analyzed, some analyses will be presented including participants who received lower doses of MOV to allow for a comprehensive assessment of this imbalance.

As shown in Table 22, when combining all MOV dose cohorts, the rates of AEs and SAEs were higher among placebo-treated participants than among MOV-treated participants. However, the overall rate of fatal AEs was higher among MOV-treated participants (6.4%) than among placebo-treated participants (2.7%). If just the MOV 800 mg group is considered, the rates of AEs, SAEs, and fatal AEs were all higher among MOV-treated participants than placebo-treated participants. Interestingly, the rate of fatal AEs was highest in the MOV 200 mg group, where the rate was approximately 3 times higher than the rate of fatal AEs observed in the placebo arm. Notably, there were no imbalances in baseline characteristics to account for the high rate of deaths in the MOV 200 mg group. However, the proportion of participants with severe COVID-19 at baseline (as opposed to mild-to-moderate) was highest in the MOV 800 mg arm (53.9% and 42.3% in the MOV 800 mg and placebo arms, respectively) and could account for some of the imbalance in deaths between the MOV 800 mg group and the placebo group.

Table 22. Adverse Event Summary During Treatment and 14-Day Follow-Up Period, MK-4482-001, IA2, All Participants as Treated Population

Adverse Event Category	MOV 200 mg (N=73)	MOV 400 mg (N=73)	MOV 800 mg (N=72)	MOV All (N=218)	Placebo (N=75)
Any AE	40 (54.8)	36 (49.3)	45 (62.5)	121 (55.5)	46 (61.3)
AEs related[a] to study drug	8 (11.0)	6 (8.2)	10 (13.9)	24 (11.0)	16 (21.3)
AEs leading to discontinuation of study drug	0	1 (1.4)	0	1 (0.5)	0
Any SAE	11 (15.1)	9 (12.3)	13 (18.1)	33 (15.1)	12 (16.0)
SAEs related[a] to study drug	1 (1.4)	0	0	1 (0.5)	0
SAEs leading to discontinuation of study drug	0	1 (1.4)	0	1 (0.5)	0
Fatal SAEs	6 (8.2)	4 (5.5)	4 (5.6)	14 (6.4)	2 (2.7)

Source: P001v01 CSR submitted to IND 147734, Table 12.1
[a] Determined by the investigator to be related to the drug
Abbreviations: AE, adverse event; IA2, interim analysis 2; MOV, molnupiravir; SAE, serious adverse event

Deaths

As previously noted, the rate of fatal AEs was higher in the overall MOV group and the MOV 800 mg group compared to the placebo group. Across all MOV dose groups, there was a total of 14 fatal AEs, none of which were assessed to be study drug–related. Table 23 below summarizes the fatal AEs. As shown, the deaths largely occurred in older participants with multiple comorbidities. Many deaths occurred long after study drug had been completed. Based on review of the narratives, the clinical reviewer agrees with the assessment that none of the events were likely study drug–related. All fatal AEs appear to have been either directly or indirectly related to COVID-19.

Numerous secondary infections were reported. Complete hematologic laboratory data were not available for all patients. However, based on available data, leukocytosis and lymphopenia were common among participants who experienced a fatal AE in both arms. The universal steroid use among these participants likely contributed to the observed leukocytosis and may have increased their risk of infection. Among the participants with lymphopenia, the low lymphocyte count was typically present at screening, suggesting that the abnormality was more likely attributable to SARS-CoV-2 (which is known to be associated with lymphopenia) than to MOV.

Table 23. Summary of Fatal Adverse Events, MK-4482-001, IA2

Study Arm	Subject ID	Age and Sex	High Risk Criteria	Concomitant COVID-19 Treatment	Preferred Term	Study Day of AE Onset Relative to Treatment	Study Day of Death	Comments
MOV 200 mg	(b) (6)	61 F	Age >60, Coronary artery disease, diabetes, and obesity	Steroids	Respiratory failure	5	22	Intubated on Day 6. Also had acute kidney injury and bacteremia SAEs.
MOV 200 mg		55 F	Diabetes	Steroids	Bacteremia	15	17	Intubated on Day 12. Also had hemorrhoids, hemoglobin decreased, and peritonitis bacterial SAEs. Blood and peritoneal fluid cultures grew *Streptococcus pneumoniae.* Leukopenia noted on Day 3, resolved by Day 9.
MOV 200 mg		72 M	Age >60, obesity	Steroids	COVID-19	10	31	Intubated on Day 10. Also had a pneumothorax SAE. Course complicated by *Klebsiella pneumoniae* bacteremia and multiorgan dysfunction.
MOV 200 mg		67 F	Age >60, chronic kidney disease, obesity, and diabetes	Steroids	Respiratory failure, COVID-19	2	17	On Day 8 high-flow oxygen was started. On Day 15 a DNR order was written, and patient was transferred to palliative care.
MOV 200 mg		71 M	Age >60, obesity, diabetes, coronary artery disease	Steroids, remdesivir	Acute respiratory failure, COVID-19	11 15	16	Noninvasive mechanical ventilation was started on Day 2. On Day 11, ECMO was started.
MOV 200 mg		73 F	Age >60, chronic kidney disease, DM	Steroids, remdesivir	Pneumonia bacterial, COVID-19	13	37	Intubated on Day 17. She was treated for bacterial pneumonia with no improvement. On Day 37 decision was made “not to prolong treatment”, she was transferred to the general ward and died that day.

Study Arm	Subject ID	Age and Sex	High Risk Criteria	Concomitant COVID-19 Treatment	Preferred Term	Study Day of AE Onset Relative to Treatment	Study Day of Death	Comments
MOV 400 mg	(b) (6)	69 F	Age >60, Obesity	Steroids	Shock	9	9	Intubated on Day 4. Blood cultures positive for *Staphylococcus aureus* and *Acinetobacter baumannii.*
MOV 400 mg		85 M	Age >60	Steroids	Septic Shock	15	18	Intubated on Day 13. Bacteremia and bacterial pneumonia were reported.
MOV 400 mg		69 M	Age >60	Steroids	COVID-19 pneumonia	5	8	Intubated on Day 8.
MOV 400 mg		71 M	Age >60, obesity, diabetes	Steroids, remdesivir	Cardiac arrest	8	8	Intubated on Day 7. On Day 8 was started on vasopressors and ultimately went into cardiac arrest. Respiratory failure, pneumonia, respiratory acidosis, lactic acidosis, and metabolic acidosis SAEs also reported.
MOV 800 mg		63 M	Age >60	Steroids	COVID-19 pneumonia	10	14	Started noninvasive mechanical ventilation on Day 3 and intubated on Day 12.
MOV 800 mg		52 M	None	Steroids	Acute Respiratory Distress Syndrome	1	16	Intubated on Day 1. Also had septic shock, hyponatremia, acute kidney injury, and cholestasis SAEs. *Klebsiella pneumoniae* and *Burkholderia cepacia* isolated from sputum.
MOV 800 mg		55 M	None	Steroids, Remdesivir	Acute respiratory Failure, COVID-19	2	38	Started noninvasive mechanical ventilation on Day 5 and was intubated on Day 14. Course complicated by DVT, acute kidney injury and pneumomediastinum. Family ultimately withdrew care.

Study Arm	Subject ID	Age and Sex	High Risk Criteria	Concomitant COVID-19 Treatment	Preferred Term	Study Day of AE Onset Relative to Treatment	Study Day of Death	Comments
MOV 800 mg	(b) (6)	65 M	Age >60, obesity	Steroids	Acute respiratory failure, COVID-19	3	19	Transferred to the ICU on Day 6 and intubated on Day 11. Patient also developed sepsis, multiorgan failure, thrombocytopenia, and gangrene of both feet. Angiogram of the legs showed bilateral obstruction of the femoral arteries and complete bilateral obstruction of the popliteal arteries. On Day 19 he underwent an urgent thrombectomy, later that day he became unstable and died.
Placebo		86 M	Age >60	Steroids	Pulmonary sepsis	11	15	Intubated on Day 11. Experienced thrombocytopenia (nadir =32 x 10^9).
Placebo		70 F	Age >60, diabetes	Steroids, remdesivir, tocilizumab	COVID-19 pneumonia	3	31	Intubated on Day 3. Experienced a nonserious pulmonary embolism on Day 11 and ventilator associated pneumonia on Day 20.

Source: EUA request (narratives in file 06d99p.pdf)
Abbreviations: AE, adverse event; COVID-19, coronavirus disease 19; ECMO, extracorporeal membrane oxygenation; DVT, deep vein thrombosis; IA2, interim analysis 2; ICU, intensive care unit; MOV, molnupiravir; SAE, serious adverse event

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Serious Adverse Events

Serious adverse events were reported in 15% of MOV-treated participants (overall) and 16% of placebo-treated participants. One participant in the MOV 200 mg intervention group had an SAE considered to be related to study intervention (Grade 3 urticaria). Among the participants who received MOV 800 mg, 13 (18.1%) experienced an SAE. SAEs reported in one or more participants in the MOV 800 mg cohort are listed in Table 24 below in order of decreasing frequency. Though not shown, at the SOC level, SAEs in the Infections and infestations SOC were more common in the MOV 800 mg arm (15.3%) than the placebo arm (12.0%). The majority of these SAEs were COVID-19 and COVID-19 pneumonia PTs. SAEs in the Respiratory, thoracic, and mediastinal disorders SOC were more common in the placebo arm (9.3%) than the MOV 800 mg arm (8.3%).

Table 24. Serious Adverse Events Reported in One or More MOV-Treated Participants, MK-4482-001, IA2, All Participants as Treated Population

Preferred Term	MOV 800 mg N=72 n (%)	Placebo N=75 n (%)
Participants with one or more SAE	13 (18.1)	12 (16.0)
COVID-19	5 (6.9)	6 (8.0)
COVID-19 pneumonia	3 (4.2)	4 (5.3)
Respiratory failure	3 (4.2)	3 (4.0)
Pneumonia	2 (2.8)	0
Pneumonia bacterial	2 (2.8)	0
Acute respiratory failure	2 (2.8)	2 (2.7)
Physical deconditioning	1 (1.4)	0
Cholestasis	1 (1.4)	0
Septic shock	1 (1.4)	0
Urinary tract infection enterococcal	1 (1.4)	0
Transaminases increased	1 (1.4)	0
Hyponatremia	1 (1.4)	0
Acute kidney injury	1 (1.4)	0
Chronic kidney disease	1 (1.4)	0
Acute respiratory distress syndrome	1 (1.4)	0
Deep vein thrombosis	1 (1.4)	0

Source: MK-4482-001 CSR, Table 14.3-9
Abbreviations: COVID-19, coronavirus disease 19; IA2, interim analysis 2; MOV, molnupiravir; SAE, serious adverse event

Other Adverse Events

The only treatment-related AE (i.e., adverse drug reaction) reported in more than one MOV 800 mg participant was nausea (n=2, 2.8%).

No participants in the MOV 800 mg arm discontinued study drug due to an AE (one MOV 400 mg participant discontinued study drug due to an AE of respiratory failure).

As in MK-4482-002, prespecified events of clinical interest for MK-4482-001 were platelet count <50,000 µL and fulfillment of Hy's Law criteria. One placebo-treated participant experienced a treatment-emergent platelet count <50,000 µL and one MOV 800 mg participant met Hy's Law laboratory criteria. The participant with potential drug-induced liver injury only satisfied the criteria for 1 day and the following day the alkaline phosphatase increased, and the criteria were no longer met. The liver function test abnormalities were thought to be due to septic shock and cholestasis, not drug-induced liver injury.

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Laboratory Findings

There were no concerning findings or apparent trends observed among chemistry laboratory parameters. The only Grade 4 chemistry abnormalities reported among participants receiving MOV 800 mg were glucose increased (n=4, more common among placebo patients) and potassium increased (n=1). Hematology laboratory abnormalities are shown in Table 25 below. Hemoglobin abnormalities were overall more common among the MOV 800 mg arm than the placebo arm. Grade 2 and greater lymphocyte abnormalities were balanced across arms and Grade 2 and greater platelet abnormalities were slightly more common in the MOV arm than the placebo arm.

Table 25. Grades 3 and 4 Abnormalities in Select Hematology Laboratory Parameters, MK-4482-001, IA2, All Participants as Treated Population

Laboratory Parameter	MOV 800 mg N=72 n/m (%)	Placebo N=75 n (%)
Hemoglobin decreased (g/dL)		
Any Grade	11/49 (22.4%)	4/48 (8.3)
Grade 1	4/49 (8.2)	1/48 (2.1)
Grade 2	4/49 (8.2)	2/48 (4.2)
Grade 3	3/49 (6.1)	1/48 (2.1)
Grade 4	0	0
Lymphocytes decreased (10^9/L)		
Any Grade	5/49 (10.2)	4/48 (8.3)
Grade 1	0	0
Grade 2	2/49 (4.1)	1/48 (2.1)
Grade 3	0	2/48 (4.2)
Grade 4	3/49 (6.1)	1/48 (2.1)
Absolute neutrophil count decreased (10^9/L)		
Any Grade	0	0
Grade 1	0	0
Grade 2	0	0
Grade 3	0	0
Grade 4	0	0
Platelets decreased (10^9/L)		
Any Grade	4/49 (8.2)	1/45 (2.2)
Grade 1	1/49 (2.0)	0
Grade 2	3/49 (6.1)	0
Grade 3	0	1/45 (2.2)
Grade 4	0	0
Leukocytes decreased (10^9/L)		
Any Grade	0	0
Grade 1	0	0
Grade 2	0	0
Grade 3	0	0
Grade 4	0	0

Source: MK-4482-001 CSR, Table 14.3-15 and response to IR submitted October 26, 2021.
For graded criteria: participants are counted once per test in the highest grade reported.
For inclusion in this analysis, both a baseline and at least one postbaseline laboratory value had to be present. Only participants with a worsened grade from baseline were included.
For the criteria that involve a comparison to baseline, a baseline value is also required.
Abbreviations: IA2, interim analysis 2; m, number of participants with at least one postbaseline test result; MOV, molnupiravir; N, number of participants in population; n number of participants with postbaseline test results that met the predetermined criterion and is worse in grade than at baseline

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4. Key Review Issues Relevant to Evaluation of Risk

This section will describe the identified pharmacology/toxicology and virology review issues with respect to mutagenicity, bone growth and cartilage findings, embryo-fetal toxicity, effect of MOV on SARS-CoV-2 spike protein sequences, and potential MOV resistance or remdesivir cross-resistance in clinical trials.

4.1. Key Review Issue #1: Mutagenicity

Background

MK-4482 (MOV; EIDD-2801) and its metabolite (N4-hydroxycytidine; NHC; EIDD-1931) were positive for mutagenicity in in vitro Ames assays, but MOV was negative in a follow-up in vivo assay. Based on the weight of evidence and expert input, as well as the short-term use (5 days), the risk of mutagenicity following treatment with MOV is low.

Assessment

Mechanistically, the nucleoside triphosphate anabolite of MOV, NHC-TP, acts as a competitive, alternative substrate for the virally encoded RNA-dependent RNA polymerase. The apparent incorporation into nascent chain viral RNA results in increased mutational frequency in the viral genome, resulting in induction of viral error catastrophe and the production of nonviable virus. Given the mechanism of action, NHC-diphosphate could theoretically be transformed by ribonucleotide reductase in human cells to the 2'-deoxyribonucleotide form and the deoxynucleotide subsequently incorporated into cellular deoxyribonucleic acid (DNA), leading to DNA mutations. To assess the genotoxic (i.e., mutagenic) potential of MOV, a battery of in vitro and in vivo mutagenicity assays was conducted by the Sponsor according to International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline S2 (R1) on genotoxicity testing and data interpretation for pharmaceuticals intended for human use. In addition, a 6-month carcinogenicity study in transgenic mice is ongoing.

Ames tests were conducted with the ester prodrug (MOV; EIDD-2801) and initial metabolite, NHC (EIDD-1931). EIDD-2801 was positive for mutagenicity in *Escherichia coli* strain WP2 uvrA and *Salmonella typhimurium* strain TA102, but negative in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537. EIDD-1931 was positive for mutagenicity in *E. coli* strain WP2 uvrA, but negative in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537. EIDD-1931 was not tested with strain TA102. The in vivo and in vitro micronucleus assays showed negative results.

In a published report, NHC has been reported to cause gene mutations in a cultured animal cell line after an extended duration of exposure (32 days), which may occur through interactions with host ribonucleotide reductase and DNA polymerases (Zhou et al. 2021).

MOV was further evaluated in two established in vivo assays for mutagenicity: The Pig-a assay and the transgenic Big Blue® rat assay. Both assays are intended for hazard identification and are powered to detect a minimum increase in mutant frequency, approximately 50 to 100% above the negative control frequency. The Pig-a assay is capable of detecting missense mutations: Of the mutations identified that produce the Pig-a phenotype, the majority are missense mutations (R. Hoeflich, personal communication, December 11, 2021); however, any attempt to extrapolate from the frequencies of phenotypically glycosylphosphatidylinositol-

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deficient (Pig-a mutant) erythrocytes that are measured by the assay to a quantitative assessment of mutation frequencies in the entire genome would be tenuous, at best.

The results of the Pig-a assay in reticulocytes and red blood cells, reflecting mutations induced in nucleated hematopoietic progenitor and stem cells, were “equivocal” (not clearly positive or negative) as the assay met only one of three acceptance criteria set in the draft test guidelines for the mammalian erythrocyte Pig-a gene mutation assay (OECD 2021). Specifically, a test chemical is considered clearly positive if all of the following criteria are met: (1) at least one of the treatment groups exhibits a statistically significant increase in the mutant reticulocyte (MUT RET) and mutant red blood cell (MUT RBC) frequency compared with the concurrent negative control; (2) the mutant frequency responses are dose-related when evaluated with an appropriate trend test; and (3) the MUT RET and/or MUT RBC frequency of any of the test chemical dose groups exceeds the upper bound limit of the historical negative control data distribution.

The results of the MOV Pig-a assay demonstrated significant increases in MUT RETs and MUT RBCs for dosed groups, which is consistent with a positive response. However, an apparent increasing response trend with dose was not statistically-significant, and the MUT RET and MUT RBC frequencies measured in MOV-treated groups did not exceed the upper bound limit of the historical negative control data distribution. Therefore, based on the draft Organisation for Economic Co-operation and Development criteria for evaluating Pig-a assay study data, the outcome of the assay was equivocal.

The Sponsor decided not to perform further analysis of the Pig-a endpoint to resolve this equivocal response, but rather to study the in vivo mutagenicity of MOV further by conducting another in vivo mutation assay, the transgenic rodent gene mutation assay using Big Blue® rats. In the transgenic Big Blue® rat model, the drug was evaluated for increased mutant frequency at the lambda cII transgene in liver and bone marrow. In that assay, MOV was clearly negative for mutagenicity.

Studies have demonstrated that nucleoside analog drugs are able to penetrate the blood-testes barrier (Reineke et al. 2001; Hu et al. 2021) and, therefore, exposure of male germ cells to NHC following treatment with MOV is possible. If NHC is detected in testes in an ongoing pharmacokinetic/distribution study in rats, an assessment of mutant frequencies in testicular germ cells from transgenic Big Blue® rats will be completed.

To confirm the relevance of exposure concentrations of the active metabolite (NHC-TP) used in the mutagenicity assays, the Agency requested tissue distribution data. The Sponsor submitted further data on NHC-TP concentrations in rat tissues and human peripheral blood mononuclear cells (PBMCs), as well as in vitro assays assessing species differences in the conversion of NHC to NHC-TP in PBMCs. Based on assessment of that information, Agency reviewers have concluded that rats were likely exposed to clinically relevant concentrations of NHC-TP during the in vivo mutagenicity assays.

A consult with colleagues from the Agency’s Center for Drug Evaluation and Research Pharmacology/Toxicology Genotoxicity Subcommittee (GSc) was submitted regarding the overall weight of evidence of the genotoxicity data. The GSc confirmed the Division’s conclusions that MOV and NHC were positive for mutagenicity in the in vitro bacterial reverse mutation (Ames) assay. The GSc also reaffirmed that the transgenic rodent (Big Blue® rat) study, and not the Pig-a study, was the primary assay for follow-up assessment of the Ames-positive findings. Lastly, the GSc confirmed that the negative response in the transgenic Big Blue® rat assay indicated that neither parent prodrug nor the metabolite NHC are in vivo mutagens. Therefore, the level of concern for mutagenicity in the clinical setting is low.

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The GSc opined that the positive results in the Ames assay were likely due to incorporation of the NHC-TP ribonucleotide into bacterial DNA. If incorporation occurs in humans, DNA replicase/repair in eukaryotic cells is highly efficient (as contrasted to bacterial replicase/repair). The negative result from the in vivo transgenic Big Blue® rat assay confirms that the ribonucleoside analog is not an in vivo mutagen under the conditions of the assay.

As noted above, given the mechanism of action, it is theoretically possible that the 2'-deoxyribonucleotide form of NHC could be incorporated into cellular DNA, leading to DNA mutations. The available mutagenicity data from somatic cell assays indicate that MOV is not mutagenic in vivo, although a positive, but not statistically significant, trend and significant increases relative to the concurrent (but not historical) negative control were noted in the equivocal Pig-a assay. Limitations of the available nonclinical mutagenicity assays preclude a determination of no risk of mutagenicity, and the ongoing carcinogenicity study and planned testicular germ cell mutation assay (if NHC is detected in testes) will assess the risk to male patients beyond 90 days.

Based on the weight of evidence and expert input, as well as the short-term use (5 days), the risk of mutagenicity following treatment with MOV is considered low.

Conclusions

Pharmacology/Toxicology Team Perspective

The mutagenicity topic was raised repeatedly during the November 30, 2021, Advisory Committee meeting, and uncertainty about genotoxicity was cited as a cause for concern by Committee members who voted either “Yes” or “No” to the single voting question. A particular concern raised was the potential effect on male germ cells that could result in birth defects. As the in vivo mutagenicity assays performed to date use somatic cells (fully differentiated precursor, and stem cells from liver and bone marrow, and peripheral reticulocytes and red blood cells as reporter cells for mutation in nucleated hematopoietic progenitor and stem cells) and not germ cells (eggs and sperm), the ability for MOV to induce mutations in germ cells has not been directly assessed. Somatic cell assays may represent a worst-case, as male germ cells, while reproductively active in adults, appear to be relatively protected from mutagenic DNA damage, including having more efficient DNA repair mechanisms than do somatic cells (Olsen et al. 2001). However, the capacity for DNA repair appears to wane as spermatogonia mature to sperm (Marchetti and Wyrobek 2008) in a process that takes 74 days in humans.

Repair mechanisms such as mismatch repair and homologous recombination that are active in the earliest phases of spermatogenesis give way to the more error-prone nonhomologous end joining process in spermatids (Garcia-Rodriguez et al. 2018). Thus, additional studies to discern the potential effects of MOV on male germ cells may be warranted: If NHC is detected in testes in an ongoing pharmacokinetic/distribution study in rats, a nonclinical assessment of mutant frequencies in testicular germ cells will be completed in early 2023. Results from a carcinogenicity study are expected by the end of 2022. Male germ cell (sperm) maturation starts in early puberty and the sperm maturation process takes 74 days; a period covered by the use of contraception for 90 days in males of reproductive potential who are exposed to MOV. The carcinogenicity study and the testicular germ cell mutation assay will provide data regarding the risk to male patients, and their offspring, beyond 90 days.

SEE ATTACHED ADDENDUM

The risk of MOV use in individuals of childbearing potential is mitigated by the recommendation for the use of contraception during MOV treatment and for 4 days after the end of treatment.

For information regarding MOV use during pregnancy, please see Section 4.3 for a discussion of the complex benefit:risk considerations.

The consensus of the Pharmacology/Toxicology review team, based on the weight of evidence and expert opinion, is that the potential for MOV to cause mutagenicity in humans is low, and the risk of mutagenicity is further reduced by the short 5-day treatment duration. The risk of MOV use in individuals of reproductive potential is mitigated by the use of contraception for 9 days in exposed females, and the use of contraception for 90 days in exposed males. MOV is recommended to be authorized for use in high risk COVID-19 infected adults for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.

Until additional data are provided to inform the risk to male germ cells, the Fact Sheet for Health Care Providers should state, “While the risk is regarded as low, studies to fully assess the potential for MOV to affect offspring of treated males have not been completed. Advise sexually active individuals with partners of childbearing potential to use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose of MOV. The risk beyond 3 months after the last dose of MOV is unknown.”

Also, the Division recommends that the treatment duration be limited to 5 days (10 doses). To this end, MOV will be dispensed in a container containing enough tablets for exactly one treatment course. Additionally, MOV is not authorized for use for longer than 5 consecutive days because the safety and efficacy have not been established.

Clinical Virology Team Leader Perspective

This reviewer is concerned about the impact on the human germline of MOV mutations in regenerating spermatagonial stem cells and meiotic cells (multiple replication cycles in the 16 days to meiosis I) during spermatogenesis. Human males produce approximately 100 million sperm/day (Amann and Howards 1980) with each sperm produced having more than a billion base pairs at which a mutagen could act (Chial et al. 2008).

NHC diphosphate is an obligate intermediate in the formation of the active metabolite of MOV and may be converted by ribonucleotide reductase to dNHC diphosphate which subsequently is incorporated into DNA after phosphorylation to the triphosphate. Incorporation of dNHC phosphate into DNA would lead to mutations in the same way that NHC leads to mutations in RNA. At some level this appears to occur as MOV has shown the potential to be a DNA mutagen to eukaryotic cells in one independent study (Zhou et al. 2021).

The Sponsor conducted studies in rodents to assess MOV’s mutagenicity using the Pig-a and Big Blue® assays. The Pig-a assay is considered the more sensitive assay for evaluating mutagens as the signal to noise ratio is higher. Spermatogenesis cannot be directly evaluated in this assay but generation of reticulocytes, which lack a nucleus, can be considered a surrogate as their phenotype represents mutations in regenerating stem cells and replicating intermediate cells. Looking at the reticulocyte results in the Pig-a assay, MOV showed a dose/response ranging from 5.52 pig-a mutations/million cells for the lowest dose to 10.98 pig-a mutations/million cells for the highest dose with a concurrent control value of 4.97 pig-a mutations/million cells.

Results from the Sponsor’s Pig-a assay were considered equivocal with two possible interpretations of the results from the Pig-a assay as presented. In the first case, the result is a low level positive and compared to positive controls, MOV is a weak mutagen. Alternatively, MOV is negative in this assay. Both results are concerning. For the first interpretation where

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MOV is a weak mutagen, these results indicate that MOV could increase the number of germline mutations. The alternative interpretation that the difference between 4.97/million cells and 10.98/million cells isn't significant raises the question as to whether the assay is sensitive enough to detect a rate of mutagenesis (e.g., ~2-fold) that would be concerning with respect to the germline.

When queried, FDA personnel working with these assays were unable to provide the limit of detection of the assay with respect to the relative increase in the number of mutations/genomes replicated. It should be noted that the Pig-a assay is designed to identify only null mutations, and NHC predominantly causes transition mutations which frequently may not result in the incorporation of stop codons or major functional changes that might lead to a null phenotype in the assay, so the actual rate of mutations may be higher than observed.

As noted above, the rate of germline mutations introduced by MOV is unknown. Furthermore, it is unclear what rate would be acceptable in the context of thirty-four individuals being exposed for each individual who benefits (i.e., number needed to treat to prevent one hospitalization or death). Given the ongoing pandemic and emerging variants, this reviewer agrees with the recommendation of the review team of authorization as there may be situations when alternative therapies are not accessible or clinically appropriate. In such cases, male patients should be counseled that there may be risks beyond 3 months due to mutations in spermatagonial stem cells so they can make an informed decision.

Review Memo, Senior Signatory Perspective

I concur with the assessment of the pharmacology toxicology review team that the potential for MOV to cause mutagenicity in humans is low, and the risk of mutagenicity is further reduced by the short 5-day treatment duration. I agree with the assessment of the clinical virology team leader and the pharmacology toxicology review team that additional data are needed to inform the risk to male germ cells, and note that the Sponsor will prioritize completion of a carcinogenicity study and a testicular germ cell mutation assay. Until these data are available, we have an obligation to be as transparent as possible with health care providers and patients.

I recommend that the Fact Sheet for Patients and Caregivers include the following information:

- For individuals who are sexually active with partners who are able to become pregnant:
  - It is not known if MOV can affect sperm, which may cause harm to your unborn baby. While the risk is regarded as low, studies to fully assess the potential for MOV to affect offspring of treated males have not been completed. You should use a reliable method of birth control (contraception) consistently and correctly during treatment with MOV and for at least 3 months after the last dose. The risk to sperm beyond 3 months is not known. Talk to your health care provider about reliable birth control methods. Talk to your health care provider if you have questions or concerns about how MOV may affect sperm cells.

I conclude that the above recommendations for the Fact Sheet for Patients and Caregivers appropriately convey the uncertainty and risk.

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4.2. Key Review Issue #2: Bone/Cartilage Formation-Related Findings

Background

MOV may affect bone and cartilage development. In a chronic (3-month) rat study, abnormal bone (growth plate) and cartilage formation were noted. Also, in embryo-fetal development (EFD) studies in rats and rabbits, delayed and incomplete ossification was noted in fetuses. Systemic exposures in pregnant rats and rabbits were approximately 8- and 7-fold, respectively, the mean clinical NHC exposure at 800 mg Q12H. As a result of the concerns related to bone and cartilage formation in development, the Sponsor is conducting a study to assess developmental effects of MOV in juvenile rats.

Assessment

Physis and Epiphysis Findings in Rats

In a 3-month repeat dose study in rats, test article-related findings included abnormalities in long bone physis (growth plate) including increased physis thickness in all male rats administered 1000 mg/kg MOV, and increased epiphysis cartilage thickness in all female rats administered 1000 mg/kg MOV and all male rats administered 500 or 1000 mg/kg MOV. Changes to cartilage associated with the trachea were noted in male rats administered 500 (6/10) or 1000 (10/10) mg/kg MOV. Growth plate-related bone and/or cartilage findings were noted at systemic exposures approximately 5-fold higher (males) and 9-fold higher (females) than the mean clinical NHC exposure at 800 mg Q12H ($AUC_{0\text{-}24hr}$ =75.6 hr*µM). The no-observed adverse effect level (NOAEL) was not defined (i.e., <150 mg/kg) for males due to weight loss at the lowest dose and was defined as 200 mg/kg/day for females.

Mild to marked increased thickness of the physis of the long bones (femur and tibia) of male rats dosed at 1000 mg/kg/day was characterized by irregularly widened physis involving the zone of hypertrophic chondrocytes, and occasional disruption of the physis. According to the study pathologist, histomorphologic features of the changes observed in the bone were indicative of an alteration in the normal physiologic progression of hypertrophic chondrocytes toward osteogenesis, resulting in impaired transformation of cartilage into new bone (endochondral ossification).

Eosinophilic cytoplasmic alteration of the chondrocytes in the cartilage of the trachea was noted in male rats administered 500 and 1000 mg/kg/day. This change did not impact the overall structure or integrity of the cartilage and did not cause airway restriction.

There were no findings in a 28-day repeat dose study in rats at similar systemic exposures (systemic exposures approximately 5-fold higher (males) and 9-fold higher (females) than the mean clinical NHC exposure at 800 mg Q12H ($AUC_{0\text{-}24hr}$ =75.6 hr*µM). This apparent discrepancy between the 28-day and 3-month repeat dose study may be related to the age of animals at the on-set of dosing. In the 28-day study rats were 8 to 9 weeks old at the start compared with 5 weeks of age at the start of the 3-month study.

Bone Effects in Rat and Rabbit Fetuses

MOV was administered orally to pregnant rats at 200, 500, and 1000 mg/kg/day from gestation days (GDs) 6 to 17 in a preliminary embryo-fetal development study. There were MOV-related skeletal malformations, variations, and delays in ossification at 1000 mg/kg/day.

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In an embryo-fetal development study in rabbits, MOV was administered orally to pregnant rabbits at 0, 125, 400, or 750 mg/kg/day from GDs 7 to 19. Incomplete caudal vertebra and metacarpal ossification appeared to occur more at 400 mg/kg (9% of litters) and 750 mg/kg (6%) than in controls (2%). Although the incidence does not appear to increase with dose, this finding is noteworthy given the effects on bone and cartilage described previously in rats. Systemic exposures in pregnant rabbits at 400 and 750 mg/kg were approximately 6 and 18 times the mean clinical NHC exposure.

Conclusions

As previously described, animal studies suggest that MOV may affect bone and cartilage growth.

COVID-19 is typically associated with a mild disease course in most pediatric patients. REGEN-COV and sotrovimab mAb regimens are authorized for the treatment of mild-to-moderate COVID-19 in adolescents (patients 12 years of age and older weighing at least 40 kg) and bamlanivimab and etesevimab also includes authorized use in pediatric patients, including neonates. A juvenile toxicity study in rats is planned to further inform the safety of MOV in pediatric patients and a draft report is expected around March 2022.

Therefore, MOV should not be authorized at this time for use in patients less than 18 years old. This will be conveyed to prescribers through a Limitation of Authorized use and a Warning and Precaution in the health care provider fact sheet.

This topic was not an area of discussion during the November 30, 2021, Advisory Committee meeting, although one Committee member made the point that in females the growth plate closes by age 16 and in many males the growth plate is closed before age 18.

In addition, the above-described bone and cartilage toxicity may also be relevant to lactating women and nursing infants potentially exposed to NHC. There are currently no data on the presence of MOV or its metabolites in human milk. However, NHC was detected in the plasma of nursing pups from lactating rats administered MOV. Based on these available data, breastfeeding is not recommended during the treatment with MOV and for 4 days after the final dose. A lactating individual may consider interrupting breastfeeding and pumping and discarding breast mild during treatment and for 4 days after the last dose. These recommendations should be included in the health care provider and patient fact sheets.

SEE ATTACHED ADDENDUM

4.3. Key Review Issue #3: Reproductive Toxicology Findings

Background

Nonclinical reproductive toxicology studies available for review include fertility studies in male and female rats, preliminary and pivotal EFD studies in rats and rabbits, and a pre- and postnatal development (PPND) study in rats.

In a preliminary EFD study in rats, the high dose was associated with reduced fetal body weight and an increase in post implantation loss, as well as external, visceral, and skeletal malformations. Systemic exposures (AUC) of NHC were approximately 8-fold the mean clinical NHC exposure. In the pivotal study, findings were limited to reduced fetal growth at systemic exposures approximately 3-fold the mean clinical NHC exposure.

There were no findings in a PPND study in rats (audited draft report). Notably, in the high dose group the mean maternal exposures to NHC were only 1.5-fold the mean clinical NHC

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exposure, significantly lower than 8-fold the clinical NHC exposures which resulted in embryo-fetal toxicity noted in the EFD study. In the PPND draft report, low concentrations of NHC, 0.09% of maternal exposures, were measured in 10-day old pups, suggesting that NHC is present in breast milk.

Due to the embryo-fetal toxicity and bone and cartilage development findings in vivo, the lower exposures tested in the PPND study, and the lack of a completed juvenile toxicology study, there are both known and possibly unknown risks for use of MOV in pregnant or lactating individuals and pediatric patients.

Assessment

Fertility Studies (Male and Female Rats)

No effects of treatment were noted on fertility parameters. Based on the lack of findings the no observed effect level (NOEL) for fertility parameters was defined as ≥500 mg/kg in males and females. Systemic exposures (AUC) of NHC at the NOEL were approximately 2 times and 6 times the mean clinical NHC exposure at 800 mg Q12H ($AUC_{0\text{-}24hr}$ =75.6 hr*μM) in males and females, respectively.

In the 3-month rat study, minimal degeneration of spermatogenic epithelium in two of 10 males administered 1000 mg/kg (high dose) was (1) characterized by segmental epithelial degeneration of isolated seminiferous tubules and spermatid retention, (2) associated with minimally increased cellular debris in the lumen of the epididymis, and (3) attributed to decreased body weight gain. At the end of the study, the decreases in males' body weight gain were -13%, -25%, and -55%, at low dose, mid dose, and high dose, respectively. The histomorphologic features of the testis were consistent with findings that have been described in rats with significant body weight suppression.

Embryo-Fetal Development (EFD) Studies

Rat

Note: In a preliminary EFD study female rats were administered doses up to 1000 mg/kg (NOAEL not defined as the study was preliminary). Findings from that study are included below. In the pivotal study rats were administered doses up to 500 mg/kg. In that study, findings were limited to reduced fetal growth at systemic exposures approximately 3 times the mean clinical NHC exposure at 800 mg Q12H (NOAEL 250 mg/kg based on maternal and developmental findings; exposures were approximately equivalent to the mean clinical NHC exposure at 800 mg Q12H).

Key study findings (from preliminary/range findings EFD study)

The 1000 mg/kg dose was also associated with reduced fetal body weight and an increase in post-implantation loss, as well as external, visceral, and skeletal malformations in surviving fetuses. Administration of 1000 mg/kg to pregnant rats from GDs 6 to17 caused a transient decrease in food consumption between GDs 6 and 8 and an associated reduction in body weight between GDs 8 and 12.

Systemic exposures (AUC) of NHC were: at 100 mg/kg: 22.5 hr*μM; at 200 mg/kg: 45.7 hr*μM; at 500 mg/kg: 217 hr*μM; and at 1000 mg/kg: 570 hr*μM, approximately 0.3, 0.6, 3, and 8 times the mean clinical NHC exposure at 800 mg Q12H ($AUC_{0\text{-}24hr}$ =75.6 hr*μM).

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External malformations

There were MOV-related fetal external malformations of the eyes (small or absent eye bulge) at 1000 mg/kg/day (three fetuses from two litters, compared to none in controls).

Visceral malformations

At 1000 mg/kg/day, there were MOV-related fetal visceral malformations (absent kidney in two fetuses from two litters, compared to none in controls). There was one fetus in the 1000 mg/kg/day group with multiple cardiovascular and associated observations (ventricular septal defect, dilated pulmonary trunk, narrowed aortic arch, malpositioned aorta, large ventricle, and fluid-filled thoracic cavity). This fetus was also observed to have local edema at external examination. Because this was a singular occurrence and ventricular septal defect with similar associated abnormalities has been observed in vehicle controls in this laboratory, the abnormalities in this fetus were considered by the study director to be incidental and unrelated to MK-4482 treatment.

Skeletal malformations

Consistent with the external malformation (small or absent eye bulge), there were MOV-related fetal coronal malformations at 1000 mg/kg/day (small or absent eye in four fetuses from three litters, compared to none in controls).

There were MOV-related skeletal malformations, variations, and delays in ossification at 1000 mg/kg/day. Specifically, there were increased incidences of rib malformations (primarily detached ribs), thoracic vertebra malformation, lumbar vertebra malformation, skull malformation, cervical ribs, trace supernumerary ribs, and incomplete ossification of thoracic vertebrae and/or sternebrae. The skull malformation observed in one fetus was a small eye socket (reduced spacing between the right frontal bone and zygomatic bone), presumably representing a small eye that was not observed at external examination. In addition, the mean number of ossified sacrocaudal vertebrae was reduced.

The incidences of cervical ribs in the 200 and 500 mg/kg/day dose groups were higher than in concurrent controls (five fetuses in two litters [litter means 4.8%] and five fetuses in three litters [litter mean 6.3%], respectively, versus two fetuses in two litters [litter mean 2.4%]).

PPND study findings

MOV was administered orally to female rats at doses up to 500 mg/kg/day (similar to the human NHC exposure at the recommended human dose) from GD 6 through lactation Day 20. No effects were observed in offspring. Low concentrations to NHC, 0.09% of maternal exposures, were measured in 10-day old pups, suggesting that NHC is present in breast milk.

Rabbit

Key study findings

Developmental toxicity included reduced fetal body weights at 750 mg/kg/day. Incomplete ossification in fetuses from rabbits administered 400 and 750 mg/kg MOV may be test article-related. Incomplete ossification (specifically caudal vertebra and metacarpal) appeared to occur more at 400 mg/kg (9% of litters) and 750 mg/kg (6%) than in controls (2%) and is noteworthy given effects on bone and cartilage seen in rats. The Sponsor concluded that these changed were not related to test article due to the lack of dose dependency and the fact that the values were within or just outside the historical ranges.

Administration of 125 mg/kg, 400 mg/kg, and 750 mg/kg to pregnant rabbits on GD 7 through 15 resulted in systemic exposures ($AUC_{0\text{-}24hr}$) of 111 hr*µM, 490 hr*µM, and 1360 hr*µM, respectively. The mean clinical NHC exposure at 800 mg Q12H was 75.6µM*hr. The NOEL was defined as 125 mg/kg based on maternal and developmental toxicity.

Conclusions

Use in Pregnancy

Given the nonclinical findings of embryo-fetal toxicity, MOV is not recommended for use during pregnancy. There are alternative authorized therapies available for the treatment of mild-to-moderate COVID-19 that do not have an embryo-fetal toxicity safety signal. However, MOV may be used during pregnancy in certain situations if the risk benefit assessment is favorable to the individual patient. If MOV is used during pregnancy, prescribing health care providers must communicate the known and potential benefits and the potential risks of using MOV during pregnancy to the patient as outlined in the Fact Sheet for Health Care Providers in Warnings and Precautions (Sections 5.1, 5.2), Use in Specific Populations (Sections 8.1, 8.3), and Nonclinical Toxicology (Section 13.1). Further, the prescriber must document that the known and potential benefits and the potential risks of MOV use during pregnancy, as outlined in the Fact Sheet for Patients and Caregivers, were discussed with the patient.

Finally, the prescribing health care provider must inform pregnant individuals of the Sponsor's pregnancy surveillance program. If the pregnant individual agrees to participate in the pregnancy surveillance program and allows the prescribing health care provider to disclose patient specific information to the Sponsor, the prescribing health care provider must provide the patient's name and contact information to the Sponsor. A toll-free number and web address will be provided in the fact sheets for health care providers and patients to report exposures.

The nonclinical embryo-fetal toxicity findings, and the use of MOV during pregnancy, were concerning to Committee members at the November 30, 2021, Advisory Committee meeting. In general, members voting "Yes" advised that MOV not be used during pregnancy, or be used only under certain situations, and after health care provider and patient discussions regarding the potential risks to the fetus. The Advisory Committee discussions were taken under consideration when formulating the recommendations for use during pregnancy as stated above.

Use in Individuals of Childbearing Potential

Regarding use in individuals of childbearing potential, given that MOV is associated with clinical benefit in high-risk adults with mild-to-moderate COVID-19, withholding MOV from individuals of childbearing potential for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate, is not justified.

It is important to minimize the risk of an individual who is unaware that they are pregnant inadvertently exposing a fetus to MOV. Therefore, unless an individual has undergone permanent sterilization, is currently using an intrauterine system or contraceptive implant, or is someone in whom pregnancy is not possible, a prescribing health care provider must assess whether an individual of childbearing potential is pregnant or not. This assessment can be based on the first day of the last menstrual period in individuals who have regular menstrual cycles, are using a reliable method of contraception correctly and consistently or have had a negative pregnancy test.

A pregnancy test is recommended if the individual has irregular menstrual cycles, is unsure of the first day of last menstrual period or is not using effective contraception correctly or consistently. Pregnancy testing will not be required for all individuals of childbearing potential as this is thought to be infeasible under the framework of an EUA and as there is a precedent for allowing drugs with evidence of embryofetal toxicity in animals but not humans to be prescribed without requiring documentation of a negative pregnancy test.

The above recommendations were discussed and agreed by the Division of Pediatric and Maternal Health and Division of Urology, Obstetrics, and Gynecology.

To further minimize the risk of embryofetal toxicity among individuals of childbearing potential, a reliable method of contraception used correctly and consistently is recommended during the 5-day treatment period and for 4 days after the last dose of MOV.

Lastly, prescribing health care provider must communicate to individuals of childbearing potential that a pregnancy surveillance program is available to monitor pregnancy outcomes in those exposed to MOV during pregnancy.

Pregnancy Surveillance Program

As described above, the Sponsor has created a pregnancy surveillance program to collect information on pregnancy outcomes in individuals who are exposed to MOV during pregnancy. A toll-free number and web address will be provided in the fact sheets for health care providers to report exposures. Under the authorization, prescribers will be required to report all known MOV exposures during pregnancy, providing the pregnant patient agrees to participate in the registry and allows the prescribing health care provider to disclose patient specific information to Merck. As the prescribing health care provider may not have ongoing involvement in the patient's care, they will be asked to provide the Sponsor with the patient's name and contact information. The Sponsor will then be required to exercise due diligence to capture pregnancy outcomes data. The outcomes data that the Sponsor intends to collect were reviewed by the Division of Antivirals and by the Division of Pediatric and Maternal Health and are considered acceptable. The Sponsor will be required to submit a monthly report summarizing pregnancy exposures and outcomes to the Division of Antivirals.

The review team acknowledges that it will be challenging to capture pregnancy exposures and pregnancy outcomes from patients who are not known to be pregnant at the time MOV is prescribed. If MOV is prescribed by a health care provider with whom the patient has a one-time encounter (e.g., an emergency room or urgent care provider), it is not reasonable to expect the prescriber to become aware of the pregnancy exposure or to report the pregnancy exposure and outcomes. To increase the likelihood of capturing these exposures, prescribers will be required to communicate to all nonpregnant individuals of childbearing potential that a pregnancy surveillance program is available to monitor pregnancy outcomes in those exposed to MOV during pregnancy and to encourage the patient to participate in the pregnancy surveillance program should they become pregnant within 6 weeks of taking MOV.

Dear Health Care Provider Letter

To further inform prescribing health care providers and treating health care providers of the many unique considerations regarding MOV use in pregnancy and in individuals of childbearing potential, a Dear Health Care Provider letter will be widely distributed by the Sponsor. This letter will also provide information about the pregnancy surveillance program and it is hoped that this will help improve reporting rates.

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4.4. Key Review Issue #4: Effect of MOV on SARS-CoV-2 Spike Protein Sequences in Clinical Trials

Background

MOV inhibits SARS-CoV-2 replication by causing the accumulation of nucleotide changes in viral RNA which ultimately render viral populations less fit or unviable (for further details, see Section XIII.1 "Mechanism of Action"). In theory, the random viral RNA mutagenic effects of MOV treatment could result in genetic changes anywhere in the viral genome, which under certain conditions could impact viral susceptibility to other antiviral agents or to the host immune response. Of particular importance, amino acid changes in the viral spike protein could contribute to reduced viral susceptibility to the host antibody response or to spike protein targeting monoclonal antibody therapeutics.

This section summarizes analyses conducted by the Sponsor and FDA to characterize MOV treatment-emergent changes in the SARS-CoV-2 spike protein sequences in clinical trials (1) to confirm the mechanism of MOV action leading to accumulation of nucleotide changes in the SARS-CoV-2 genome, and (2) to determine if MOV treatment causes changes in the viral spike protein that could facilitate SARS-CoV-2 evolution or immune escape.

Assessment

SARS-CoV-2 Sequence Analysis Methods

Viral next generation sequencing (NGS) analyses from MOV clinical trials were conducted in a central laboratory, and detailed methods are described in an NGS assay validation report and a nonclinical information amendment (SDN 10). Briefly, viral RNA samples from NP and oropharyngeal (OP) swabs with sufficient RNA levels to meet quality control criteria (defined as >22,000 copies/mL) were subjected to reverse-transcriptase polymerase chain reaction amplification and full genome sequencing using the Ion Torrent NGS platform. The Ion AmpliSeq SARS-CoV-2 Research panel consists of two primer pair pools that target 237 amplicons (both strands sequenced) specific to the SARS-CoV-2 virus and five human expression controls.

According to the Sponsor, this panel, with an amplicon length range of 125 to 275 bp, provides >99% coverage of the SARS-CoV-2 genome. A variant frequency cutoff was not used but most reported variant frequencies were >2%. Variants were reported relative to the prototypic reference isolate, Wuhan-Hu-1 (GenBank:MN908947.3). Nucleotide mutation rates were defined as the number of nucleotide changes observed in postbaseline samples compared with the baseline sequence per 10,000 bases across the entire viral genome (~30,000 bases).

The NGS data from MK-4482-002, Part 1 and MK-4482-001 were submitted both in raw format (.fastq files) and also in .xpt STDM and an analysis-ready ADaM-like format. Independent FDA analyses of the .xpt files were conducted to characterize treatment-emergent amino acid changes in MOV- and placebo-treated participants in these trials. Treatment-emergent amino acid changes (i.e., detected in postbaseline samples but not baseline samples, regardless of NP/OP sample type) based on a variant sensitivity threshold of 5% were identified in the viral spike sequences and compared between MOV- and placebo-treated participants. Raw NGS fastq data from a subset of participants were also independently analyzed to confirm/corroborate the analyses of the .xpt data.

For MK-4482-002, Part 2, limited SARS-CoV-2 sequence analysis data were reported at the time of this review, so the treatment-emergent amino acid analyses focused primarily on MK-4482-002, Part 1 (outpatient population/Phase 2) and MK-4482-001 (hospitalized population/Phase 2).

Analysis of SARS-CoV-2 RNA Mutation Rates: MK-4482-002, Part 2

Based on available data from a small subset of participants (12%, 92/762), and consistent with the MOV mechanism of action, MOV treatment was associated with a modest but significantly higher nucleotide mutation rate in SARS-CoV-2 populations in NP swab samples collected on Day 5 (EOT) (Table 26).

Table 26. SARS-CoV-2 RNA Mutation Rate (Number of Nucleotide Changes/10,000 Nucleotides Sequenced Across Entire Genome), MK-4482-002, Part 2

		MK-4482 800 mg				Placebo				
Visit	Analysis Parameter	N	Median	Min	Max	N	Median	Min	Max	P-Value MOV vs. PBO[a]
Baseline	Number of SARS-CoV-2 Mutations Relative to Reference (NP Swab)	42	13.0	8.7	19.7	50	12.7	9.7	15.7	0.272
Day 5 (EOT)	Number of SARS-CoV-2 Mutations Relative to Baseline (NP Swab)	42	2.5	0.0	46.3	50	1.3	0.0	30.0	0.005

Source: FDA analysis of Sponsor-related mutation rates
[a] Wilcoxon test
Abbreviations: EOT, end of treatment; MOV, molnupiravir; N, number of participants; NP, nasopharyngeal; PBO, placebo; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Analyses conducted by the Sponsor indicate most of the nucleotide mutations observed were cytidine (C) ↔ uridine (U) and guanosine (G) ↔ adenosine (A) transition mutations, again consistent with the MOV mechanism of action, although MOV treatment was associated with increases in all types of analyzed nucleotide changes (Table 27).

Table 27. Mean Numbers of SARS-CoV-2 RNA Transition, Transversion and Other Nucleotide Changes Relative to Baseline, MK-4482-002, Part 2

		Transitions				Transversions								Other
Treatment	N	C:U	U:C	G:A	A:G	C:A	C:G	U:A	U:G	G:U	G:C	A:C	A:U	(In/Del)
MOV	42	6.6	1.8	3.6	2.2	0.2	0.1	0.1	0.2	1.6	0.1	0.2	0.4	1.7
Placebo	50	4.1	1.1	0.4	0.5	0.1	0.0	0.0	0.0	1.0	0.0	0.1	0.2	1.2

Source: adapted from p002v02eff, pg. 153
Abbreviations: A, adenosine; C, cytidine; Del, deletion; In, insertion; G, guanosine; MOV, molnupiravir; N, number of participants; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; U, uridine

Analysis of SARS-CoV-2 RNA Mutation Rates: MK-4482-002, Part 1 and MK-4482-001

Consistent with the results from MK-4482-002, Part 2, MOV treatment in MK-4482-002, Part 1 was associated with a higher rate of detected nucleotide changes in postbaseline viral genomes in NP swab samples (Table 28). Again, most of the nucleotide mutations observed were C↔U and G↔A transition mutations, although MOV treatment was associated with increases in all types of analyzed nucleotide changes (Table 29).

Table 28. Numbers of SARS-CoV-2 Nucleotide Changes Relative to Baseline per 10,000 Bases Analyzed, NP Swab Samples, MK-4482-002, Part 1

Visit	MK-4482 200 mg		MK-4482 400 mg		MK-4482 800 mg		Placebo	
	N	Mean Change (SD)	N	Mean Change (SD)	N	Mean Change (SD)	N	Mean Change (SD)
SARS-CoV-2 RNA Mutation Rate (per 10,000 bases)								
Day 3	29	4.4 (13.95)	32	6.1 (23.90)	27	2.4 (3.29)	29	0.9 (0.51)
EOT (Day 5)	14	7.9 (14.60)	15	6.7 (7.83)	11	8.7 (8.38)	15	2.0 (3.39)
Maximum at Day 3 or EOT (Day 5)	30	7.6 (16.52)	32	8.5 (24.13)	27	5.6 (6.56)	31	1.5 (2.40)

SD=Standard deviation.
N=Number of participants with baseline and at least one postbaseline test result in the specified analysis window.
The mutation rate is calculated as number of nucleotide mutations compared to the baseline sequence per 10,000 bases across the entire viral genome (30,000 bases).
Day 3 includes post-baseline records up to day 4 relative to randomization. EOT (Day 5) includes post-baseline records from day 5 (relative to randomization) up to day 7. End of treatment visits occurring earlier than day 5 (relative to randomization) are included in the Day 3 visit.

Source: Sponsor's analysis, Part 1 CSR pg. 183
Abbreviations: EOT, end of treatment; NP, nasopharyngeal; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Table 29. Mean Numbers of Types of SARS-CoV-2 Nucleotide Changes Relative to Baseline, NP Swab Samples, MK-4482-002, Part 1

			Transitions				Transversions								Other Nucleotide
Visit	Treatment	N	C:U	U:C	G:A	A:G	C:A	C:G	U:A	U:G	G:U	G:C	A:C	A:U	Changes
Day 3	MK-4482 200 mg	33	4.5	1.5	1.0	0.7	0.1	0.0	0.0	0.0	1.4	0.1	0.1	0.2	1.2
	MK-4482 400 mg	35	6.3	2.6	0.7	0.5	0.0	0.1	0.0	0.1	2.6	0.2	0.2	0.2	1.9
	MK-4482 800 mg	31	2.2	0.4	1.5	0.5	0.0	0.0	0.0	0.0	0.2	0.0	0.1	0.0	0.6
	Placebo	32	1.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.2	0.0	0.1	0.0	0.4
EOT (Day 5)	MK-4482 200 mg	19	7.3	2.1	2.1	1.1	0.0	0.1	0.0	0.0	2.6	0.2	0.2	0.5	1.5
	MK-4482 400 mg	17	6.4	1.4	4.2	2.2	0.1	0.0	0.0	0.1	0.5	0.1	0.0	0.2	0.8
	MK-4482 800 mg	14	9.0	2.5	5.7	2.6	0.0	0.0	0.0	0.1	0.9	0.0	0.0	0.0	1.1
	Placebo	20	2.6	0.2	0.2	0.3	0.1	0.0	0.0	0.0	0.5	0.1	0.1	0.1	0.6

N = number of participants with both baseline and post-baseline SARS-CoV-2 gene sequencing data at the reported visit.

Source; Sponsor's analysis, p002vrv01vir, pg. 6
Abbreviations: A, adenosine, C, cytidine; EOT, end of treatment; G, guanosine; NP, nasopharyngeal; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; U, uridine

The Sponsor conducted additional analyses of SARS-CoV-2 nucleotide mutation rates focusing on all minor nucleotide variants detected at frequencies of 0.4 to 10%. These analyses similarly detected a higher frequency of nucleotide mutations in MOV- versus placebo-treated participants. Statistical analyses conducted by the Sponsor indicated a linear MOV dose-response relationship in the numbers of minor nucleotide variants detected, and this relationship remained when controlling for viral RNA levels in samples.

In MK-4482-001, consistent with the results from MK-4482-002, Parts 1 and 2, a modest increase in overall SARS-CoV-2 mutation rate was detected in NP swab viral RNA samples in MOV-treated participants compared to placebo-treated participants. A clearer MOV dose-response relationship in viral mutation rate in NP samples was again observed when analyses were restricted to minor nucleotide variants detected at frequencies of 0.4 to 10%.

Analysis of Spike Treatment-Emergent Amino Acid Changes: MK-4482-002, Part 1

Results for all three MOV arms in MK-4482-002, Part 1 were pooled for analyses of treatment-emergent amino acid changes in the spike protein. Specific amino acid changes or nucleotide structural mutations detected at the same amino acid position in ≥ two participants (pooled MOV- and placebo-treated) were identified and tabulated. The NGS analyses were generally restricted to samples collected through Day 5 (EOT), so these analyses would not identify changes that emerged or persisted at later timepoints.

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Results of these analyses are summarized in Table 30. Consistent with the MOV mechanism of action, a greater proportion of participants in the MOV arms relative to the placebo arm had at least one treatment-emergent amino acid substitution or other structural nucleotide change (deletion, insertion) detected in the spike gene, and amino acid changes were scattered throughout the coding sequence. A total of 81 emergent spike substitutions/changes were detected among 38 MOV-treated participants and nine placebo-treated participants. Each of the nine placebo-treated participants had one treatment-emergent spike amino acid substitution detected, while a total of 72 substitutions were detected in the 38 MOV-treated participants (median one substitution per participant, range 1–7). Amino acid changes, including substitutions, insertions, or deletions, were detected in multiple participants at several spike amino acid positions, mostly in MOV-treated participants.

Table 30. Treatment-Emergent Amino Acid Changes (Through Day 5/EOT) Detected at ≥5% Frequency in Spike Sequences, MK-4482-002, Part 1

AA Change	# Participants in MOV Arms (Pooled, n=113)	# Participants in Placebo Arm (n=39)
Any treatment-emergent spike AA change	38 (34%)	9 (23%)
Total number of AA changes	72	9
Total number of AA changes per participant	1-7 per participant (18 with ≥2 changes)	1 per participant
AA positions with ≥2 participants with change		
NTD aa 139-145	5	0
ΔP139-Y145	1[a]	
P139S	1[a]	
ΔL141-Y144	1[a]	
ΔL141-Y144, Fins	1[a]	
ΔY145	1[a]	
G261I/V	2	0
S297L	1	1
T385I	2	0
E484K	2	0
P681H	2	0
S884F	1	1
A1022T	2	0

Source: FDA analysis
[a] Each of these is detected in a separate participant at variant frequencies of ~6 to 20%
Abbreviations: AA, amino acid; EOT, end of treatment; MOV, molnupiravir

Of particular interest, in multiple participants MOV treatment was associated with amino acid changes at sites/regions of the spike protein that are likely under immune or other evolutionary selective pressure. Amino acid changes at these sites are found in some SARS-CoV-2 variants of public health importance (e.g., see (Plante et al. 2021) for review; (Stanford 2021)). Our analyses identified or confirmed the following:

- Five MOV-treated participants (0 placebo-treated participants) had treatment-emergent amino acid substitutions, insertions, or deletions in the region of amino acids P139-Y145 in the N-terminal domain (NTD). This is an exposed region of the spike protein that is believed to be under strong antibody selective pressure (Harvey et al. 2021), and deletions or substitutions in this region are found in several important SARS-CoV-2 variants.

- Two MOV-treated participants (0 placebo-treated participants) had treatment-emergent E484K, which is a key receptor-binding motif substitution associated with neutralizing antibody escape and is present in several important SARS-CoV-2 variants.
- Two MOV-treated participants (0 placebo-treated participants) had treatment-emergent P681H, which is adjacent to the spike furin cleavage site and is present in multiple SARS-CoV-2 variants, and is in the same position where a P681R substitution has been hypothesized to enhance infectivity of the Delta variant (Liu et al. 2021).

Importantly, analyses of raw NGS data from the participants with the noted NTD changes confirmed the analyses of the .xpt analysis datasets. For example, while the ION Torrent NGS platform is prone to reporting single base insertion or deletion artifacts in homopolymeric sequence reads, the NGS reads in these NTD regions were generally of high quality and clearly indicated deletions of stretches of amino acid codons (i.e., multiples of 3, up to 21 nt).

Analysis of Spike Treatment-Emergent Amino Acid Changes: MK-4482-001

Similar analyses of SARS-CoV-2 spike sequence were conducted for the clinical trial MK-4482-001 (hospitalized population) (Table 31). Consistent with the MOV mechanism of action and the results from MK-4482-002, Part 1, participants treated with MOV in MK-4482-001 were more likely to have at least one detected treatment-emergent spike amino acid change, compared with those treated with placebo. Again, some notable observations include the following:

- Five MOV-treated participants (one placebo-treated participant) had treatment-emergent amino acid substitutions or deletions in the region of amino acids P139-Y145 in the NTD.
- Two MOV-treated participants (0 placebo-treated participants) had treatment-emergent P681H, adjacent to the spike furin cleavage site.
- One MOV-treated participant (0 placebo-treated participants) had treatment-emergent N501Y, which is another important spike change that contributes to neutralizing antibody escape and virus attachment.

The treatment-emergent changes noted above were detected in six (7%) MOV-treated participants and one (4%) placebo-treated participant. Three of these changes were detected in one MOV-treated participant, and in a large fraction of sequences (32 to 77%): ΔY145, N501Y, and P681H. This same participant had several other treatment-emergent amino acid changes in the spike protein and elsewhere in the genome, and the Sponsor reported that the viral clade designation changed for this participant between baseline and Day 3, so it is unclear if this reflects extensive MOV-associated mutagenicity, coinfection with another SARS-CoV-2 variant, or a technical issue. All of the other changes were detected in separate participants at relatively lower variant frequencies (5 to 12%).

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Table 31. Treatment-Emergent Amino Acid Changes Detected at ≥5% Frequency in Spike Sequences, MK-4482-001, Part 1

AA Change	# Participants in MOV Arms (Pooled, n=89)	# Participants in Placebo Arm (n=27)
Any treatment-emergent spike AA change	31 (35%)	5 (19%)
AA positions with ≥2 participants with change		
del_L141-Y144	2	0
G142V	1	0
ΔY145	2	1
A262S	1	1
N501Y	1[a]	0
P681H	2	0

Source: FDA analysis
[a] Treatment-emergent only in one participant but noted because it is associated with reduced susceptibility to some monoclonal antibodies.
Abbreviations: AA, amino acid; MOV, molnupiravir

Analyses To Explore Potential Clinical Relevance of Detected Spike Treatment-Emergent Amino Acid Changes

Additional analyses from MK-4482-002, Part 1 were conducted to explore the potential clinical impact of the MOV treatment-emergent changes in the spike protein, focusing particularly on the NTD changes and deletions of amino acids 139 to 145, and substitutions E484K and P681H. A total of seven (6%) MOV-treated participants had these treatment-emergent changes in the spike protein. Two participants had two of these changes detected: P139S+P681H and ΔP139-Y145+P681H. In all seven participants, these spike changes of interest were detected as minority variants comprising 5 to 20% of the viral RNA population.

These seven participants represent only a subset of the spike amino acid changes detected in MOV- or placebo-treated participants, and several other emergent amino acid changes were detected in MOV- and/or placebo-treated participants at positions of unknown significance throughout the spike protein. Five of the seven participants tested negative for anti-SARS-CoV-2 antibody at baseline, while results were not reported for the other two participants.

As shown in Figure 5, participants with the key spike amino acid changes of interest (changes in amino acids 139 to 145, E484K and P681H) had a shallower median decline in viral RNA levels in NP swab samples between the Day 3 and Day 5 (EOT) visits. However, this difference was transient, and it is unclear if this reflects a true difference or if this is attributed to the small sample size in the spike amino acid change group, as results for all individual participants show substantial variability in these results.

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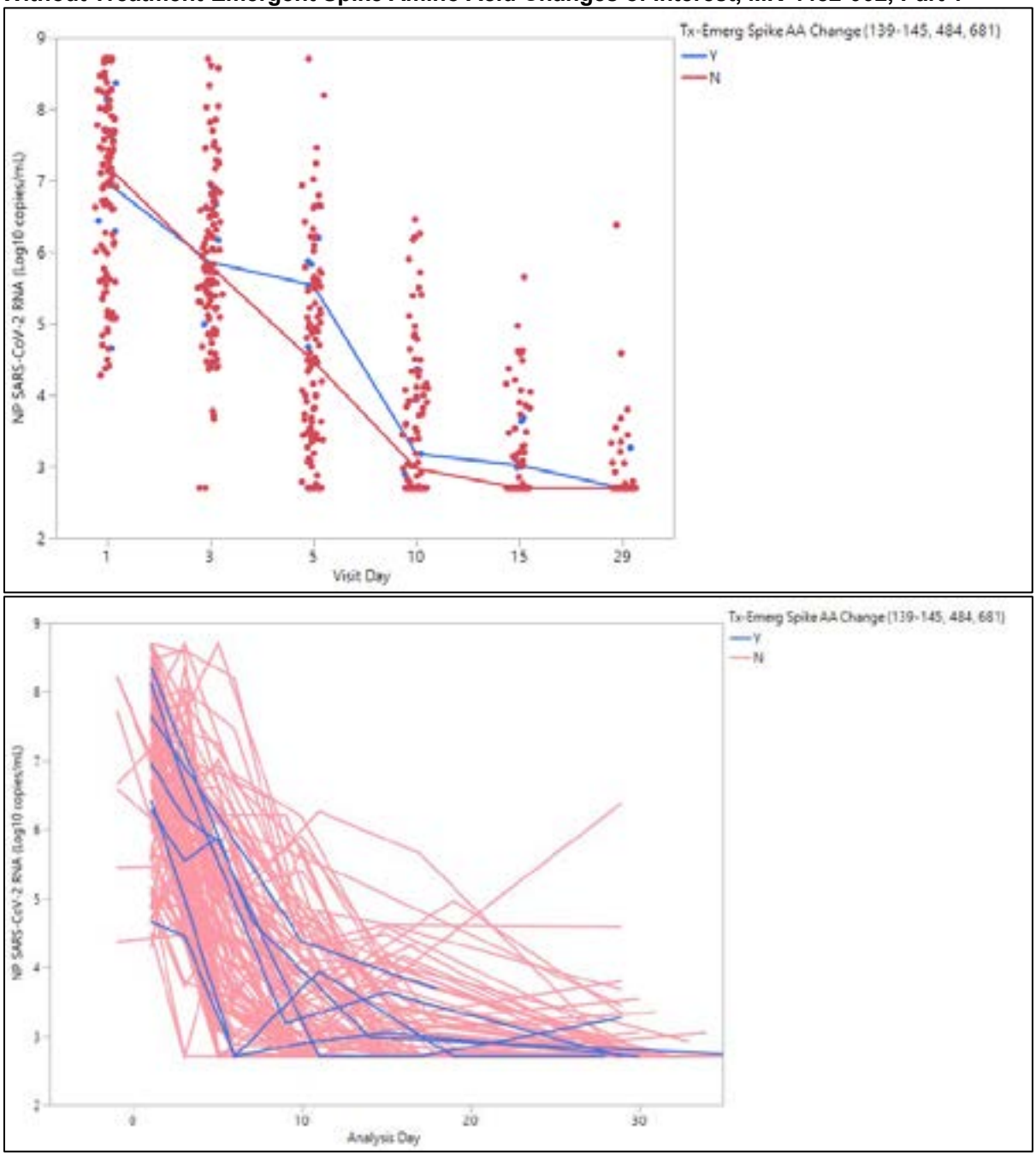
Figure 5. Viral RNA Levels in NP Swabs in MOV-Treated Participants Among Those With or Without Treatment-Emergent Spike Amino Acid Changes of Interest, MK-4482-002, Part 1



Source: FDA analysis
Note: Viral RNA shedding data are not shown for placebo-treated participants or participants without available sequence analysis data. Treatment-emergent sp ke amino acid changes were identified in samples collected on Day 3 or Day 5 (EOT); sequence analysis data are not available for later timepoints. Trendline in top panel shows median values. The bottom panel shows results for individual participants.
Abbreviations: AA, amino acid; MOV, molnupiravir; NP, nasopharyngeal; RNA, r bonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

There was no evidence that the emergence of these spike protein amino acid changes affected the levels of cell culture infectious virus in NP or OP specimens, although it should be noted that culturable virus was rarely detected across the entire study population (~10 to 20% at baseline, 0 to 4% postbaseline, NP samples). Of the seven participants with the key spike changes of interest, only one participant had cell culture infectious virus detected in an NP or OP specimen, and it was a baseline sample.

Furthermore, there was no evidence that the emergence of these spike amino acid changes contributed to enhanced disease, at least based on the clinical endpoint of hospitalization or death. None of the seven participants noted above reached this endpoint through Day 29. In addition, there was no clear evidence that participants with any treatment-emergent spike change were more or less likely to reach the clinical endpoint, although the hospitalization rate was low overall in MK-4482-002, Part 1.

Other observations and considerations from these analyses include the following:

- While treatment-emergent spike protein amino acid changes appeared to be detected at a higher rate in MOV-treated participants, it should be recognized that treatment-emergent spike amino acid changes were also observed in some participants treated with placebo, consistent with this being a protein under natural evolutionary pressure.
- A majority of the spike protein amino acid changes were detected as minority variants. Considering all of the 72 treatment-emergent spike amino acid changes detected in MOV-treated participants in MK-4482-002, Part 1, 56 (78%) of these changes were detected in <15% of the sequence population.
- Consistent with most changes occurring as minority variants, when sequence data were available for multiple postbaseline samples (NP or OP swabs, Day 3 or Day 5/EOT), the treatment-emergent spike amino acid changes were detected only in one sample, indicating compartmentalized or transient detection of these changes. Note that 38% (57/152) of participants in the MK-4482-002, Part 1 dataset had data from only a single postbaseline sample.
- Transition mutations are the types of mutations most often enriched by MOV and directly tied to its mechanism of action, but the types of nucleotide changes leading to the observed amino acid changes in spike were not all transition mutations. Other nucleotide changes leading to spike amino acid changes in these datasets included transversions, deletions and insertions. However, MOV (or more specifically, NHC-triphosphate) apparently can increase the rate of other types of nucleotide changes detected in clinical viral specimens. Also, in theory, some changes such as deletions could arise from error repair mechanisms. In any case, any uncommon types of nucleotide changes could become enriched in the viral population if they confer a selective advantage.
- In a few individual participants, numerous treatment-emergent spike changes were detected in association with other changes elsewhere in the genome, as noted above for the MK-4482-001 participant with treatment-emergent ΔY145, N501Y, and P681H. It is unclear if this reflects extensive MOV-driven mutagenesis and selection, coinfection with multiple SARS-CoV-2 variants, or a technical issue.

Conclusion

Collectively, these analyses indicate MOV treatment may increase the rate of emergence of SARS-CoV-2 populations with amino acid changes in the viral spike protein, consistent with its

mutagenic mechanism of action. However, there remain many uncertainties regarding these findings and their clinical and public health implications.

At the individual patient level, there was no evidence that the emergence of spike amino acid changes affected virologic or clinical outcomes in outpatients with COVID-19 in MK-4482-002, Part 1. However, the Division recognizes that the available data are limited, and in theory, MOV treatment-emergent changes in spike (or in other immune or drug targets) could have different clinical implications in different patient populations.

It is challenging to predict the broader public health risk of MOV treatment-associated spike amino acid changes. The most concerning public health risk would be that MOV mutagenesis could contribute to the emergence of novel SARS-CoV-2 variants with important phenotypic properties, such as reduced susceptibility to antibody-based therapeutics or vaccine-induced immune responses.

On the other hand, on a per-patient basis the transmissibility of such variants is likely quite low. Most spike protein changes observed in MK-4482-002, Part 1 were detected as minority variants. Even in the absence of an antiviral effect, overall viral shedding levels will be declining rapidly by the time a MOV-associated spike amino acid variant emerges in treated outpatients with COVID-19. The antiviral activity of MOV, which is linked directly to its mutagenic activity, likely accelerates this viral clearance. Consistent with MOV accelerating clearance of replication competent, transmissible SARS-CoV-2, there is evidence from a nonclinical study in ferrets that MOV can reduce SARS-CoV-2 transmission to untreated contact animals (Cox et al. 2020). There was no clear evidence that emergence of spike protein amino acid changes in MK-4482-002, Part 1 was associated with a rebound in viral RNA shedding, and cell culture infectious virus was not detected in any MOV-treated participants by Day 5/EOT (and only in 4% of placebo-treated participants at Day 5).

It also has to be recognized that the SARS-CoV-2 spike protein acquires genetic changes frequently, regardless of any MOV mutagenic activity. In the placebo arm in MK-4482-002, Part 1, 23% of participants with available data had a detected treatment-emergent amino acid change in the spike protein. Natural immune responses and other beneficial treatments and vaccines can also influence SARS-CoV-2 evolution. Therefore, it is unclear to the Division if treatment of outpatients with COVID-19 with MOV would change current patterns and trajectories of SARS-CoV-2 evolution.

This topic was discussed extensively during the November 30, 2021, Advisory Committee meeting and mixed perspectives were expressed by the Committee members. Some members had major concerns about the potential for MOV-associated mutagenesis of the SARS-CoV-2 spike gene to facilitate SARS-CoV-2 evolution, while others seemed less concerned on the basis that MOV may not have a substantial impact on SARS-CoV-2 evolution that is already occurring naturally. One Committee member noted that the overall impact of MOV on SARS-CoV-2 spike protein evolution may be minimal given that selective pressures on the spike protein (which are not directly affected by MOV) are the primary driver of SARS-CoV-2 evolution, and the impact of a MOV-associated increase in SARS-CoV-2 mutation rate may be minimized by the beneficial effect of MOV in facilitating viral clearance.

Most Committee members agreed that additional studies are warranted to characterize this risk, particularly in MOV-treated immunocompromised patients. Furthermore, Committee members recommended steps should be taken to maximize viral clearance in MOV-treated patients and minimize any potential risk of developing and transmitting new SARS-CoV-2 variants, such as advising patients to complete the 5-day dosing regimen.

To provide more insight into the mechanisms and individual patient and public health risks of MOV-associated SARS-CoV-2 spike changes, the Division has requested that the Sponsor continue to collect, analyze, and report viral sequencing data from the full randomized population in MK-4482-002, Part 2. In addition, the Division is requesting that the Sponsor conduct SARS-CoV-2 cell culture infectivity assays for any MK-4482-002 clinical specimens in which encoded amino acid changes are detected in the viral spike gene. These analyses will include MOV-treated immunocompromised patients from MK-4482-002, Part 2.

As additional studies are conducted to further characterize the risk of MOV-associated SARS-CoV-2 evolution, this risk is mitigated, in part, by the restriction of the EUA to patients without other treatment options, which in effect minimizes unnecessary use of MOV. Also further mitigating this risk, the Fact Sheet for Health Care Providers includes language recommending that patients complete the full 5-day treatment course and remain physically isolated in accordance with public health recommendations, which are intended to maximize viral clearance and minimize any potential risk of developing and transmitting new SARS-CoV-2 variants.

In summary, the Division currently does not have major concerns about the potential for MOV to enrich for low level variants with spike protein amino acid changes within an individual treated patient. However, it remains unclear if the potential for MOV-associated changes in the SARS-CoV-2 spike protein presents a significant risk to public health, considering the potential for widespread use of MOV. The additional studies and recommendations noted above are intended to further characterize and mitigate this theoretical risk, and thus help to optimize the risk-benefit profile of MOV.

4.5. Key Review Issue #5: Analyses of Potential MOV Resistance or Remdesivir Cross-Resistance in Clinical Trials

Background

The mechanism of MOV anti-SARS-CoV-2 activity involves interactions between the active triphosphate (NHC-TP), the template, and the viral replicase complex, primarily the viral RNA-dependent RNA polymerase (RdRp, nonstructural protein 12 [nsp12]). The viral 3'-5'-exoribonuclease (ExoN, nsp14) could also play a role in the mechanism of action and antiviral activity of MOV, as this viral protein has proof-reading activity that can correct errors in the SARS-CoV-2 genome. Multiple other nonstructural viral proteins (nsps7–10) are cofactors in the viral replicase complex and thus could also interact directly or indirectly with NHC or its metabolites. In theory, the development of SARS-CoV-2 resistance to MOV could involve amino acid changes in any of these viral proteins. Coronavirus resistance selection studies in cell culture did not identify any clear MOV or NHC resistance-associated substitutions.

Remdesivir (Gilead 2020) is an approved SARS-CoV-2 nucleotide analog RNA polymerase inhibitor indicated for adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization. Like MOV/NHC, the active triphosphate of remdesivir is a substrate of the viral RdRp (nsp12) and incorporates into viral RNA, although inhibition of viral replication is thought to occur primarily by RNA chain termination, not mutagenesis. Nevertheless, because both MOV and remdesivir interact with the viral RdRp, amino acid changes in RdRp associated with resistance to one drug could affect the antiviral activity of the other, referred to as cross-resistance. Amino acid changes in nsp12 reported to be potentially associated with reduced susceptibility or resistance to remdesivir

include F480L, D484Y, V557L, and E802A/D. None of these substitutions appeared to reduce NHC antiviral activity in cell culture using a SARS-CoV-2 replicon-based phenotypic assay.

This section summarizes analyses conducted by the Sponsor and FDA to characterize MOV treatment-emergent changes in the SARS-CoV-2 nsp12 and nsp14 in clinical trials to identify potential MOV resistance pathways, and to assess the potential for enrichment of viruses with cross-resistance to remdesivir.

Assessment

The same MK-4482-002, Part 1 and MK-4482-001 SARS-CoV-2 NGS analysis datasets described above for assessments of spike protein amino acid changes were used to characterize amino acid coding changes in the SARS-CoV-2 nsp12 (RdRp), and nsp14 (ExoN) genes. Again, results for all three MOV arms in each Phase 2 trial were pooled for analyses of treatment-emergent amino acid changes. Specific amino acid changes detected at the same amino acid position in ≥ two participants (pooled MOV- and placebo-treated) were identified for each trial and tabulated.

Results of these analyses are summarized in Table 32 and generally showed no clear patterns of MOV treatment-emergent amino acid substitutions in nsp12 or nsp14 in MK-4482-002, Part 1 or MK-4482-001. Consistent with the MOV mechanism of action, a greater proportion of participants in the MOV arms relative to the placebo arms had at least one treatment-emergent amino acid substitution or other change (e.g., deletion, insertion) detected in these targets, with the exception of nsp12 in MK-4482-001, and amino acid changes were scattered throughout the coding sequences.

There were no amino acid positions in nsp12 where treatment-emergent substitutions (or any other change) were detected at a ≥5% frequency in ≥ two participants in the pooled MOV/placebo population in MK-4482-002, Part 1. In MK-4482-001, only a single nsp12 substitution (G44V) was detected in ≥ two participants, and it was enriched in the placebo group.

In both MK-4482-002, Part 1 and MK-4482-001, no emergent amino acid changes were detected in any participants at any of the following potential remdesivir resistance-associated positions in nsp12: F480, D484, V557, or E802.

In nsp14, A220S/V and V466I were each detected in two (2%) MOV-treated participants in MK-4482-002, Part 1. The impact of these changes is unknown. In a SARS-CoV-2 replicon system, nsp14 A220S or A220V site-directed substitutions did not reduce NHC antiviral activity. No nsp14 substitutions were detected at the same position in ≥ two participants in MK-4482-001.

Table 32. Treatment-Emergent Amino Acid Changes (Through Day 5/EOT) Detected at ≥5% Frequency in nsp12 or nsp14, MK-4482-002, Part 1 and MK-4482-001

MK-4482-002, Part 1	# Participants in MOV Arms (Pooled, n=113)	# Participants in Placebo Arm (n=39)
nsp12 (RdRp)		
Any AA change	16 (14%)	2 (5%)
AA Positions with ≥2 participants with change		
None		
nsp14 (ExoN)		
Any AA change	16 (14%)	3 (8%)
AA Positions with ≥2 participants with change		
N129D	1	1
A220S/V	2 (1 S, 1 V)	0
V466I	2	

MK-4482-001	# Participants in MOV Arms (Pooled, n=89)	# Participants in Placebo Arm (n=27)
nsp12 (RdRp)		
Any AA change	9 (10%)	4 (15%)
AA positions with ≥2 participants with change		
G44V	1	2
nsp14 (ExoN)		
Any AA change	8 (9%)	0 (0%)
AA positions with ≥2 participants with change		
None		

Source: FDA analysis
Abbreviations: AA, amino acid, EOT, end of treatment; MOV, molnupiravir; nsp, nonstructural protein

Additional exploratory analyses were conducted to identify MOV treatment-associated amino acid changes in other viral nonstructural proteins (nsps1–11, nsp13, nsp15, or nsp16). In general, MOV treatment-emergent amino acid changes were scattered throughout these proteins, consistent with the random mutagenic effect of MOV, but there were no clear patterns of amino acid changes indicative of MOV resistance emergence.

Conclusion

In Phase 2 trials MK-4482-002, Part 1 and MK-4482-001, MOV treatment was not associated with any clear patterns of emergent amino acid changes in the nsp12 (RdRp) or nsp14 (ExoN) proteins that could indicate possible drug resistance. In addition, there was no evidence that MOV treatment enriched for SARS-CoV-2 variants with amino acid changes at nsp12 (RdRp) amino acid positions potentially associated with reduced SARS-CoV-2 susceptibility to remdesivir.

Therefore, the Division does not view MOV resistance or cross-resistance to remdesivir as significant risk issues at this time. Additional analyses of viral sequencing data from the larger MK-4482-002, Part 2 trial will be evaluated as they become available to continue to monitor these potential risks. Note that this topic was not discussed at the November 30, 2021, Advisory Committee meeting.

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X. Specific Populations

- Safety and PK data are not available in pediatrics, pregnant or lactating women, patients with moderate or severe hepatic impairment, or patients with severe renal impairment. MOV is not authorized for use in pediatrics and not recommended in pregnant individuals. Breastfeeding is not recommended for 9 days (5 days of treatment with MOV and for 4 days after the final dose).
- No dose adjustment is recommended in geriatric patients and patients with any degree of renal or hepatic impairment.

XI. Human Clinical Pharmacology

1. Absorption, Distribution, Metabolism, and Excretion

- MOV is a prodrug, which is hydrolyzed by carboxylesterases (CES1 and CES2) to NHC either during or after absorption based on in vitro study results. Both MOV and NHC have high solubility and high intestinal permeability.
- A high-fat meal did not significantly impact the AUC (AUC_{last} and $AUC_{0\text{-}inf}$) of MOV or NHC, but it decreased the geometric mean of C_{max} of NHC by 36% and delayed median T_{max} by 2 hours. Decrease in the geometric mean C_{max} of NHC is not expected to be clinically relevant and thus MOV can be given with or without food.
- NHC is taken up by nucleoside uptake transporters into tissues, and intracellularly phosphorylated to the pharmacologically active triphosphate anabolite NHC-TP by host kinases, and then ultimately degraded to uridine and/or cytidine via the same pathways as those involved in endogenous pyrimidine metabolism.
- NHC is not bound to plasma proteins, whereas the plasma protein binding of MOV was not assessed.
- MOV is a weak substrate of human concentrative nucleoside transporter (CNT)1, not a substrate of CNT2, CNT3, equilibrative nucleoside transporter (ENT)1 or ENT2.
- NHC is a substrate of CNT1, CNT2, CNT3 and ENT2, and it could not be excluded as a substrate of ENT1 based on the 1.8-fold increase in NHC uptake in MDCKII-ENT1 cells. However, no apparent inhibition of this ENT-1 mediated transport was observed due to the parallel inhibition of endogenous uptake of NHC by S-(4-Nitrobenzyl)-6-thioinosine, a known inhibitor of ENT, in the control MDCKII cells.
- The percentage of MOV dose administered recovered in urine over the time interval of 0 to 12 hours was ~3% (coefficient of variation percent, 81.6%) following multiple oral doses of 800 mg Q12H MOV.
- The effective half-life of NHC is 3.3 hours.

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2. Drug-Drug Interactions

No clinical drug-drug interaction studies have been conducted for MOV or NHC.

Potential drug-drug interaction liability of MOV or NHC as a victim (effect of other drugs on the absorption and disposition of MOV and NHC) is based on in vitro study results:

- MOV and NHC exhibits high solubility over gastrointestinal pH values and high intestinal permeability, thus gastric pH modifying agents are not expected to have a meaningful effect on MOV and NHC absorption.
- MOV and NHC are not substrates of CYP enzymes or human P-gp and breast cancer resistance protein transporters.
- MOV is a weak substrate of human concentrative nucleoside transporter 1 (CNT1), and is not a substrate of CNT2, CNT3, equilibrative nucleoside transporter1 (ENT1) or ENT2.
- The uptake of NHC into cells is mediated by host nucleoside transporters. NHC is a substrate of CNT1, CNT2, CNT3 and ENT2, and it could not be excluded as a substrate of ENT1. Based on the high transport capacity and functional redundancy of nucleoside transporters, coupled with the lack of clinically significant CNT or ENT mediated drug-drug interactions reported in the literature, clinically meaningful drug-drug interactions mediated by alteration of these transporters are not anticipated.
- The formation of NHC-TP from NHC is mediated by host kinases important in the regulation of endogenous pyrimidine nucleosides.

Potential drug-drug interaction liability of MOV or NHC as a perpetrator (effect of MOV or NHC on the absorption and disposition of other drugs) is based on in vitro study results. The mean $C_{max,ss}$ of MOV and NHC is 0.026μM and 8.99μM at the dose of 800 mg MOV every 12 hours, respectively.

- The potential for MOV and NHC to be reversible inhibitors of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 was evaluated in the range of 0.13 to 100μM. At 100μM, neither MOV or NHC inhibited 50% of the marker activity of any CYPs tested, therefore, 50% inhibitory concentration (IC_{50}) values of MOV and NHC are greater than 100μM. At concentrations of 10 and 50μM, neither MOV nor NHC demonstrated time-dependent inhibition of any CYP enzyme (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4) evaluated.
- IC_{50} values of MOV and NHC are greater than 100μM (concentration range of MOV and NHC evaluated: 0.3 to 100μM) for OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2K, and MRP2 and greater than 1000μM (concentration range of MOV and NHC evaluated: 3 to 1000μM) for MDR1 (P-gp) and breast cancer resistance protein.
- Neither MOV nor NHC produced an induction response in CYP1A2, 2B6, and 3A4 mRNA or enzyme activity at concentrations up to 20μM (concentrations of MOV and NHC evaluated: 0.1 to 20μM).

Due to the concerns regarding the potential embryo-fetal toxicity, a reliable method of contraception is advised to individuals of childbearing potential for 9 days (5 days of treatment and for 4 days after the last dose of MOV), and thus the drug-drug interaction potential with hormonal contraceptives was considered. Overall, the potential in vivo drug-drug interaction liability of MOV or NHC as a victim or perpetrator appears to be low and it is unlikely that MOV

or NHC will have a clinically significant pharmacokinetic drug-drug interaction with co-administered drugs, including hormonal contraceptives. The drug-drug interaction between MOV/NHC and concomitant medications, including other treatments for mild-to-moderate COVID-19, has not been evaluated.

3. Pharmacokinetics

The method validation and study sample analyses used to measure MOV and/or its metabolites in plasma, urine, and PBMC were found to be acceptable. All samples were analyzed within established analyte stability duration.

The prodrug MOV is rapidly metabolized to NHC, resulting in little to no systemic exposure of MOV. The pharmacokinetics of plasma NHC in healthy participants and patients with COVID-19 and the pharmacokinetics of NHC-TP in PBMCs in healthy participants after multiple oral doses of MOV are shown in Table 33 and Table 34, respectively. Pharmacokinetics of NHC has not been evaluated in specific populations including pediatrics, several renal impairment, moderate and severe hepatic impairment, pregnant women, and lactating women. Population PK analysis results indicated that [age (in adults ≥18), body weight, BMI, sex, race, ethnicity, mild hepatic impairment, mild-to-moderate renal impairment, disease severity] did not have a clinically significant effect on NHC exposures (refer to Figure 10 in Section XXVII.8).

Table 33. Pharmacokinetic Parameters of Plasma NHC After Multiple Oral Doses of 800 mg MOV Every 12 Hours

Parameter	Healthy Participants Geometric Mean (CV%)	Patients With COVID-19 Geometric Mean (CV%)
N	6	449 (178 for C_{max})
C_{max} (ng/mL)	2970 (16.8)	2330 (36.9)
$AUC_{0\text{-}12h}$ (ng/mL*hr)	8330 (17.9)	8260 (41)
C_{12h} (ng/mL)	16.7 (42.8)	31.1 (124)

Source: Reviewer's table based on study report MK-4482-004 for healthy participants and population pharmacokinetic memo for patients with COVID-19 patients
Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; COVID-19, coronavirus disease 2019; CV, coefficient of variation; MOV, molnupiravir; N, number of participants; NHC, N3-hydroxycytidine

Table 34. Pharmacokinetic Parameters of NHC-TP in PBMCs After Multiple Oral Doses of 800 mg MOV Every 12 Hours in Healthy Participants

Parameter	Geometric Mean (CV%)
N	6
C_{max} (nM)	28600 (48.6)
$AUC_{0\text{-}12h}$ (nM*hr)	275000 (46.5)
C_{12h} (nM)	16200 (42.7)

Source: Reviewer's table based on preliminary PK data from study P012.
Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; CV, coefficient of variation; MOV, molnupiravir; N, number of participants; NHC-TP, N3-hydroxycytidine triphosphate; PBMCs, peripheral blood mononuclear cells

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XII. Additional Nonclinical Data to Support Safety

Nonclinical reproductive toxicology, bone/cartilage toxicity, and genetic toxicology findings are discussed in Section IX.4 above. Other nonclinical safety data that do not rise to the level of risk mitigation were:

1. Central Nervous System

- No effects were noted for the central nervous system or body temperature in vivo in rats up to 16 times the human exposure (C_{max}).

2. Cardiovascular System

- Low risk of QT prolongation in vitro
- There were no effects on electrocardiogram or cardiovascular endpoints up to 5 times the clinical exposure in vivo in dogs.

3. Respiratory System

- No effects noted in rats up to 16 times the human exposure (C_{max}).

4. PK/ADME/TK

- Oral bioavailability was 37–45% in mice. Dose proportional exposure was noted with NHC and NHC-triphosphate in the brain, spleen, lung, and heart. The spleen and lung (in that order) had the most exposure to both NHC and NHC-triphosphate.
- In dogs and ferrets, tissue concentrations of NHC-TP tended to be greater than tissue concentrations of NHC. Conversely, in rats and monkeys, tissue concentrations of NHC tended to be greater than tissue concentrations of NHC-TP.

5. 7-Day Toxicology Findings

- Mild hematology decreases and slight AST/ALT increases in rats at 7 days.
- High dose toxicity in dogs associated with shock and tachycardia as well as decreases in testicular and epididymis weights (males) and ovaries and uterine weights (females) at 7 days in dogs.

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6. 28-Day Toxicology Findings

- There were no toxicologically significant findings in rats at NHC exposures up to 4 to 8 times the human exposure.
- In dogs, significant findings included the following:
  - Severe thrombocytopenia, 10-fold decrease in platelet counts, with subsequent hemorrhage in multiple tissues, especially in the GI track, but also in brain, spinal cord, gall bladder, thymus and mediastinal tissue and urinary bladder
  - Severe/marked bone marrow cellularity decreases at 17 and 50 mg/kg in femur and sternum
  - 10-fold increase (males) and 250-fold increase (females, with no observable erythroid precursors) in bone marrow M:E ratio at 50 mg/kg
  - Platelet values in treated dogs tended to match control animals during the recovery period
  - Systemic exposures to NHC at the NOAEL were 0.1-fold the clinical NHC AUC at 800 mg Q12H

7. 3-Month Toxicology Findings

- Bone and cartilage effects were noted (discussed in Section IX.4 above.
- Other findings included the following:
  - Decreased mean body weight gain and food consumption at exposures approximately equivalent to the mean clinical NHC exposure at 800 mg Q12H
  - Seminiferous tubule degeneration in 2 of 10 males and depletion of secretory acidophil cells of the pituitary in 9 of 10 males at exposures 15-fold the mean clinical NHC exposure at 800 mg Q12H.

8. Ongoing Studies

A study in juvenile rats to assess the potential impact of MOV on bone and cartilage development is ongoing. Until that study is complete and has been reviewed by the Agency, MOV is not advised for use in pediatric patients.

A carcinogenicity study in a transgenic mouse model is ongoing and will be reviewed upon submission.

A pharmacokinetic/distribution study in rats, specifically to determine distribution of NHC to testes, is ongoing. If NHC is detected in testes, the Sponsor will complete an assessment of mutant frequencies in testicular germ cells from transgenic Big Blue® rats.

SEE ATTACHED ADDENDUM

XIII. Nonclinical Data to Support Efficacy

1. Mechanism of Action

MOV is a 5'-isobutyrate prodrug of a mutagenic cytidine ribonucleoside analogue, β-D-N^4-hydroxycytidine (NHC, EIDD-1931). MOV is hydrolyzed by esterases to generate NHC, which circulates systemically. After cellular uptake, NHC is phosphorylated by host cell kinases to generate the active 5'-triphosphate, NHC-TP. The triphosphate acts as a competitive alternative substrate by the SARS-CoV-2 RdRp, nsp12, and the NHC-monophosphate (NHC-MP) is incorporated into RNA in place of the monophosphates of C or U, which is attributed to the N^4-hydroxycytosine base of NHC having two tautomeric forms allowing base pairing with either G or A (Flavell et al. 1974).

Over time, as NHC-MP is incorporated into viral RNA genomes and copied, changes accumulate in the viral genome, particularly G↔A and C↔U transition mutations, ultimately resulting in defective viral genomes. The mechanism of action of NHC as a viral RNA mutagen is well established and supported by data from several biochemical, cellular, and animal studies, as well as data showing increased numbers of nucleotide mutations in SARS-CoV-2 genome sequences from human participants treated with MOV in clinical trials.

2. Summary of Data Reviewed for Nonclinical Virology-Related Studies

Mechanism of Action and Cell Culture Antiviral Activity Studies

- In biochemical assays, NHC-TP could be used as a substrate by recombinant SARS-CoV-2 RdRp for incorporation into RNA. NHC competes primarily with C for incorporation into RNA, but it can also compete with U and thus can incorporate into RNA opposite of G or A in the RNA template leading to transition mutations (Gordon et al. 2021; Kabinger et al. 2021).
- NHC-TP is weakly competitive with natural ribonucleotides for use as a substrate by the SARS-CoV-2 RdRp. According to Gordon et al., 2021, SARS-CoV-2 RdRp shows a 30-fold preference for cytidine triphosphate over NHC-TP. Selectivity of the SARS-CoV-2 RdRp for other host ribonucleotides over NHC-TP was even greater at 171-, 424- and 12,841-fold for uridine triphosphate, adenosine triphosphate and guanosine triphosphate, respectively.
- The incorporation of NHC-MP does not cause RNA chain termination like other conventional antiviral nucleoside analogues. Rather, the RNA chain can continue to elongate, and subsequently, the incorporated NHC-MP can be used as a template by the viral RdRp for incorporation of G or A, further increasing the numbers of transition mutations (Gordon et al. 2021; Kabinger et al. 2021).
- In cell-based assays, NHC inhibited the replication of multiple different coronaviruses (including human coronaviruses and mouse hepatitis virus [MHV]), which was associated with increases in nucleotide changes, primarily transition mutations, throughout the viral genomes (Agostini et al. 2019; Sheahan et al. 2020).

- MOV antiviral activity in a Middle East respiratory syndrome coronavirus (MERS-CoV) mouse model was associated with increased numbers of transition mutations in viral genomes (Sheahan et al. 2020).
- NHC had cell culture antiviral activity against SARS-CoV-2 across multiple independent experiments and in a variety of cell types, with 50% effective concentration (EC_{50}) values at sub- to low micromolar concentrations (range: 0.32 to 2.66μM in A549 and Vero E6 cells), and selectivity indices generally >10.
- NHC had consistent cell culture antiviral activity against SARS-CoV-2 isolates representing different variants of concern/interest, including B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta).
- NHC had nonantagonistic antiviral activity with remdesivir against SARS-CoV-2 in a cell culture assay.
- NHC had no or minimal binding with mouse, rat, dog, cynomolgus monkey or human plasma proteins, as measured by equilibrium dialysis.

Assessments of Cytotoxicity and Off-Target Activity

- NHC had a wide range of 50% cytotoxicity (CC_{50}) values across a variety of different human and animal cell types. The most sensitive cell line evaluated was human lymphoid CEM cells, for which NHC had a CC_{50} value of 7.5μM (Sticher et al. 2020).
- MOV inhibited the proliferation of human bone marrow progenitor cells with CC_{50} values of 24.9μM and 7.7μM for erythroid and myeloid progenitor proliferation, respectively, in 14-day colony formation assays. The cytotoxicity of NHC in this assay was not determined, but it is assumed that NHC would have similar CC_{50} values in this assay based on NHC generally having comparable or lower CC_{50} and EC_{50} values than MOV across a variety of cell culture assays.
- NHC-TP is a weak substrate for human mitochondrial RNA polymerase resulting in incorporation of NHC-MP into mitochondrial RNA. The efficiency of NHC-TP as a substrate for mitochondrial RNA polymerase was estimated to be approximately 740-fold lower compared to natural cytidine triphosphate. Cell-based assays indicate NHC generally does not have highly specific effects on mitochondrial function (Sticher et al. 2020).
- There are multiple published reports that NHC-TP can act as a substrate for other RNA polymerases, including the human nuclear DNA-dependent RNA polymerase II enzyme that is responsible for mRNA synthesis. However, NHC-TP appears to have some selectivity for viral RNA polymerases over host RNA polymerases, and incorporation of NHC-MP by host RNA polymerases appears to be relatively inefficient compared to natural nucleotides (Stuyver et al. 2006; Suzuki et al. 2006; Toots et al. 2019). Incorporation of NHC-MP was not observed in cellular RNAs in ferret and mouse studies of MOV based on analyses of transition mutation rates in polymerase chain reaction-amplified complementary DNA (Toots et al. 2019; Sheahan et al. 2020).
- In biochemical assays, NHC-TP did not inhibit the human DNA polymerases α, β, or γ, with IC_{50} values >1,000μM (Sticher et al. 2020).

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Resistance Development in Cell Culture and Cross-Resistance

- MOV (primarily from studies with NHC) appears to have a relatively high resistance barrier, and to date, there are no known amino acid changes in SARS-CoV-2 that confer resistance to MOV or NHC.
- The full potential for cross-resistance between MOV/NHC and remdesivir remains unknown and should continue to be monitored and characterized in clinical and nonclinical studies, although based on currently available data there is no clear evidence of a cross-resistance signal between MOV/NHC and remdesivir. The active metabolites of both MOV/NHC and remdesivir interact with the viral RdRp complex and are incorporated into elongating viral RNA genomes, but their precise mechanisms of action differ in that remdesivir causes RNA chain termination, while NHC incorporation does not cause chain termination but leads the accumulation of mutations in viral genomes.
- Resistance to NHC was not readily selected by repeated passage of MHV or MERS-CoV in cell culture in the presence of NHC (Agostini et al. 2019). In this study MHV and MERS-CoV were passaged 30 times in the presence of increasing concentrations of NHC (up to 5μM for MHV, up to 6.5μM for MERS-CoV) in two independent passages for each virus. The passaged viruses had modest changes in susceptibility to NHC, with approximately 2-fold increases in EC_{90} values. Consistent with the mutagenic activity of NHC, the passaged viruses had numerous synonymous and nonsynonymous nucleotide mutations scattered throughout their genomes (27 to 162 total nucleotide changes after 30 passages).
- For NHC-passaged each virus, there was one position in nsp12 where amino acid substitutions emerged in both independent NHC passages: A234T/V in MHV and V558I in MERS-CoV, corresponding to positions V234 and V557 in SARS-CoV-2, respectively. The nsp12 V558I substitution that emerged in NHC-selected MERS-CoV is notable as this corresponds to the same amino acid position where a remdesivir resistance-associated substitution was identified in MHV (V553L) and SARS-CoV-1 (V557L) (Agostini et al. 2018). However, analysis of SARS-CoV-2 sequence data from clinical trials did not identify MOV treatment-emergent substitutions at this position.
- None of the following reported remdesivir resistance-associated substitutions in nsp12 conferred reduced phenotypic susceptibility to NHC in a SARS-CoV-2 replicon system: F480L (Agostini et al. 2018), D484Y (Martinot et al. 2021), V557L (Martinot et al. 2021), E802A (Szemiel et al. 2021), and E802D (Agostini et al. 2018). In all cases NHC EC_{50} values for the site-directed mutant replicons were <1.6-fold relative to a wild-type replicon. These substitutions reduced remdesivir activity in the same assay by 1.6- to 2.5-fold.
- The SARS-CoV-2 replicon system was also used to assess the impact of the following substitutions in nsp12 and nsp14, which were detected as possible MOV treatment-emergent substitutions in the Sponsor's Phase 2 resistance analyses: NSP12_T739I, NSP14_A220S, NSP14_A220T, NSP14_A220V, NSP14_S503L, and NSP14_S503P. NHC EC_{50} values for replicons with these substitutions were all <1.6-fold relative to a wild-type replicon.

Activity in Animal Models of SARS-CoV-2 Infection

MOV was shown to have antiviral activity in multiple animal models of SARS-CoV-2 infection, particularly when first administered prior to, or soon after viral challenge. Key published studies are summarized briefly as follows:

- MOV had anti-SARS-CoV-2 activity in a humanized mouse model in which immune deficient mice are implanted subcutaneously in the back with human lung tissue, referred to as human “lung-only mice” (Wahl et al. 2021). Mice were orally administered a relatively high dose of MOV (500 mg/kg) or vehicle control, 12 hours prior, 24 hours post- or 48 hours post-inoculation of the human lung tissue with SARS-CoV-2 (USA-WA1/2020), followed by twice daily (BID) dosing thereafter. Lung tissue was harvested 48 hours following virus inoculation or initiation of treatment. All three MOV dosing strategies were associated with reduced levels of virus detected in the lung tissues.
- MOV anti-SARS-CoV-2 activity was demonstrated in a nonlethal ferret model of infection (Cox et al. 2020). In one experiment, ferrets were challenged intranasally with 105 plaque-forming unit SARS-CoV-2 (2019-nCoV/USA-WA1/2020) and then administered MOV at 5 or 15 mg/kg BID starting 12 or 36 hours postchallenge. MOV dosing was associated with reduced SARS-CoV-2 viral titers in nasal washes within 12 hours of initiating dosing, and also in nasal turbinate tissues collected on Day 4 postchallenge. In a second experiment, infected ferrets were treated with MOV or vehicle and cohoused with uninfected and untreated contact ferrets. The contact ferrets of vehicle-treated infected animals began to shed SARS-CoV-2 within 20 hours of cohousing, while no virus (plaque-forming unit or RNA) was detected in the ferrets that were in contact with MOV-treated ferrets, indicating MOV inhibited SARS-CoV-2 transmission in this model.
- MOV (250 mg/kg) was active in a nonlethal Syrian hamster model of SARS-CoV-2 infection when administered starting at 12 hours prior to or 12 hours following viral challenge (Rosenke et al. 2021). Another independent study using the Syrian hamster model showed MOV (200 mg/kg) had consistent antiviral activity against SARS-CoV-2 B.1-G (Wuhan isolate), B.1.1.7 (Alpha), or B.1.351 (Beta) variants (Abdelnabi et al. 2021).

Substantially different doses of MOV were used to demonstrate antiviral activity in different animal species, which can be attributed to differences in efficiency of NHC-TP production in tissues. For example, in ferrets, oral doses as low as 5 mg/kg BID were associated with anti-SARS-CoV-2 activity (Cox et al. 2020). NHC is also active against influenza virus with EC_{50} values similar to those against coronaviruses, and it was shown that similarly low doses of MOV had activity against influenza virus in ferrets (Toots et al. 2019).

On the other hand, much higher doses of MOV (≥400 mg/kg BID) were needed for optimal anti-SARS-CoV-1) and anti-influenza virus activity in mice (Yoon et al. 2018; Sheahan et al. 2020). Following a single oral dose of MOV, comparable lung NHC-TP levels were detected in mice that received MOV at a 635 mg/kg dose and ferrets that received MOV at a 20 mg/kg dose. Furthermore, the plasma C_{max} levels of NHC associated with these lung NHC-TP concentrations were 12-fold higher in mice compared to ferrets. During the review this observation raised questions about whether tissue NHC-TP concentrations reach clinically relevant levels in rodent mutagenicity studies, but further analyses of NHC-TP concentrations in different animal species indicate clinically relevant concentrations of NHC-TP are likely achieved at the MOV doses evaluated in nonclinical rodent studies (see also Section IX.4.1 on mutagenicity risk).

XIV. Supply Information

Quantity of drug product needed for one treatment course per individual for proposed emergency authorized use (adults, pediatrics): 40 capsules are required for each treatment course.

SEE ATTACHED ADDENDUM

The Sponsor stated in an email dated December 13, 2021, that they have completed manufacturing of the 3.1 million patient treatment courses currently allocated to the U.S. market based on the agreed terms of the Biomedical Advanced Research and Development Authority contract. Packaging of capsules has initiated with (b) (4) patient treatment courses already packaged and located in their distribution center. The Sponsor stated that they plan to continue packaging in order to have the entire 3.1 million patient treatment courses available for release by the end of January 2022.

XV. Chemistry, Manufacturing, and Controls Information

The active ingredient, MOV, is manufactured (b) (4). MOV is an ester prodrug of N3-hydroxycytidine (NHC). Its structure was adequately characterized, and its manufacturing was sufficiently described and was found reasonable to produce consistent drug substance. (b) (4) is an adequately justified starting material and complies with the principles of ICH Q11. Drug substance in-process controls during development and EUA drug substance specifications were determined to be suitable to assure the quality of the drug substance.

Two specified impurities ((b) (4)) with limits above the ICH Q3A qualification threshold were confirmed to be acceptable by the nonclinical reviewer for this EUA. The risk for elemental impurities, nitrosamines, and residual solvents were adequately addressed by controls at the starting material and API manufacturing sites and by confirmatory testing by the Office of Pharmaceutical Quality's Office of Testing and Research. Data supported a 24-month drug substance retest period.

The Sponsor proposes to use drug substance from four manufacturers for inclusion in this application (b) (4)). There are two drug substance intermediate suppliers which supply these sites: (b) (4)). Further, drug substance from three development manufacturers were also used to manufacture EUA drug product: ((b) (4)).

Batch data from all sites were found to be comparable with respect to quality and all met the proposed specification. API from all seven drug substance manufacturers will be used in drug product for the initial EUA distribution. The three developmental drug substance suppliers are being phased out for production, while some newer commercial suppliers such as (b) (4) have provided release data for only a few batches. Although the manufacturing process slightly differs during development (i.e., process 1A, 1B, 1C, 1D, and 1E reported), all processes (b) (4). The chemistry, manufacturing, and controls information submitted demonstrates an appropriate risk-based approach to controlling drug substance quality for an initial EUA.

The drug product are 200 mg strength capsules packaged in 40-count high-density polyethylene bottles with a polypropylene induction sealed closure. (b) (4) % w/w of the capsule fill is drug substance with (b) (4) % microcrystalline cellulose ((b) (4)), (b) (4) % hydroxypropyl cellulose ((b) (4)), (b) (4) % croscarmellose sodium ((b) (4)) and (b) (4) % magnesium stearate ((b) (4)). All inactive ingredients including the capsule and inks are Compendial.

The Sponsor initially proposed to distribute 34 million capsules without an imprint, which was 25% of the Sponsor's planned U.S. government supply. After discussions with the Office of New Drugs, the Sponsor was informed on November 16, 2021, by the Agency that, "The public health benefits of having all solid oral dosage forms contain imprinting include, among other things, the ability to easily and uniquely identify the drug product dispensed, in this case for self-administration, and to reduce the potential for medication errors. Given the importance of imprinting, FDA intends to authorize only those finished capsules of MOV that contain imprinting at this time."

Each 200 mg strength capsule has a total fill weight target of (b) (4) mg. The manufacturing process includes (b) (4). The process was developed from lab scale, scale up to pilot scale, then to commercial scale. The process parameter ranges and proposed IPCs and their limits are adequately justified. The drug product is manufactured at three sites: (b) (4), and (b) (4). The manufacturing process used at each site was comparable, as was the quality of product from each of the sites.

The Sponsor was informed on November 16, 2021, that their data supported a 24-month expiry period.

XVI. Manufacturing Site Inspections

All of the manufacturing sites evaluated listed below are associated with IND 147734, and the commercial Sponsor is Merck Sharp & Dohme., a subsidiary of Merck & Co., Inc.

Table 35. Manufacturing Site Inspections

Manufacturing Site Identifier	Drug Substances / Intermediates/ Drug Product / Testing /Labeler / Packager	Location (U.S. and Non-U.S.)	Inspection Dates	GMP Status (if Known)
(b) (4)	DS and DS intermediate manufacturing and testing	(b) (4)		Acceptable
	DS and DS intermediate manufacturing for initial EUA batches only			Acceptable
	DS manufacturing and testing for initial EUA batches only			Acceptable
	DS and DS intermediate manufacturing and testing for initial EUA batches only			Acceptable
	DS and DS intermediate manufacturing and testing			Acceptable
	DS and DS intermediate manufacturing and testing			Acceptable[1]
	DS and DS intermediate manufacturing and testing			Acceptable

(b) (4)	DS Intermediate manufacturing	(b) (4)	Acceptable
	DS Intermediate manufacturing testing for DS		Acceptable
	DS Intermediate manufacturing		Acceptable
	DP manufacturing and testing		Acceptable
(b) (4)	DP manufacturing and testing	(b) (4)	Acceptable
(b) (4)	DP manufacturing packaging, and testing	(b) (4)	Acceptable
	Testing for DS		Acceptable
	Testing for DS		Acceptable
	Testing for DS		Acceptable
(b) (4)	Testing for DP	(b) (4)	Acceptable
(b) (4)	Microbial Testing for DP	(b) (4)	Acceptable
(b) (4)	Labeler / Packager	(b) (4)	Acceptable
(b) (4)	abeler / Packager	(b) (4)	Acceptable
	esting for DS		Acceptable
	tarting material manufacturing		OAI[2]
	tarting material manufacturing		OAI[3]

[1] (b) (4) was inspected by the FDA from (b) (4). No issues were identified, and the inspection was classified NAI.

[2] (b) (4) was inspected by FDA from (b) (4) and determined that the inspection classification of this facility is OAI, and the facility will remain on Import Alert 66-40. To mitigate the risk, the Sponsor has committed to performing additional screening for foreign contamination (e.g., (b) (4)) on all lots of (b) (4) used in the manufacture of MOV API.

[3] (b) (4) was last inspected by the FDA from (b) (4) and determined that the inspection classification of this facility is OAI. To mitigate the risk, the Sponsor has committed to performing additional (b) (4) testing for all lots of (b) (4) used in the manufacture of MOV API until further notification by FDA.

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[8]:

- The Sponsor will manufacture MOV to meet all quality standards and per the manufacturing process and control strategy as detailed in the Sponsor's EUA request. The Sponsor will also test the API starting material for additional quality attributes agreed upon by the Sponsor and the Agency. 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 MOV 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
  - 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.

  The Sponsor 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, the Sponsor must recall them.

  If not included in its initial notification, the Sponsor must submit information confirming that the Sponsor 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. The Sponsor must submit this information as soon as possible but no later than 45 calendar days from the initial notification.
- The Sponsor will list MOV 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.

8 See the evaluation documented in OMQ's Authorization Recommendation Memo for Emergency Use Authorization in CMS Case #621564,], as well as OPQ's Chemistry, Manufacturing, and Controls EUA Assessment Memo, dated December 21, 2021, associated with EUA 108.

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XVII. Clinical Trial Site Inspections

Clinical trial site inspections were not conducted for this EUA. Office of Scientific Investigations (OSI) requested the following information to determine if a good clinical practice inspection was warranted. Based on review of the submitted data and documents, OSI did not observe any signals that would trigger a good clinical practice inspection during the review of the EUA.

OSI's information request (IR) on November 11, 2021, for Part 2 of MK-4482-002 included requests for site-specific information such as number of participants screened, enrolled, randomized, and discontinued; efficacy and safety data by country and site; and the Sponsor's quality assurance plan, including their monitoring plan and data management plan.

OSI reviewed the Sponsor's November 19, 2021, response to the IR. The Sponsor's site monitoring plan and data management plan appeared adequate. The line listings provided by the Sponsor were not enough to determine if there were any outliers in the efficacy result or reported AEs and SAEs by country and by site for Part 2 of MK-4482-002. The majority of the data from this study were obtained outside the United States.

A follow-up IR was sent in order to obtain additional information to determine if there were any outliers with respect to efficacy or safety. OSI reviewed the Sponsor's December 6, 2021, response regarding the incidence of hospitalization or death through Day 29 by country and site in the mITT population; and AEs and SAEs by country and site during treatment and the 14-day follow-up period in all study participants. It appears that Brazil and Guatemala were outliers for incidence of hospitalization or death through Day 29. However, in Guatemala, the results favored placebo. There did not appear to be any outliers for AEs. In terms of SAEs, at least one SAE was reported in the majority of countries. The three countries without a participant with a reported SAE randomized a small number of participants (Argentina n=1; France n=7; and Germany n=2).

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

At the time of this review, the COVID-19 Treatment Guidelines Panel recommends using either bamlanivimab plus etesevimab, or casirivimab plus imdevimab or sotrovimab to treat outpatients with mild-to-moderate COVID-19 who are at high risk of clinical progression. The strength of the evidence for using anti-SARS-CoV-2 mAbs varies depending on the medical conditions and other factors that place patients at high risk for progression to severe COVID-19 and/or hospitalization. See the National Institutes of Health (NIH) COVID-19 Treatment Guidelines (NIH 2021) for further details.

The Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients With COVID-19 (IDSA 2021) states: Among ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease, the Infectious Diseases Society of

America guideline panel suggests bamlanivimab/etesevimab, casirivimab/imdevimab, or sotrovimab rather than no neutralizing antibody treatment. (Conditional recommendation, Moderate certainty of evidence)

XX. Advisory Committee Summary

Below is a summary of the Advisory Committee discussion (FDA 2021)[9].

Questions to the Committee

Discussion 1: Potential Use of MOV During Pregnancy, Both in Terms of Risk and Benefit

1. Comment if you think MOV should be accessible for use in pregnancy in certain scenarios, and if so, please describe what those scenarios might be.
2. Do the concerns regarding the use of MOV during pregnancy extend to the use of MOV in individuals of childbearing potential? If so, are there mitigation strategies that should be considered?

Committee Discussion

Committee members described the following as possible scenarios in which MOV should be made accessible to pregnant individuals: those with multiple comorbidities who are early in their disease course and are not being effectively treated with monoclonal antibodies (mAbs), or for whom alternative treatments are not available or accessible. Committee members also considered the pregnancy trimester a possible factor in deciding to use MOV. There appeared to be consensus that MOV should not be used in the first trimester.

In general, Committee members agreed that the decision to use MOV should be made using a shared decision-making approach to ensure that pregnant individuals are informed of MOV's potential fetal risks. One Committee member stated that there would not be a scenario in which they would recommend MOV to a pregnant individual.

With regards to use of MOV in individuals of childbearing potential, the Committee members agreed with the Agency's proposed mitigation strategies to confirm that a woman is not pregnant and is using effective contraception before taking MOV. Several Committee members noted that a shared decision-making approach should still be used in these individuals. Please see the transcript for details of the Committee's discussion.

Discussion 2: Concern Regarding Observed Increased Rate of Viral Mutations Involving Spike Protein Among Participants Receiving MOV

1. Comment on what, if any, additional risk mitigation strategies or limitations on the authorized population could be considered.

[9] See the following website for the Advisory Committee meeting information and event materials: https://www.fda.gov/advisory-committees/advisory-committee-calendar/november-30-2021-antimicrobial-drugs-advisory-committee-meeting-announcement-11302021-11302021

2. What monitoring strategies should be considered to better understand and mitigate these concerns?

Committee Discussion

Overall, most Committee members expressed concerns over the mutagenicity of MOV on the viral genome, particularly in the spike gene. Committee members agreed that there should be risk mitigation strategies for individuals receiving MOV to prevent escape of potentially novel viral variants. One Committee member recommended the continued use of precautions such as avoiding sharing rooms with individuals on treatment, wearing masks, and completing two negative SARS-CoV-2 tests prior to ending isolation.

Another Committee member suggested using pharmacies to facilitate viral sampling of individuals receiving MOV as a monitoring strategy to better understand the risk of generating and spreading viral variants. However, one Committee member noted that the overall impact of MOV on viral evolution may be minimal given that selective pressures on the spike protein, which are not directly affected by the drug, are the primary driver of SARS-CoV-2 evolution.

Although some other Committee members similarly noted their concerns over the increased rate of viral mutations are lessened given the drug's ability to quickly reduce virus production, there were specific concerns over prolonged viral replication in immunocompromised individuals. These Committee members expressed a need for additional studies in immunocompromised individuals. Please see the transcript for details of the Committee's discussion.

Vote

1. Do the known and potential benefits of MOV outweigh the known and potential risks of MOV when used for the treatment of mild-moderate COVID-19 in adult patients who are within 5 days of symptom onset and are at high risk of severe COVID-19, including hospitalization or death?

    a. If yes, please describe the appropriate authorized population such as risk factors for disease progression and pregnant individuals. Please comment on the proposed risk mitigation strategies and if additional risk mitigation strategies are needed.
    b. If no, please describe your reasons for concluding that the overall benefit-risk for MOV is not favorable for any population based on the data available at this time.

Vote Result

Yes: 13 No: 10 Abstain: 0

Committee Discussion

A slight majority of Committee members voted that the known and potential benefits of MOV outweighed its known and potential risks when used for the treatment of mild-moderate COVID-19 in adult patients who are within 5 days of symptom onset and are at high risk of severe COVID-19, including hospitalization or death.

Committee members who voted "Yes" described the authorized population as high-risk, unvaccinated individuals. Some Committee members stated they would not recommend MOV in pregnant individuals unless alternative treatments were not available. These Committee members also recommended against its use during the first trimester of pregnancy. Several Committee members who voted "Yes" expressed concern about potential mutagenicity. In general, Committee members were supportive of the Agency's proposed risk mitigation

strategies and mentioned additional strategies such as shared decision-making prior to treatment and minimizing household contacts while on treatment.

Committee members who voted “No” cited the following as reasons for concluding that the overall benefit-risk ratio was unfavorable: (1) a high number-needed-to-treat compared with placebo, (2) unclear efficacy against the Delta variant, (3) potential to drive viral mutations, and (4) mutagenicity risks. Several Committee members also expressed concerns over monitoring treatment adherence. Overall, Committee members agreed there is a need for additional safety data, as well as further studies in the vaccinated and immunocompromised. Please see the transcript for details of the Committee’s discussion.

XXI. Benefit-Risk Assessment and Recommendations for Emergency Use

In a single Phase 3 trial in1433 high-risk adults with mild-to-moderate COVID-19, a 5-day course of the oral antiviral MOV was associated with an adjusted risk difference of -3% and an adjusted relative risk reduction of 30% in hospitalization or death through Day 29 compared to placebo. Notably, at an interim analysis of data from 50% of the planned population (N=775), MOV was associated with a 48% relative reduction, which led to the trial being stopped early for efficacy. The cause of the decrease in efficacy between the first and second half of the trial remains unclear. At the time of this review, no therapies are FDA-approved for the treatment of mild-to-moderate COVID-19, though three mAb regimens requiring IV or SC administration are authorized under EUA for this use.

MOV was generally safe and well tolerated among clinical trial participants. However, several potential risks to patients have been identified based on findings from the available nonclinical data and include the risk of embryo-fetal toxicity, impaired bone and cartilage growth, and mutagenicity. Additional nonclinical data are being collected to better understand the risks these findings pose to patients, including a juvenile toxicology study, carcinogenicity study, and a germ cell study. Lastly, in addition to the known and potential risks to individual patients, there is also a potential risk based on the finding of an increased rate of amino acid changes in the SARS-CoV-2 spike protein among participants treated with MOV. The clinical and public health implications of this finding remain uncertain. Fortunately, these changes did not appear to be associated with hospitalization or death among the small subset of participants from MOV clinical trials for whom these data are available. However, on a large scale, these changes could, in theory, enhance SARS-CoV-2 spike protein evolution. It is not clear that further restrictions on the authorized population would be sufficient to meaningfully impact this trajectory should these theoretical concerns be realized.

Given that the potential risks of MOV are offset by only modest clinical benefit and given that there are other authorized products for the same use that have more favorable benefit-risk profiles, the review team has concluded that MOV should be authorized as a second line agent. Specifically, we recommend that MOV be authorized for the treatment of mild-to-moderate COVID-19 in adults with a positive result of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who are at high risk for progression to severe COVID-19, including hospitalization or death and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate. The authorization will be limited to patients who are within 5 days of symptom onset.

Within the framework of second-line usage, high-risk for progression to severe disease will be defined in accordance with the CDC’s high-risk criteria. Data on efficacy in various high-risk

subgroups represented in MK-4482-002 will be reported in the fact sheet to inform the benefit/risk assessment of MOV use in individual patients. Similarly, prescribers should factor a patient's COVID-19 vaccination status into the benefit/risk assessment. Irrespective of COVID-19 vaccination status, MOV may provide benefit in high risk patients with mild-to-moderate COVID-19 for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.

Given the embryo-fetal toxicity and bone and cartilage findings, the use of MOV during pregnancy is generally not recommended. However, the review team, taking into consideration the data and the advice of the Advisory Committee members, has concluded that there may be certain clinical situations in which the known and potential benefits of MOV outweigh the potential risks of MOV use during pregnancy. There will be a Warning and Precaution in the health care provider fact sheet describing the potential for fetal harm should MOV be used during pregnancy. The prescribing health care provider will be required to document that the patient has been informed about the benefits and risks of taking MOV during pregnancy. Further, the Agency has proposed recommendations for contraception use and assessing pregnancy status. Lastly, the Sponsor will collect data on pregnancy exposures and outcomes via a pregnancy surveillance program.

Given potential impact of MOV on bone and cartilage growth, the generally benign COVID-19 disease course in pediatric patients, and the availability of other therapies authorized for use in pediatric patients, there are no situations in which the known and potential benefits of MOV are thought to outweigh the known and potential risks in pediatric patients. Therefore, MOV will not be authorized for use in pediatric patients and the health care provider fact sheet will include a Warning and Precaution describing the potential risks to pediatric patients.

Lastly, the overall risk of mutagenicity in humans is considered low. The risk of mutagenicity in association with MOV use under the EUA will be further reduced by the short, 5-day treatment course and statements on the Fact Sheets stipulating that MOV not be authorized for use for more than 5 consecutive days and that MOV be dispensed in the original container as a single treatment course. In addition, until data regarding the potential for MOV to induce germ cell mutations, male patients will be advised to use effective contraception for 90 days after the last dose of MOV. The risk beyond 3 months after the last dose of MOV is unknown.

In conclusion, the totality of the currently available data regarding the potential benefits and risks of MOV support its use only as a second line agent for the treatment of mild-to-moderate COVID-19. Specifically, we recommend that MOV be authorized for the treatment of mild-to-moderate COVID-19 in adults with a positive result of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who are at high risk for progression to severe COVID-19, including hospitalization or death and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate. FDA has also determined that the known and potential benefits of MOV, when used for the treatment of mild-to-moderate COVID-19 as described in Section III, 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 MOV as described above.

In addition, to support an ongoing benefit/risk assessment of MOV use under the EUA, the Sponsor will be required to conduct several additional assessments, including a pregnancy surveillance program with mandated reporting by prescribers (provided the patient agrees to participate in the pregnancy surveillance program and allows the prescriber to disclose patient specific information to the Sponsor), an investigation into the inconsistent efficacy results in MK-

4482-002, a transgenic rodent germ cell gene mutation assay, and various clinical and nonclinical virology analyses as a condition of the authorization.

XXII. Considerations for Adverse Event Monitoring

This product will be used either in clinical trials under IND or in clinical practice under EUA. In clinical trials, FDA IND safety reporting regulations will apply. In clinical practice, EUA-labeled product will be made available. In the setting of a pandemic where practicing physicians will have many 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 MOV use and considered potentially related to MOV within 7 calendar days from the health care provider's awareness of the event. The reports should include unique identifiers and the words "MOV use for COVID-19 under Emergency Use Authorization (EUA)."

XXIII. 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.

The review team provided the Office of the Assistant Secretary for Preparedness and Response with a checklist tool for prescribers that outlines all patient eligibility criteria and mandatory prescriber requirements. Use of the checklist tool is discretionary. The checklist may be provided to help states and sites manage the mandatory requirements for MOV use.

XXIV. 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 and Caregivers is as follows:

- Each carton contains one bottle of forty 200 mg MOV tablets (one treatment course).
  - The fact sheets will include the global URL www.molnupiravir.com.
  - The carton has a QR code on it, which directs users to the Global URL www.molnupiravir.com. The global labeling site www.molnupiravir.com will allow users to select their country for country-specific information.

.....FDA agrees with the plan for implementation for dissemination of the following fact sheets:

- Fact Sheet for Health Care Providers (See Section XXVII.3)
- Fact Sheet for Patients and Caregivers (See Section XXVII.4)

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XXV. Outstanding Issues/Data Gaps

Nonclinical

- Results of a pharmacokinetic (PK) study in wild-type Fisher 344 rats to establish if NHC or NHC-TP is detected in testes. The study should include plasma exposure levels that meet/exceed the human exposure for NHC. Results of the PK study will be submitted by March 2022.
- If the results of the PK study demonstrate NHC or NHC-TP distribution to testes, conduct a male germ cell mutation assay in the Big Blue® rat model. A protocol for the Big Blue® rat assay will be submitted no later than 30 days after the PK results are submitted to FDA (April 2022). Results from the Big Blue® rat assay will be submitted by July 2023.

Clinical

- Conduct a thorough investigation into the differences in efficacy observed in the first and second half of Part 2 of MK-4482-002. This assessment should involve the synthesis of data, including, but not limited to, the agreed upon additional baseline serology testing, a detailed comparison of baseline characteristics (including demographic, clinical disease, and virologic characteristics), and an exploration of potential differences in standard of care by region and over time. A preliminary report will be submitted by March 2022. The final report, including additional serology results, will be submitted by September 2022.

Clinical Virology

- Submit the complete viral shedding results and full genome SARS-CoV-2 nucleotide sequencing results from the full randomized population in MK-4482-002, Part 2. Viral sequencing analyses should include all baseline and end-of-treatment (Day 5) samples with sufficient RNA levels for analysis, as well as all post-treatment samples with viral RNA levels ≥100,000 copies/mL. Cell culture infectivity assessments should be conducted for any clinical specimens in which amino acid changes were detected in the SARS-CoV-2 spike protein. Submissions should include summary report(s) and associated datasets (including analysis-ready datasets and raw fastq NGS data). A separate summary should be provided describing the results of the viral shedding and sequencing analyses specifically from immunocompromised patients.
- Evaluate the cell culture antiviral activity of MOV against an authentic SARS-CoV-2 isolate representative of the Omicron variant.
- Provide samples as requested of the authorized MOV to HHS for evaluation of activity against emerging global viral variants of SARS-CoV-2, including specific amino acid substitution(s) of interest (e.g., variants that are highly prevalent or that harbor substitutions in the target protein(s)) within 5 business days of any request made by HHS. Analyses performed with the supplied quantity of authorized MOV may include, but are not limited to, cell culture potency assays, biochemical assays, and in vivo efficacy assays.
- Establish a process for monitoring genomic database(s) for the emergence of global viral variants of SARS-CoV-2 and provide reports to the Agency on a monthly basis summarizing any findings as a result of its monitoring activities and as needed, any follow-up assessments planned or conducted.

- Assess the activity of the authorized MOV against any global SARS-CoV-2 variant(s) of interest (e.g., variants that are prevalent or becoming prevalent that harbor substitutions in the target protein or in protein(s) that interact with the target protein).

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XXVII. Appendices

1. MK-4482-002, Part 1 Efficacy

The primary and secondary efficacy endpoints are the same for Part 1 of the trial as those for Part 2 of the trial, described above.

The proportion of participants who were hospitalized or died through Day 29 was comparable across intervention groups. No participant died and 11 participants were hospitalized through Day 29 (Table 36).

Table 36. Incidence of Death or Hospitalization Through Day 29, MK-4482-002, Part 1, mITT Population

			Treatment vs. Placebo		
Treatment	**N**	**n (%)**	**Unadjusted Risk Difference**	**Adjusted** Risk Difference **% (95% CI)[a]**	**p-Value[b]**
MOV 200 mg	74	1 (1.4)	-4.1	-4.1 (-12.2, 2.5)	0.1676
MOV 400 mg	77	3 (3.9)	-1.5	-1.5 (-9.9, 6.2)	0.6668
MOV 800 mg	74	3 (4.1)	-1.4	-1.3 (-9.6, 6.4)	0.7141
Placebo	74	4 (5.4)			
Pairwise Comparison Among MK Treatment Groups			**Unadjusted Difference**	**Adjusted** Risk Difference **% (95% CI)[a]**	**p-Value[b]**
MOV 400 mg vs. MOV 200 mg			2.5	2.5 (-3.9, 9.8)	0.3351
MOV 800 mg vs. MOV 200 mg			2.7	2.7 (-3.7, 10.1)	0.3121
MOV 800 mg vs. MK-4482 400 mg			0.2	0.3 (-7.3, 8.3)	0.9342

Source: Clinical study report, Table 11-1
[a] Adjusted differences, the corresponding confidence intervals and p-values are based on Miettinen & Nurminen method stratified by time of symptom onset (≤5 days, >5 days)
[b] Nominal 2-sided p-value
Unknown Day 29 survival status is treated as failure
Abbreviations: CI, confidence interval; mITT, modified intent-to-treat; MOV, molnupiravir

Post hoc subgroup analyses showed clinical benefit of MOV for participants with time to symptom onset within 5 days of randomization and at increased risk for severe disease (i.e., having at least one baseline risk factor; Table 37).

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Table 37. Incidence of Hospitalization or Death Through Day for Participants With Symptom Onset ⩾5 Days and at Increased Risk for Severe Disease, mITT Population

			Treatment vs. Placebo	
Treatment	**N**	**n (%)**	**Risk Difference % (95% CI)[a]**	**p-Value[b]**
MOV 200 mg	38	1 (2.6)	-9.1 (-24.5, 3.5)	0.1307
MOV 400 mg	38	2 (5.3)	-6.5 (-22.3, 7.5)	0.3224
MOV 800 mg	31	1 (3.2)	-8.5 (-24.1, 6.1)	0.2004
Placebo	34	4 (11.8)		
Pairwise Comparison Among MOV Treatment Groups			**Risk Difference % (95% CI)[a]**	**p-Value[b]**
MOV 400 mg vs. MOV 200 mg			2.6 (-9.0, 15.1)	0.5584
MOV 800 mg vs. MOV 200 mg			0.6 (-10.8, 14.0)	0.8845
MOV 800 mg vs. MK-4482 400 mg			-2.0 (-14.7, 11.7)	0.6820

Source: Clinical study report, Table 14.2-47
[a] Adjusted differences, the corresponding confidence intervals and p-values are based on Miettinen & Nurminen method
[b] Nominal 2-sided p-value
Abbreviations: CI, confidence interval; mITT, modified intent-to-treat; MOV, molnupiravir

2. Additional Analyses by Baseline Serostatus, MK-4482-002, Part 2

Among participants with anti-SARS-CoV-2 N antibody detected at baseline, SARS-CoV-2 RNA levels in NP swabs were ~4 $\log_{10}$ copies/mL lower compared to those without detected baseline anti-SARS-CoV-2 antibody (Figure 6). Baseline anti-SARS-CoV-2 N antibody-positive participants showed reduced declines in NP viral RNA levels over time regardless of treatment arm, which is expected given the lower viral RNA levels at baseline.

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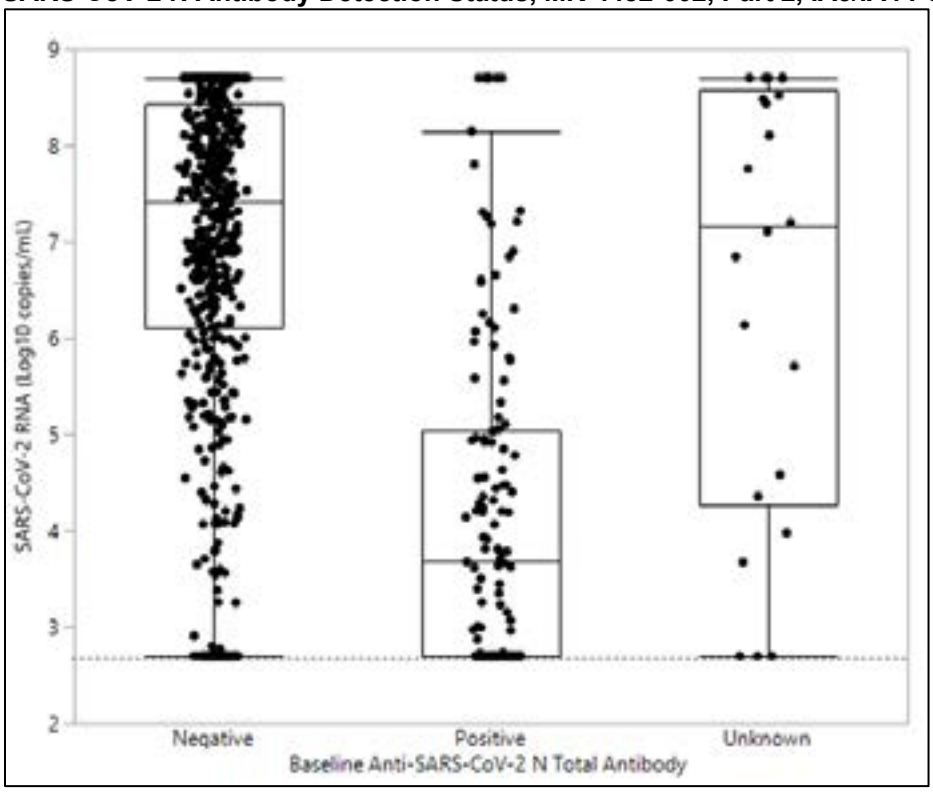
Figure 6. SARS-CoV-2 RNA Levels in NP Swab Specimens at Baseline, According to Baseline Anti-SARS-CoV-2 N Antibody Detection Status, MK-4482-002, Part 2, IA3/IA4 Population



Source: FDA analysis
Abbreviations: IA3/IA4, interim analysis 3 and 4; NP, nasopharyngeal; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Presumably those who first developed anti-SARS-CoV-2 antibody as a result of the current infection would have more likely enrolled relatively later in the course of their infection. However, an analysis of time from symptom onset shows a comparable breakdown in both antibody-negative and antibody-positive participants (Table 38). These results could be interpreted to indicate that most of the positive baseline antibody results are a result of prior infection, not the early development of an antibody response as a result of the current infection.

Table 38. Breakdown of Time From Symptom Onset According to Baseline Anti-SARS-CoV-2 N Antibody Detection Status, MK-4482-002, Part 2, IA3/IA4 Population

Time From Symptom Onset	BL Anti-SARS-CoV-2 Aby Negative	BL Anti-SARS-CoV-2 Aby Positive
1	4% (24/586)	1% (2/139)
2	14% (83/586)	8% (11/139)
3	30% (177/586)	35% (48/139)
4	33% (192/586)	32% (44/139)
5	19% (110/586)	24% (34/139)
≤3 days	48% (284/586)	44% (61/139)
4-5 days	52% (302/586)	56% (78/139)

Source: FDA analysis
Abbreviations: Aby, antibody; BL, baseline; IA3/IA4, interim analysis 3 and 4; SARS-CoV-2, severe acute respiratory syndrome

Further analyses were conducted to assess the potential impact of baseline COVID-19 severity on treatment effect among participants who were seropositive at baseline. As shown in Table 39 below, these analyses revealed that among participants with anti-SARS-CoV-2 antibodies and

mild COVID-19 at baseline, no treatment effect was observed. Among participants with baseline anti-SARS-CoV-2 antibodies present and moderate disease, no participants met the primary endpoint in either the MOV or placebo group. The finding that the rate of hospitalization or death was higher among antibody positive participants with mild COVID-19 than those with moderate COVID-19 in both arms is unexpected and may be attributable to the small size of each of these subgroups. The treatment effect in participants without baseline anti-SARS-CoV-2 antibodies was similar among those with mild and moderate COVID-19 at baseline.

Table 39. Incidence of Hospitalization or Death Through Day 29 by Baseline COVID-19 Severity and Anti-SARS-CoV-2 Baseline Antibody Status. MK-4482-002, Part 2

Baseline COVID-19 Severity and SARS-CoV-2 Baseline Antibody Serostatus	MOV 800 mg N=385 n/m (%)	Placebo N=377 n/m (%)	Difference (MOV – Placebo) % (95% CI)[a]
Mild and antibody positive	2/40(5.0)	2/41 (4.9)	0.1 (-12.0, 12.4)
Mild and antibody negative	8/173 (4.6)	18/148 (12.2)	-7.5 (-14.3, -1.6)
Moderate and antibody positive	0/30 (0)	0/28 (0)	0 (-12.3, 11.5)
Moderate and antibody negative	15/125 (12.0)	30/138 (21.7)	-9.7, (-18.8, 0.6)

Source: Response to October 26, 2021, Information Request, Table 6
[a] The corresponding confidence interval is based on Miettinen & Nurminen method.
Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.
Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; m, number of participants in the modified intent-to-treat population with the corresponding group; MOV, molnupiravir; N, total number of participants; n, number of participants died or hospitalized through Day 29; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

As was the case with MOV, vaccinated individuals were not represented in the trials supporting the authorizations of the monoclonal antibodies for similar intended uses. However, the monoclonal antibodies are authorized for use in outpatients at high risk for progression to severe COVID-19, including hospitalization or death, regardless of vaccination status. There are data available from an outpatient REGEN-COV clinical trial showing clinical benefit in both participants with a positive and negative baseline SARS-CoV-2 antibody status. Specifically, in a Phase 3 trial in high-risk outpatients with mild-to-moderate COVID-19 (COV-2067), among the subset of participants who were SARS-CoV-2 seropositive at baseline, there was a trend toward a decreased rate of COVID-19-related hospitalization or all-cause death through Day 29 among participants who received REGEN-COV 1200 mg compared to placebo and the relative risk reduction was similar in participants who were seropositive and seronegative at baseline (see Table 40).

These data supported the decision to authorize monoclonal antibodies for use in both vaccinated and unvaccinated individuals. Notably, similar data are not available from other outpatient monoclonal antibody programs, either because it was not collected or because the subgroup participants who were seropositive at baseline was too small to detect a benefit in the active treatment arm compared to the placebo arm.

Table 40. COVID-19-Related Hospitalization or All-Cause Death Through Day 29 by Baseline Serostatus in Trial COV-2067

Subpopulation	REGEN-COV 1200 mg Events/N (%)	Placebo Events/N (%)	Relative Risk Reduction (95% CI)
Baseline Seropositive	1/177 (0.6)	6/164 (3.7)	85% (NA, 98%)
Baseline Seronegative	3/500 (0.6)	18/519 (3.5)	83% (42%, 95%)

Source: (Weinreich et al. 2021)
Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; N, total number of participants; NA, not applicable

3. Fact Sheet for Health Care Providers

4. Fact Sheet for Patients and Caregivers

5. PubMed Literature Search

Not applicable

6. Key Literature References

See XXVI. References

7. Other Review Elements

Not applicable

8. Pharmacometrics Review

1. Population PK Analysis

1.1 Review Summary

In general, the Sponsor's population PK analysis is considered acceptable for the purpose of descriptive labeling and covariate identification. The Sponsor's analyses were verified by the reviewer, with no significant discordance identified.

More specifically, the developed model was used to support the current submission as outlined in Table 41.

Table 41. Specific Comments on Sponsor's Final Population PK model

		Utility of the Final Model	Reviewer's Comments
Support Sponsor's proposed labeling statements about intrinsic and extrinsic factors	**Intrinsic factor**	"Population PK analysis results indicated that age, sex, race, ethnicity, or disease severity do not meaningfully influence the PK of NHC." **Pediatric Patients** MOV has not been studied in pediatric patients. **Patients With Renal Impairment** Renal clearance is not a meaningful route of elimination for NHC. In a population PK analysis, mild-to-moderate renal impairment did not have a meaningful impact on the PK of NHC. The PK of NHC has not been evaluated in patients with eGFR less than 30 mL/min/1.73m^2 or on dialysis."	The statement is acceptable. Covariate analysis using the Sponsor's basic model demonstrates that no evident difference (between 80-125%) exists based on age (in adults ≥18), sex, race, ethnicity, or disease severity (Figure 10). The magnitude of change in NHC CL in patients with mild and moderate renal impairment (6 and 22% decrease) was insufficient to warrant a dose adjustment in this population.

Utility of the Final Model	Reviewer's Comments
Description of NHC Exposure Table 3: Pharmacokinetics of NHC After Multiple Oral Administration of 800 mg Molnupiravir Every 12 Hours NHC Geometric Mean (%CV) **Pharmacokinetics in Patients** AUC_{0-tau} (ng*hr/mL)*: 8260 (41.0) C_{max} (ng/mL)*: 2330 (36.9) C_{trough} (ng/mL)*: 31.1 (124) **Pharmacokinetics in Healthy Subjects** AUC_{0-tau} (ng*hr/mL): 8330 (17.9) C_{max} (ng/mL): 2970 (16.0) C_{trough} (ng/mL): 15.7 (42.8) AUC Accumulation Ratio: 1.09 (11.8) **Absorption** T_{max} (hr)†: 1.50 [1.00 – 2.02] Effect of Food: 39% reduction in C_{max}, no effect o AUC **Distribution** Plasma Protein Binding (in vitro): 0% Apparent Volume of Distribution (L)*: 142 **Elimination** Effective $t_{1/2}$ (hr): 3.3 Apparent Clearance (L/hr)*: 76.9 Fraction of dose excreted in urine over the time interval of 0-12 hours: 3% (81.6%) Values were obtained from a Phase 1 study of healthy subjects, unless otherwise indicated *Values were obtained from population PK analysis	The table of NHC PK exposure estimates is acceptable. The model captures the central tendency of the data with low relative standard error. The reviewer was able to reproduce these numbers with no discordance.

Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; CL, clearance; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; NHC, N3-hydroxycytidine; PK, pharmacokinetics; T_{max}, time to maximum plasma concentration; MOV, molnupiravir

1.2 Introduction

The primary objectives of the Sponsor's analysis were to

- develop a population PK model for MK-4482 using NHC plasma concentrations collected in Trials MK-4482-004, MK-4482-006, MK-4482-001, and MK-4482-002;
- identify and quantify the effects of intrinsic and extrinsic factors influencing the plasma PK of NHC; and
- predict metrics of exposures that will be used for parallel development of viral dynamics and exposure-response models.

1.3 Model Development

Data

The analyses were based on PK data from four studies. The study design, study population, and timing of blood samples varied among the four clinical studies. Brief descriptions of the studies included are presented in Table 42 and Table 43.

The final NONMEM data file for analysis contained 3754 PK observations from 571 participants. Table 44 provides summary statistics of the baseline demographic covariates in the analysis dataset.

Table 42. Summary of Studies With PK Sampling Included in Population PK Analysis

Study Number/ Phase	Study Title	Participants	Duration of Dosing
MK-4482-P004[a]/ Phase 1	A Randomized, Double-Blind, Placebo-Controlled, First-in-Human Study Designed to Evaluate the Safety, Tolerability, and Pharmacokinetics of EIDD-2801 Following Oral Administration to Healthy Volunteers	Male or female adult healthy participants (N = 94[b])	SAD cohorts: 1 dose MAD cohorts: Q12h dosing on Days 1 to 5 and 1 dose on Day 6
MK-4482-P006[a]/ Phase 2a	A Phase IIa, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Safety, Tolerability, and Efficacy of EIDD-2801 to Eliminate SARS-CoV-2 Viral RNA Detection in Persons with COVID-19	Male or female, symptomatic, adult outpatients with SARS-CoV-2[c] (N = 22[b])	5 days
MK-4482-P001/ Phase 2/3	A Phase 2/3, Randomized, Placebo-Controlled, Double-Blind Clinical Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MK-4482 in Hospitalized Adults with COVID-19	Male or female, symptomatic, adult inpatients with SARS-CoV-2[d] (N = 225 for Phase 2 + 500 for Phase 3[b])	5 days
MK-4482-P002/ Phase 2/3	A Phase 2/3, Randomized, Placebo-Controlled, Double-Blind Clinical Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MK-4482 in Non-Hospitalized Adults with COVID-19	Male or female, symptomatic, adult outpatients with SARS-CoV-2[d] (N = 225 for Phase 2 + 500 for Phase 3[b])	5 days

Source: Sponsor's Population PK Report, Table 1
Abbreviations: COVID-19, coronavirus disease 2019; MAD, multiple ascending dose; PK, pharmacokinetic; Q12H, every 12 hours; RNA, ribonucleic acid; SAD, single ascending dose; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Table 43. Summary of Dosing Regimens and PK Sampling Plans

Study Number/Phase	Dosing Regimen[a]	Pharmacokinetic Sampling Plan
MK-4482-P004[a]/ Phase 1	SAD: 8 cohorts of 6 participants receiving 1 dose under fasted conditions at 50, 100, 200, 400, 600, 800, 1200, and 1600 mg	Prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 15, 24, 36, 48, and 72 h after dosing
	Food effect: 1 cohort of 6 participants receiving a 200-mg dose following a high-fat breakfast	Prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 15, 24, 36, 48, and 72 h after dosing
	MAD: 7 cohorts of 6 participants receiving Q12h dosing at 50, 100, 200, 300, 400, 600, and 800 mg from Day 1 to Day 5 and 1 dose on Day 6	Day 1: prior to the 1st dose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, and 12 h after the 1st dose Day 4: prior to the 1st dose Day 6: prior to the last dose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 15, 24, 48, 72, and 192 h after the last dose
MK-4482-P006[a]/ Phase 2a	Q12h dosing at 200 mg over 5 days	Day 5: prior to dosing and approximately 1 h and 2 h after dosing
MK-4482-P001/ Phase 2/3	Phase 2: Q12h dosing at 200, 400, and 800 mg over 5 days Phase 3: Q12h dosing over 5 days; dose to be determined by interim analysis of Phase 2 data	Phase 2: Prior to the 1st dose on Day 5, and 1, 3, 5, and 8 h after the 1st dose on Day 5 Phase 3: Prior to the 1st dose on Day 5, and 1 h and 5 h after the 1st dose on Day 5
MK-4482-P002/ Phase 2/3		Phase 2: Prior to the 1st dose on Day 5, and 1.5 h after the 1st dose on Day 5 Phase 3: Prior to the 1st dose on Day 5, and 1.5 h after the 1st dose on Day 5

Source: Sponsor's Population PK Report, Table 2
Abbreviations: MAD, multiple ascending dose; PK, pharmacokinetic; Q12H, every 12 hours; SAD, single ascending dose

Table 44. Summary of Baseline Demographic Covariates for Analysis

Variable		MK-4482-P001 (n = 189)	MK-4482-P002 (n = 194)	MK-4482-P004 (n = 100)	MK-4482-P006 (n = 66)	Overall (n = 549)
Age (y)	Mean (SD)	56.3 (13.9)	48.8 (14.4)	58.8 (13.3)	41.2 (15.7)	48.7 (15.7)
	Median	56	50	35.5	37	50
	Min, Max	19, 91	18, 81	20, 60	19, 82	18, 91
Body Mass Index (kg/m^2)	Mean (SD)	30.2 (6.13)	29.7 (6.1)	21.8 (2.8)	27.3 (5.04)	28.7 (5.87)
	Median	28.9	29.7	25	27	27.7
	Min, Max	17.5, 48.8	18.1, 49.1	19, 29.9	19.8, 43.9	17.5, 49.1
Estimated Glomerular Filtration Rate (mL/min/1.73 m^2)	Mean (SD)	88.3 (24.7)	86 (19.2)	89.2 (16.3)	91 (19.5)	88 (20.5)
	Median	87.1	84.1	87.8	94	86.7
	Min, Max	32.2, 162	37, 147	56.9, 142	37.9, 128	32.2, 162
Body Weight (kg)	Mean (SD)	86.2 (20)	84 (18.4)	75.8 (10.8)	81 (18.4)	82.9 (18.2)
	Median	85	81.6	75.8	76.5	80.7
	Min, Max	50.7, 172	48, 134	48, 101	51, 131	48, 172
Sex, N (%)	Male	108 (57.1)	95 (49)	83 (83)	32 (48.5)	318 (57.9)
	Female	81 (42.9)	99 (51)	17 (17)	34 (51.5)	231 (42.1)
Racial Category, N (%)	White or Caucasian	139 (73.5)	145 (74.7)	93 (93)	56 (84.8)	433 (78.9)
	Black or African American	7 (3.7)	14 (7.22)	4 (4)	5 (7.58)	30 (5.46)
	American Indian or Alaska Native	4 (2.12)	5 (2.58)	0 (0)	0 (0)	9 (1.64)
	Native Hawaiian or other Pacific Islander	1 (0.529)	0 (0)	0 (0)	0 (0)	1 (0.182)
	Asian	18 (9.52)	1 (0.515)	0 (0)	2 (3.03)	21 (3.83)
	Other	20 (10.6)	29 (14.9)	3 (3)	3 (4.55)	55 (10)
Ethnicity, N (%)	Non-Hispanic or Latino	117 (61.9)	131 (67.5)	99 (99)	44 (66.7)	391 (71.2)
	Hispanic or Latino	72 (38.1)	63 (32.5)	1 (1)	22 (33.3)	158 (28.8)
Geographic Region, N (%)	North America	26 (13.8)	66 (34)	0 (0)	66 (100)	158 (28.8)
	Europe	98 (51.9)	88 (45.4)	100 (100)	0 (0)	286 (52.1)
	Asia Pacific	9 (4.76)	0 (0)	0 (0)	0 (0)	9 (1.64)
	Latin America	56 (29.6)	34 (17.5)	0 (0)	0 (0)	90 (16.4)
	Africa	0 (0)	6 (3.09)	0 (0)	0 (0)	6 (1.09)

Variable		MK-4482-P001 (n = 189)	MK-4482-P002 (n = 194)	MK-4482-P004 (n = 100)	MK-4482-P006 (n = 66)	Overall (n = 549)
Hepatic Function Category (Modified Child-Pugh Criteria), N (%)	Normal function	146 (77.2)	191 (98.5)	100 (100)	63 (95.5)	500 (91.1)
	Mild impairment	41 (21.7)	2 (1.03)	0 (0)	3 (4.55)	46 (8.38)
	Moderate impairment	2 (1.06)	1 (0.515)	0 (0)	0 (0)	3 (0.546)
Hepatic Function Category (Modified NCI Criteria), N (%)	Normal function	177 (93.7)	190 (97.9)	100 (100)	66 (100)	533 (97.1)
	Mild impairment	12 (6.35)	4 (2.06)	0 (0)	0 (0)	16 (2.91)
Renal Function Category, N (%)	Normal function	84 (44.4)	83 (42.8)	47 (47)	36 (54.5)	250 (45.5)
	Mild impairment	80 (42.3)	97 (50)	52 (52)	27 (40.9)	256 (46.6)
	Moderate impairment	25 (13.2)	14 (7.22)	1 (1)	3 (4.55)	43 (7.83)
Formulation, N (%)	Oral solution	0 (0)	0 (0)	36 (36)	0 (0)	36 (6.56)
	Capsule	189 (100)	194 (100)	64 (64)	66 (100)	513 (93.4)
Hospitalization Status, N (%)	Healthy	0 (0)	0 (0)	100 (100)	0 (0)	100 (18.2)
	Non-hospitalized	0 (0)	194 (100)	0 (0)	66 (100)	260 (47.4)
	Hospitalized	189 (100)	0 (0)	0 (0)	0 (0)	189 (34.4)
Baseline Disease Severity, N (%)	Healthy	0 (0)	0 (0)	100 (100)	0 (0)	100 (18.2)
	Mild	25 (13.2)	82 (42.3)	0 (0)	0 (0)	107 (19.5)
	Moderate	82 (43.4)	112 (57.7)	0 (0)	0 (0)	194 (35.3)
	Severe	82 (43.4)	0 (0)	0 (0)	0 (0)	82 (14.9)
	Missing	0 (0)	0 (0)	0 (0)	66 (100)	66 (12)
High Risk of Severe Illness, N (%)	No	0 (0)	52 (26.8)	100 (100)	27 (40.9)	179 (32.6)
	Yes	0 (0)	142 (73.2)	0 (0)	39 (59.1)	181 (33)
	Missing	189 (100)	0 (0)	0 (0)	0 (0)	189 (34.4)
Baseline Rendezvous Use, N (%)	No	141 (74.6)	194 (100)	0 (0)	66 (100)	401 (73)
	Yes	48 (25.4)	0 (0)	0 (0)	0 (0)	48 (8.74)
	Missing	0 (0)	0 (0)	100 (100)	0 (0)	100 (18.2)

Source: Sponsor's Population PK Report, Table 5
Abbreviations: N, number of participants; NCI, National Cancer Institute; SD, standard deviation

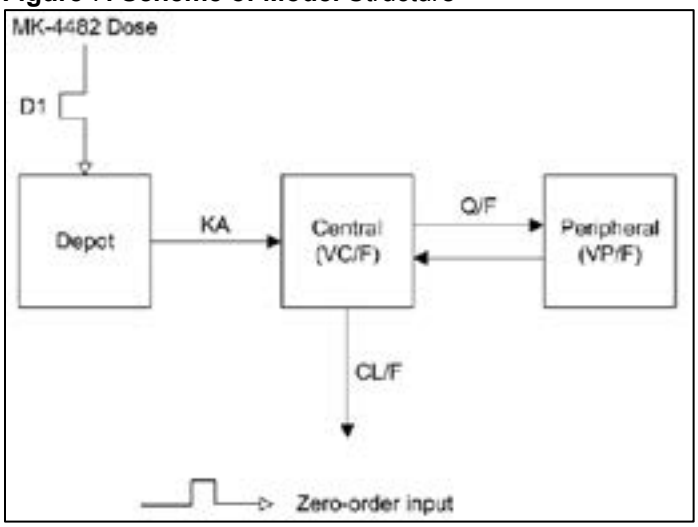
Base Model

The final base model was a two-compartment PK model with saturable absorption, and first-order elimination from the central compartment. The effect of weight was estimated as an allometric exponent on CL/F and also for BMI on Vc/F. Sex was included as a factor on Vc/F. and the effect of food was included on D1 (Figure 7).

Interindividual variability (IIV) was modelled assuming a log-normal distribution for patient level random effects. Residual variability was tested as additive, proportional or both on the dependent variable. Additive models on ln-transformed dependent variable were investigated as well. Model evaluation and selection of the base model were based on standard statistical criteria of goodness-of-fit such as a decrease in the minimum objective function value (OFV),

accuracy of parameter estimation (i.e., 95% confidence interval excluding 0), successful model convergence, and diagnostic plots.

Figure 7. Scheme of Model Structure



Source: Sponsor's Population PK Report, Figure 11
Abbreviations: CL, clearance; F, bioavailability; KA, absorption rate constant; Q, organ blood flow; VC, volume of central compartment; VP, volume of peripheral compartment

Reviewer's Comments

The Sponsor's use of a zero-order input to the depot compartment is somewhat atypical but applied to account for limitations of trying to fit the base model that was identified in healthy patients to all of the population PK data. The Sponsor was unable to achieve model convergence with full dataset and sought to use zero-order input to a depot for reasons of parsimony.

Covariate Analysis

Covariate parameters shown in Table 45 were added to the base model using forward inclusion. Graphical analysis, clinical judgment, physiologic relevance, and mechanistic plausibility were used to determine which covariates should be tested with the various PK parameters. Additionally, collinearity of covariates was assessed to ensure that no collinear covariates were added to the model.

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Table 45. Planned Covariate Analyses

Covariate	Absorption Terms	Elimination Terms	Volume Terms	NHC to NHC-TP Transformation Terms
Body Weight	X	X	X	X
Body Mass Index	X	X	X	X
Age		X	X	X
Sex		X	X	X
Racial Classification	X	X	X	X
Ethnicity	X	X	X	X
Geographic Region	X	X	X	X
Fed Status	X			
SARS-CoV-2 Status	X	X	X	X
Hospitalization	X	X	X	X
Illness Severity	X	X	X	X
eGFR		X		
Baseline Remdesivir Use		X	X	

Source: Sponsor's Population PK Report, Table 3
Abbreviations: eGFR, estimated glomerular filtration rate; NHC-TP, N3-hydroxycytidine triphosphate; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

1.4 Final Model

The parameter estimates for the final covariate model are listed in Table 46. The goodness-of-fit plots for the final covariate model for all data are shown in Figure 8. The Visual Predictive Check (VPC) plot for the final covariate model with all data is shown in Figure 9.

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Table 46. Parameter Estimates (RSE) and Median (95% CI) for the Final Model

Parameter		Final Parameter Estimate		Magnitude of Variability	
		Population Mean	%RSE	Final Estimate	%RSE
CL/F	Apparent central clearance in 80-kg participants (L/h)	76.9	2.01	41.1 %CV	14.9
	Power of body weight effect (-)	0.421	20.4		
VC/F	Apparent central volume in 28-kg/m^2 BMI male participants (L)	72.0	6.40	40.0 %CV	35.8
	Proportional shift in female participants (-)	-0.313	18.1		
	Power of BMI effect (-)	0.753	28.4		
Q/F	Apparent distribution clearance (L/h)	3.35	6.73	NE	NA
VP/F	Apparent peripheral volume (L)	70.0	14.8	NE	NA
KA	First-order absorption rate constant (1/h)	0.830	2.81	NE	NA
D1	Zero-order absorption duration (h)	0.802	4.83	42.8 %CV	15.9
	Proportional shift due to high-fat meal (-)	5.68	10.4		
	Proportional shift in oral solution (-)	-0.644	5.71		
	Proportional shift in hospitalized patients (-)	-0.265	22.4		
PHF	Probability of unknown high-fat meal (-)	0.250	FIXED	NE	NA
Residual Variability in Phase 1 Studies		0.123	9.58	35.1 %CV	NA
Residual Variability in Phase 2 Studies		0.268	5.33	51.7 %CV	NA
Minimum Value of the Objective Function = 38916.167					

Abbreviations: BMI, body mass index; %CV, coefficient of variation expressed as a percent; IIV, interindividual variability; NA, not applicable; NE, not estimated; NHC, β-d-N4-hydroxycytidine; %RSE, relative standard error expressed as a percent.

Note: Shrinkage estimates: 9.0% for IIV in CL/F, 36.6% for IIV in VC/F, and 39.0% for IIV in D1.

Source: Sponsor's Population PK Report, Table 13

Abbreviations: CI, confidence interval; CL, clearance; F, bioavailability; KA, absorption rate constant; Q, organ blood flow; VC, volume of central compartment; VP, volume of peripheral compartment

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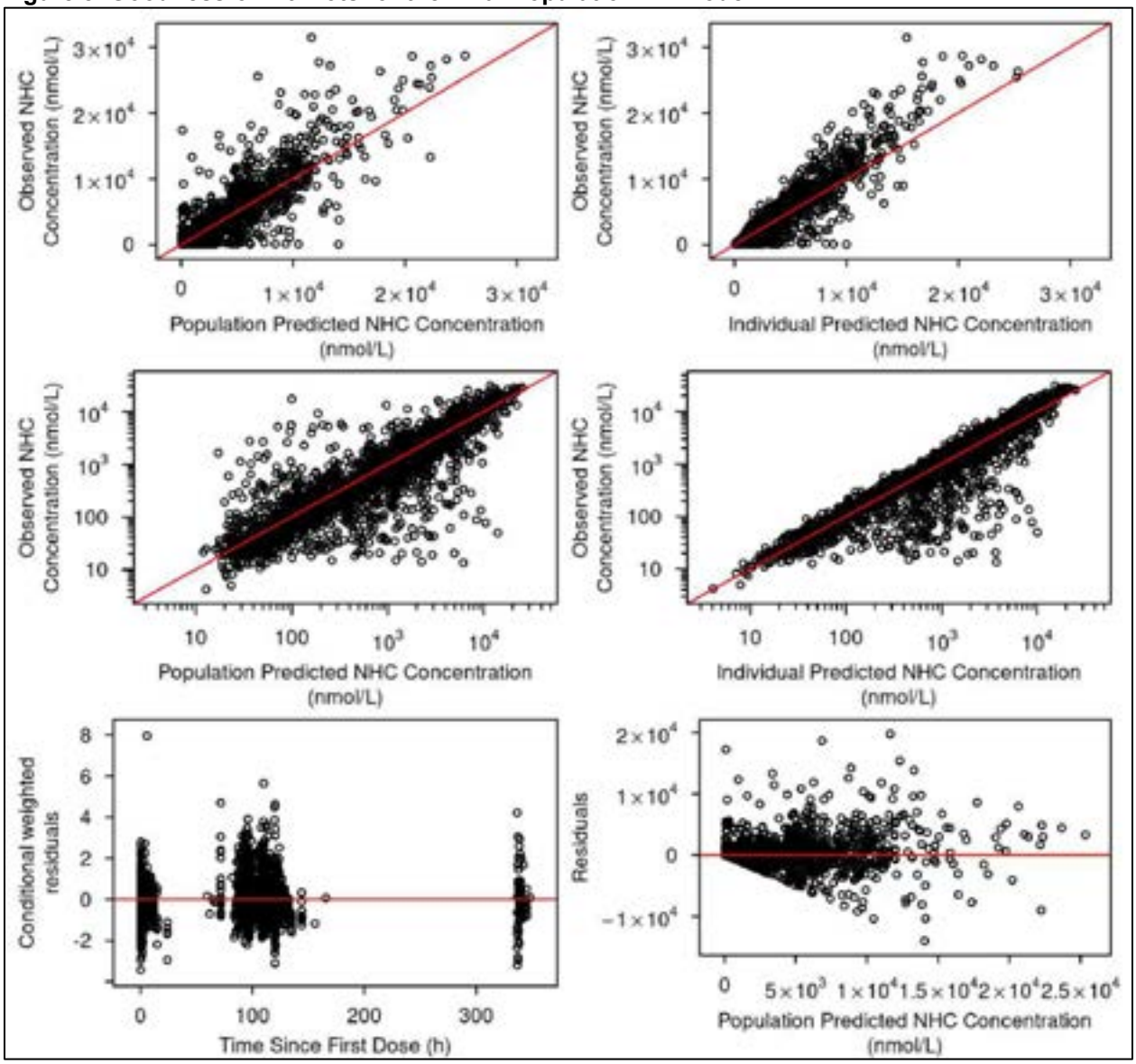
Figure 8. Goodness-of-Fit Plots for the Final Population PK Model



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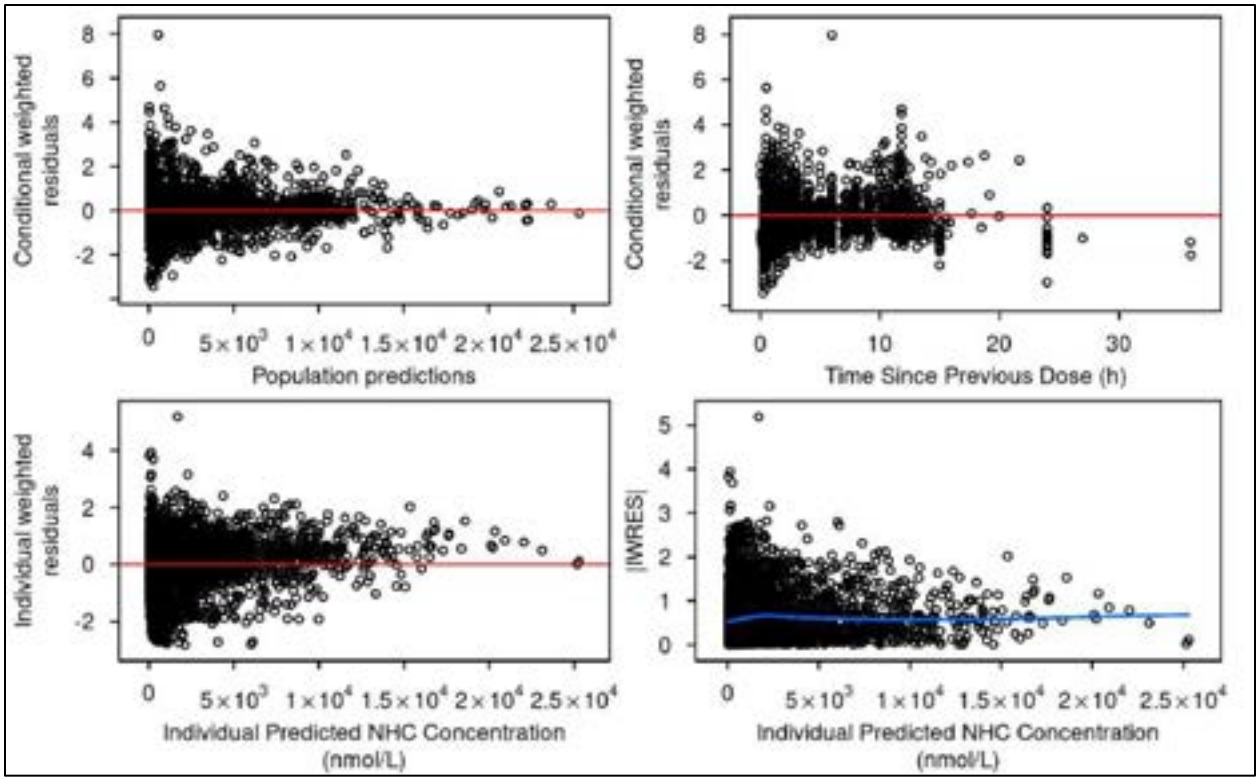

Source: Sponsor's Population PK Report, Figure 15
Abbreviations: NHC, N3-hydroxycytidine; PK, pharmacokinetic

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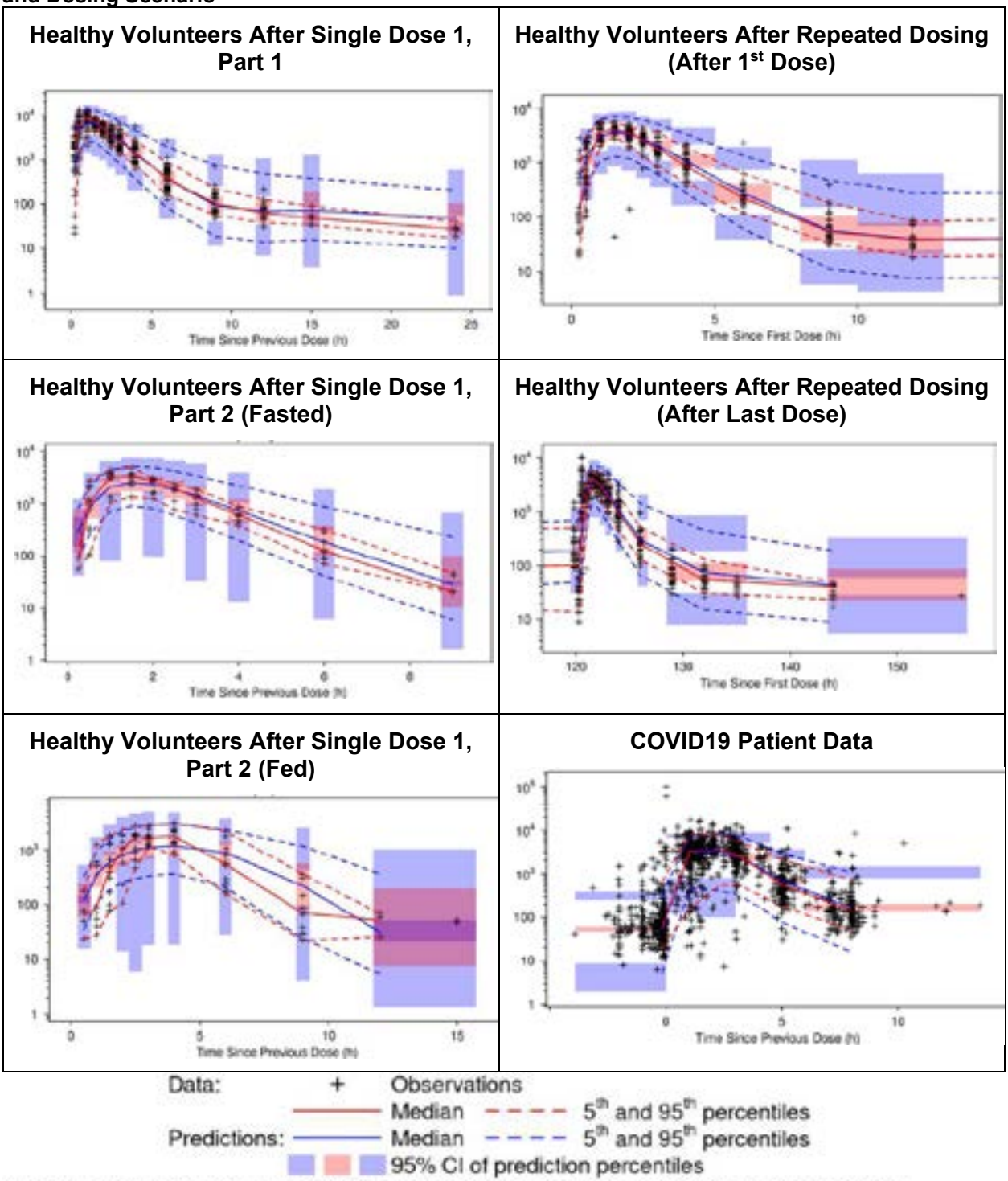
Figure 9. Prediction Corrected VPC Plots for the Final Population PK Model by Patient Population and Dosing Scenario

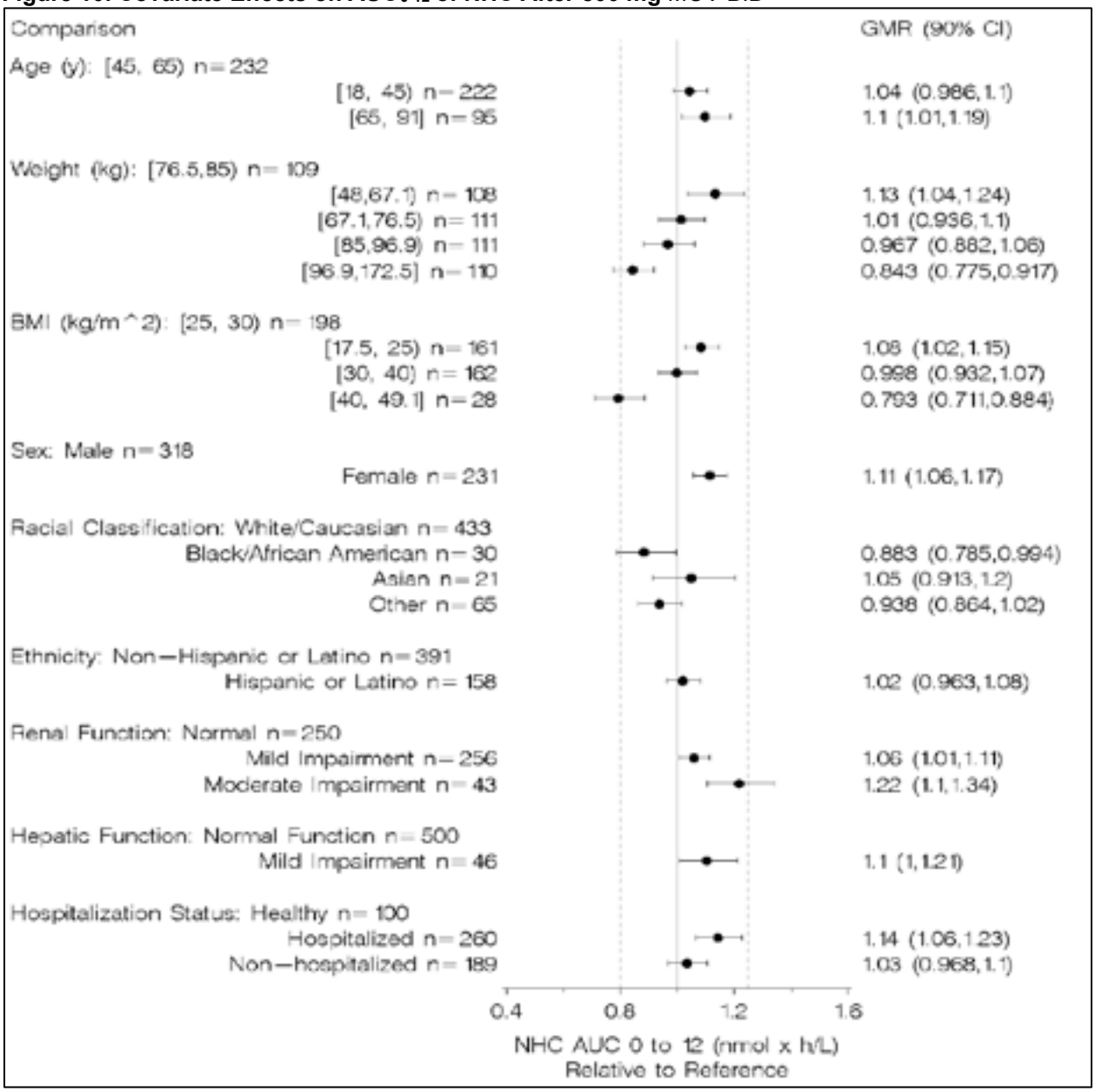


Medians and percentiles are plotted at the median time since previous dose of the data observed within each time since previous dose interval.

Source: Sponsor's Population PK Report, Figure 17–19
Y-axis Indicates NHC Concentrations
Abbreviations: CI, confidence interval; NHC, N3-hydroxycytidine; PK, pharmacokinetic; VPC, visual predictive check

The effects of various intrinsic and extrinsic factors on MOV $AUC_{0\text{-}12h}$ are depicted in Figure 10.

Figure 10. Covariate Effects on $AUC_{0\text{-}12}$ of NHC After 800 mg MOV BID



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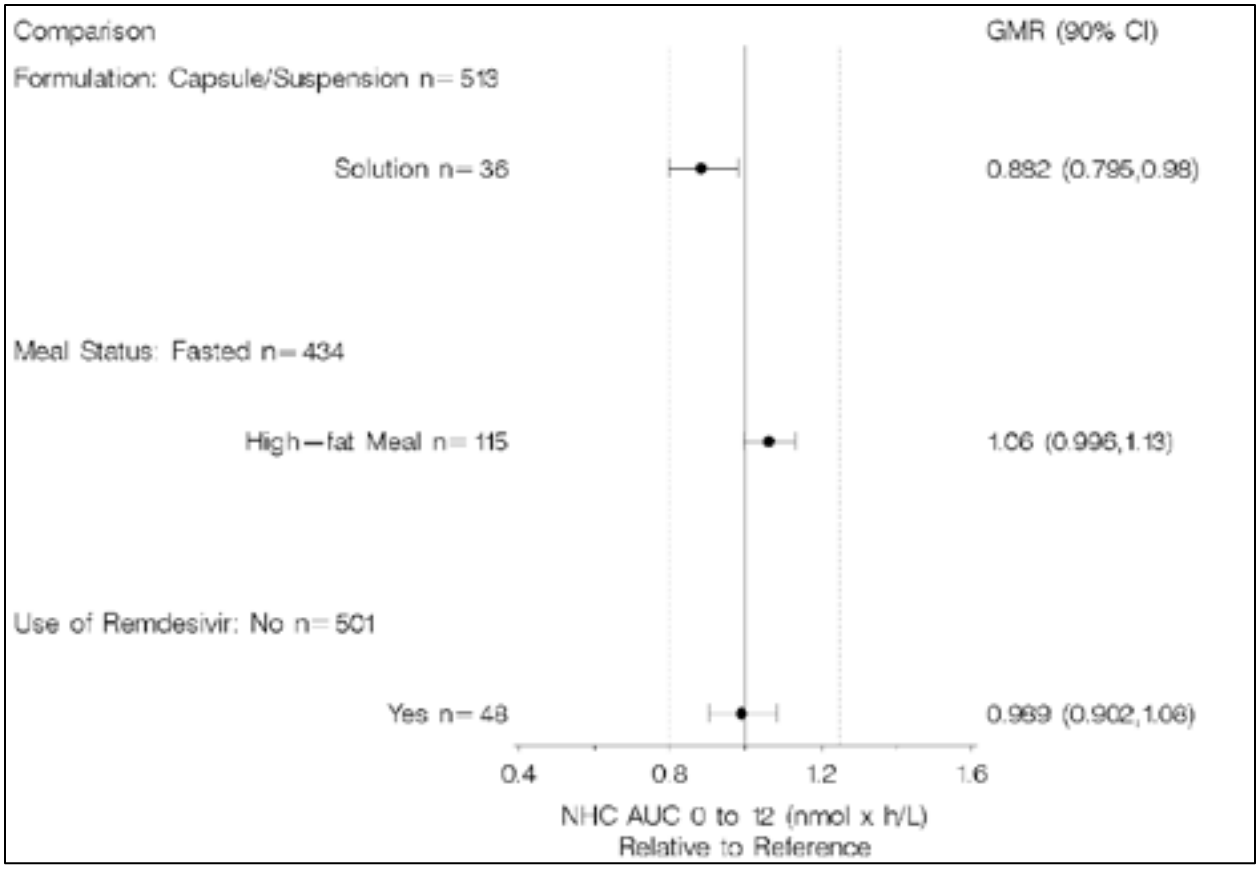

Source: Sponsor's Population PK Report, Figure 27
Abbreviations: AUC, area under the curve; BID, twice daily; CI, confidence interval; GMR, geometric mean ratio; MOV, molnupiravir; NHC, N3-hydroxycytidine

Reviewer's Comments

The Sponsor's covariate analysis suggests that the statements regarding no effect of age (in adults ≥18), sex, race, ethnicity, or disease severity on NHC, in the fact sheet, are acceptable. Additionally, the conclusions that mild-to-moderate renal impairment, body weight, BMI did not have clinically meaningful effects on NHC exposure is also acceptable. See further discussion regarding the Sponsor's exposure-response analyses. The Sponsor's assessment of hepatic impairment predominantly included those with normal hepatic function (n=500) and those with mild hepatic impairment (n=46). That being said, mild hepatic impairment did not have a significant effect on MOV clearance.

1.5 Summary of NHC Pharmacokinetic Exposures

The Sponsor applied the final population PK model with the corresponding individual Bayesian estimates to simulate NHC exposures after 5 days of dosing 800 mg BID MOV for every participant included in population PK dataset. Secondary PK parameters of C_{max}, C_{trough}, and AUC_{0-12} of NHC are shown in Table 47.

Table 47. Model Predicted NHC Plasma Exposures After the Last Dose of 800 mg BID

Variable		MK-4482-P001	MK-4482-P002	MK-4482-P004	MK-4482-P006	Overall	Patients With COVID-19[a]
Maximum Concentration (nmol/L)	Mean (SD)	9530 (3110)	NA[b]	10600 (2140)	NA[b]	9910 (2640)	9530 (3110)
	Geom. mean (%CV)	8990 (36.9)		10400 (20.7)		9460 (32.6)	8990 (36.9)
	Median	9260		10600		9870	9260
	P5, P95	4580, 15600		7570, 14800		5050, 15400	4580, 15600
	n	178		100		278	178
Trough Concentration (nmol/L)	Mean (SD)	230 (555)	413 (1470)	102 (69.1)	185 (472)	266 (954)	302 (1050)
	Geom. mean (%CV)	110 (123)	132 (141)	87.7 (55.7)	117 (73)	113 (113)	120 (124)
	Median	68.9	102	83.2	102	95.6	97.9
	P5, P95	34.5, 860	41.8, 1280	42.3, 284	59.4, 286	39.2, 382	39.2, 860
	n	189	194	100	66	549	449
AUC_{0-12} (nmol x h/L)	Mean (SD)	32500 (16100)	38000 (30100)	29800 (6880)	34600 (12900)	34200 (21100)	35200 (25000)
	Geom. mean (%CV)	30100 (38)	33200 (46.9)	29100 (22.3)	33200 (27.6)	31300 (38.3)	31900 (41)
	Median	28800	30800	28700	32300	29900	30200
	P5, P95	10800, 56800	19600, 80900	20600, 39800	24400, 49100	19600, 56800	19500, 65200
	n	189	194	100	66	549	449

Abbreviations: AUC_{0-12}, area under the NHC concentration versus time curve from 0 to 12 h postdose; C_{max}, maximum NHC concentration; %CV, coefficient of variation expressed as a percent; Geom., geometric; n, number of participants; NA, not applicable; NHC, β-d-N4-hydroxycytidine; Px, xth percentile; SD, standard deviation.

[a] Excludes data from Study MK-4482-P004.

[b] C_{max} distribution was assessed based upon the subset of the analysis population in which the absorption peak could be reliably described.

Source: Sponsor's Population PK Report, Figure 17–19

Abbreviations: BID, twice daily; COVID-19, coronavirus disease 2019; MOV, molnupiravir; PK, pharmacokinetic

Reviewer's Comments

The Sponsor's model appears reasonably unbiased based on the above goodness of fit plots (Figure 8 and Figure 9) for describing the PK of NHC. The values in Table 47 were reproduced and are acceptable for labeling purposes.

2. Exposure-Response for Secondary Virologic Efficacy Endpoints

The Sponsor performed exposure-response for the virologic endpoints in Trials MK-4482-001 and MK-4482-002. The evidence shown in these exposure response relationships is supportive of using the 800 mg dose.

The analyses were performed with data from both MK-4482-001 and MK-4482-002 for the following three virologic endpoints:

- Probability of mutation rate >9 per 10,000 bases relative to baseline
- Viral load change from baseline
- Probability of undetectable viral load on Day 29

Mut*ation Rate Relative to Baseline*

Data from patients in Trials MK-4482-001 and MK-4482-002 revealed 2/22 (9%), 4/25 (16%), 3/24 (13%), and 9/18 (50%) participants in the placebo, 200, 400, and 800 mg groups, respectively, had >9 nucleotide mutations per 10,000 bases suggesting the presence of a dose-response relationship. Exposure-response analysis (logistic regression) of the mutation rate data identified a trend (p=0.10) at >3 and >6 thresholds and a significant relationship (unadjusted p-value of <0.05) at the >9 threshold (number of nucleotide mutations per 10,000 bases across the viral genome (30,000 bases), compared to the baseline (Day 1) sequence).

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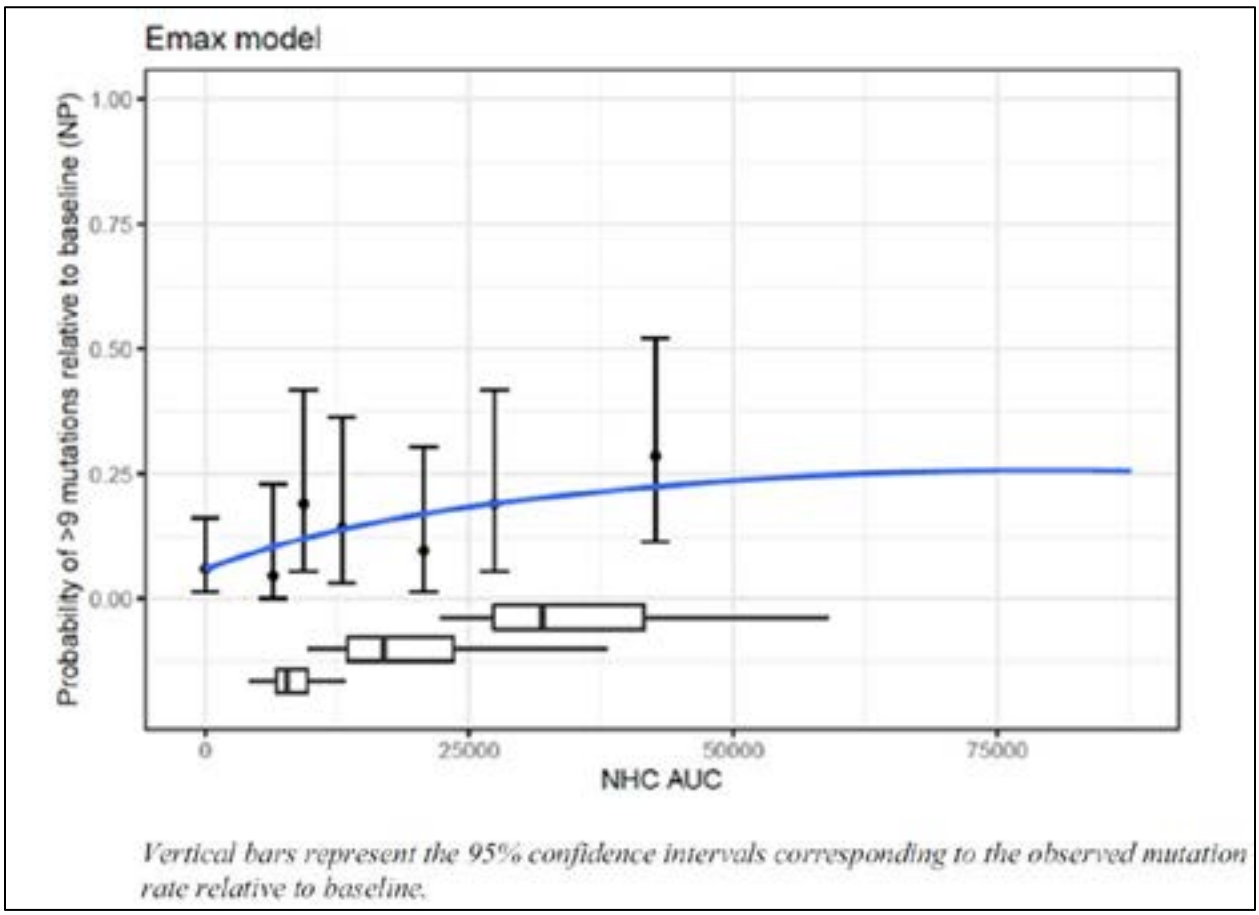
The Sponsor concluded that “Mutation rate exposure-response relationship was best described by Emax logistic regression models, which indicate that the drug effect may be saturating at exposures in the range of the 800 mg dose based on the estimated plateau that is apparent in Figure 11.”

Figure 11. Logistic Regression Relationship for Probability of Mutation Rate >9 per 10,000 Base Pairs Relative to Baseline

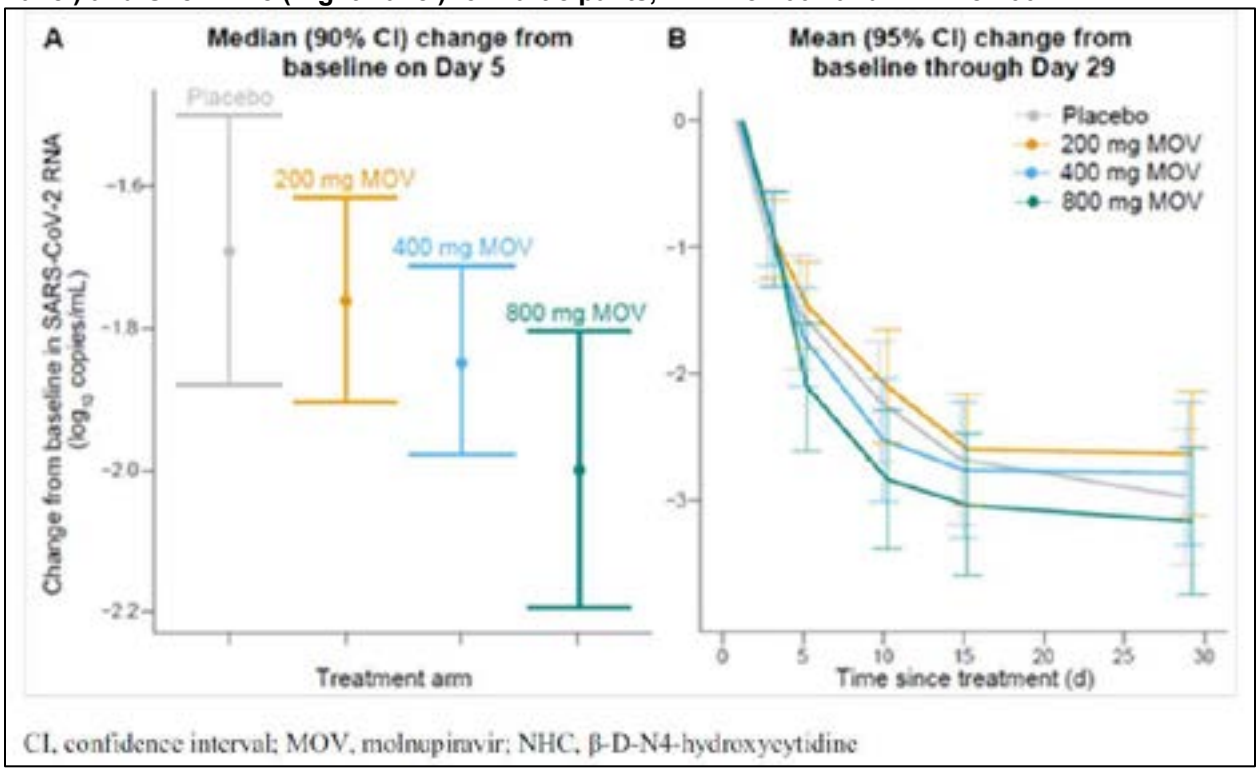


Source: Sponsor’s EUA Application Report, Figure 13
Abbreviations: AUC, area under the curve; NHC, N3-hydroxycytidine

Viral Load Change From Baseline and Probability of Undetectable Viral Load on Day 29

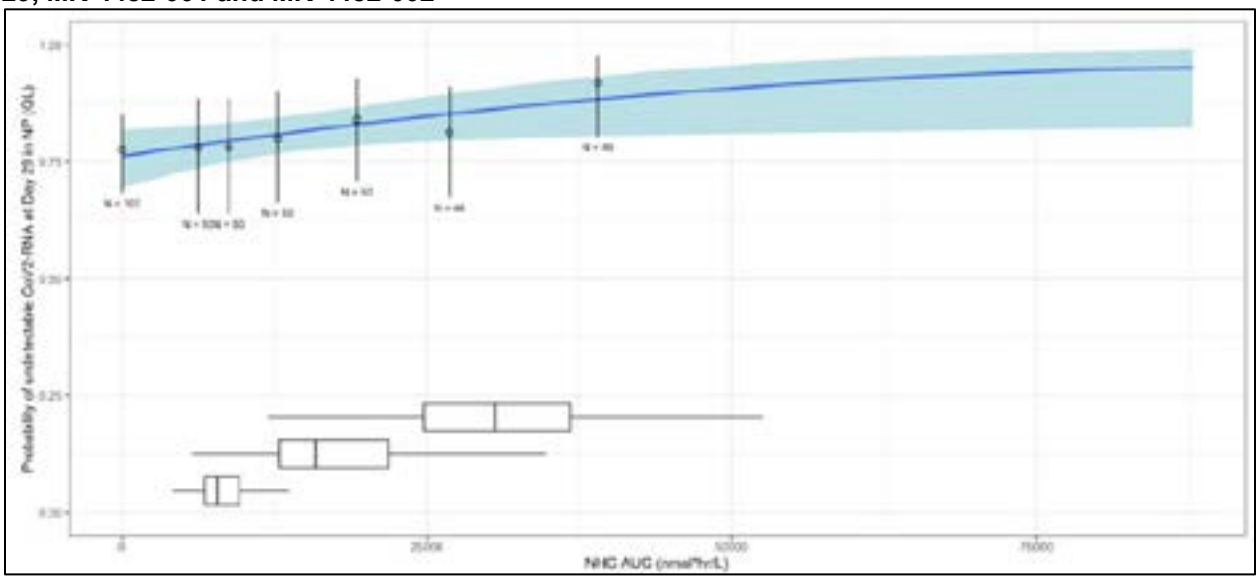
The Sponsor's viral load data by dose in Trials MK-4482-001 and MK-4482-002 suggest 800 mg provides the most reduction in SARS-COV-2 RNA copies when compared to placebo, 200, and 400 mg dose levels (Figure 12 and Figure 13).

Figure 12. Viral Dynamic Model Relationship Between MOV Dose and Viral Load on Day 5 (Left Panel) and Over Time (Right Panel) for Participants, MK-4482-001 and MK-4482-002



Source: Sponsor's EUA Application Report, Figure 14
Note: Data are included for patients where the time since symptom onset was ≤5 days
Abbreviations: RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Figure 13. Logistic Regression Relationship for the Probability of Undetectable Viral Load on Day 29, MK-4482-001 and MK-4482-002



Note: Pred Prob (95% CI): lowess of the predicted probability and 95% CI (to smooth out influence of exposure);
Obs: Open symbols respresenting the observed proportion of subjects with undetectable RNA for each sextile of exposure, plotted at the median of the sextile;
Vertical bars representing the 95% exact confidence intervals corresponding to the observed proportion of subjects with undetectable RNA;
Boxplots show the distribution of exposures at different dose levels

Source: Sponsor's EUA Application Report, Figure 15
Abbreviations: AUC, area under the curve; CI, confidence interval; COV-2, coronavirus 2; NHC, N3-hydroxycytidine; RNA, r bonucleic acid

Based on the Sponsor's dose- and exposure-response assessments, the 800 mg dose of MOV appears to yield the greatest virologic response of the studied treatments.

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FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR MOLNUPIRAVIR

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)
These highlights of the EUA do not include all the information needed to use molnupiravir under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for molnupiravir.

MOLNUPIRAVIR capsules, for oral use
Original EUA Authorized Date: 12/2021

MANDATORY REQUIREMENTS FOR ADMINISTRATION OF MOLNUPIRAVIR UNDER EMERGENCY USE AUTHORIZATION

Refer to FULL FACTSHEET for details.

----------EUA FOR MOLNUPIRAVIR----------

The U.S. Food and Drug Administration (FDA) has issued an EUA for the emergency use of the unapproved molnupiravir, a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults with positive results of direct SARS-CoV-2 viral testing who are at high risk for progressing to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate. Molnupiravir is not FDA-approved for any use including for use for the treatment of COVID-19. Prior to initiating treatment with molnupiravir, carefully consider the known and potential risks and benefits. (1)

LIMITATIONS OF AUTHORIZED USE (1)

- Molnupiravir is not authorized
  - for use in patients less than 18 years of age (5.2)
  - for initiation of treatment in patients requiring hospitalization due to COVID-19. Benefit of treatment with molnupiravir has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19. (2.1)
  - for use for longer than 5 consecutive days.
  - for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

Molnupiravir 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 molnupiravir belongs (i.e., anti-infectives).

Molnupiravir is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of molnupiravir 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 the box in the beginning of the Full Fact Sheet for details on mandatory requirements for administration of molnupiravir under emergency use authorization.

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----------

- 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food. (2.1)
- Take molnupiravir as soon as poss ble after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset. (2.1)
- 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. (2.1)
- Molnupiravir is not authorized for use for longer than 5 consecutive days because the safety and efficacy have not been established. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 200 mg (3)

----------CONTRAINDICATIONS----------

No contraindications have been identified based on the limited available data on the emergency use of molnupiravir authorized under this EUA. (4)

----------WARNINGS AND PRECAUTIONS----------

- Embryo-Fetal Toxicity: Molnupiravir is not recommended for use during pregnancy. (5.1, 8.1, 8.3)
- Bone and Cartilage Toxicity: Molnupiravir is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth. (5.2, 8.4, 13.2)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥ 1%) are diarrhea, nausea, and dizziness. (6.1)

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to molnupiravir (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 Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ USA at 1-800-672-6372 or Fax 215-616-5677 (6.4)

----------DRUG INTERACTIONS----------

No drug interactions have been identified based on the limited available data on the emergency use of molnupiravir authorized under this EUA. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: The use of molnupiravir is not recommended during pregnancy. Advise individuals of childbearing potential to use effective contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of molnupiravir. (8.1, 8.3)
- Lactation: Breastfeeding is not recommended during treatment and for 4 days after the last dose of molnupiravir. A lactating individual may consider interrupting breastfeeding and may consider pumping and discarding breast milk during treatment and for 4 days after the last dose of molnupiravir. (8.2)

See FACT SHEET FOR PATIENTS AND CAREGIVERS.

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* Sections or subsections omitted from the EUA are not listed

FULL FACT SHEET FOR HEALTHCARE PROVIDERS

MANDATORY REQUIREMENTS FOR ADMINISTRATION OF MOLNUPIRAVIR UNDER EMERGENCY USE AUTHORIZATION

In order to mitigate the risks of using this unapproved product under the EUA and to optimize the potential benefit of molnupiravir, the following steps are required. Use of molnupiravir under this EUA is limited to the following (all requirements must be met):

1. Treatment of mild-to-moderate COVID-19 in adults with a positive result of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who are at high risk for progression to severe COVID-19, including hospitalization or death and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate *[see Limitations of Authorized Use (1)]*.

2. As the prescribing healthcare provider, review the information contained within the "Fact Sheet for Patients and Caregivers" with your patient or caregiver prior to the patient receiving molnupiravir. Healthcare providers must provide the patient/caregiver with an electronic or hard copy of the "Fact Sheet for Patients and Caregivers" prior to the patient receiving molnupiravir and must document that the patient/caregiver has been given an electronic or hard copy of the "Fact Sheet for Patients and Caregivers".

3. The prescribing healthcare providers must inform the patient/caregiver that:
    i. Molnupiravir is an unapproved drug that is authorized for use under this Emergency Use Authorization.
    ii. There are no adequate, approved, available products for the treatment of COVID-19 in adults who have mild-to-moderate COVID-19 and are at high risk for progressing to severe COVID-19, including hospitalization or death.
    iii. Other therapeutics are currently authorized for the same use as molnupiravir. 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.
    iv. There are benefits and risks of taking molnupiravir as outlined in the "Fact Sheet for Patients and Caregivers."
    v. Merck Sharp & Dohme has established a pregnancy surveillance program.
    vi. Females of childbearing potential should use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of molnupiravir.
    vii. Males of reproductive potential who are sexually active with females of childbearing potential should use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose.

4. The prescribing healthcare provider must assess whether a female of childbearing potential is pregnant or not, if clinically indicated *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.3)].*

5. Based on findings from animal reproduction studies, molnupiravir may cause fetal harm when administered to pregnant individuals. If molnupiravir is used during pregnancy, prescribing healthcare providers must communicate to the patient the known and potential benefits and the potential risks of molnupiravir use during pregnancy, as outlined in the "Fact Sheet for Patients and Caregivers" *[see Warnings and Precautions (5.1, 5.2), Use in Specific Populations (8.1, 8.3) and Nonclinical Toxicology (13.1)].*

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6. If the decision is made to use molnupiravir during pregnancy, the prescriber must document that the known and potential benefits and the potential risks of molnupiravir use during pregnancy, as outlined in the "Fact Sheet for Patients and Caregivers," were discussed with the patient.

7. The prescribing healthcare provider must document that a pregnant individual was made aware of Merck Sharp & Dohme's pregnancy surveillance program at 1-877-888-4231 or pregnancyreporting.msd.com.
    a. If the pregnant individual agrees to participate in the pregnancy surveillance program and allows the prescribing healthcare provider to disclose patient specific information to Merck Sharp & Dohme, the prescribing healthcare provider must provide the patient's name and contact information to Merck Sharp & Dohme.

8. The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all medication errors and serious adverse events potentially related to molnupiravir within 7 calendar days from the healthcare provider's awareness of the event *[see Adverse Reactions (6.4)]*.

For information on clinical studies of molnupiravir and other therapies for the treatment of COVID-19, see www.clinicaltrials.gov.

1 EMERGENCY USE AUTHORIZATION

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product molnupiravir for treatment of mild-to-moderate COVID-19 in adults:

- 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. Refer to CDC website[1] for additional details, and for
- whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.

LIMITATIONS OF AUTHORIZED USE

- Molnupiravir is not authorized for use in patients who are less than 18 years of age *[see Warnings and Precautions (5.2)]*.
- Molnupiravir is not authorized for initiation of treatment in patients hospitalized due to COVID-19[2]. Benefit of treatment with molnupiravir has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19 *[see Dosing and Administration (2.1)]*.
- Molnupiravir is not authorized for use for longer than 5 consecutive days.
- Molnupiravir is not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

Molnupiravir 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 molnupiravir belongs (i.e., anti-infectives).

Molnupiravir is not approved for any use, including for use for the treatment of COVID-19.

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[1] 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] Should a patient require hospitalization after starting treatment with molnupiravir, the patient may complete the full 5 day treatment course per the healthcare provider's discretion.

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Prior to initiating treatment with molnupiravir, carefully consider the known and potential risks and benefits *[see Warnings and Precautions (5.1, 5.2), Use in Specific Populations (8.1, 8.3) and Nonclinical Toxicology (13.1)]*.

Molnupiravir is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of molnupiravir 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 Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2, a novel coronavirus. The Secretary of 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 FDA 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:

- 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

Other therapeutics are currently authorized for the same use as molnupiravir. 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.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Emergency Use of Molnupiravir in Adult Patients

The dosage in adult patients is 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food *[see Clinical Pharmacology (12.3)]*. Take molnupiravir as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset *[see Emergency Use Authorization (1) and Clinical Studies (14)]*.

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 *[see Patient Counseling Information (17)]*.

Molnupiravir is not authorized for use for longer than 5 consecutive days because the safety and efficacy have not been established.

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If the patient misses a dose of molnupiravir within 10 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 10 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.

Should a patient require hospitalization after starting treatment with molnupiravir, the patient may complete the full 5 day treatment course per the healthcare provider's discretion.

2.2 Dosage Adjustments in Specific Populations
No dosage adjustment is recommended based on renal or hepatic impairment or in geriatric patients *[see Use in Specific Populations (8.5, 8.6, 8.7)]*.

3 DOSAGE FORMS AND STRENGTHS
Capsules: 200 mg, Swedish Orange opaque size 0 capsules. The capsules have the corporate logo and "82" printed in white ink.

4 CONTRAINDICATIONS
No contraindications have been identified based on the limited available data on the emergency use of molnupiravir authorized under this EUA.

5 WARNINGS AND PRECAUTIONS
There are limited clinical data available for molnupiravir. Serious and unexpected adverse events may occur that have not been previously reported with molnupiravir use.

5.1 Embryo-Fetal Toxicity
Based on findings from animal reproduction studies, molnupiravir may cause fetal harm when administered to pregnant individuals. There are no available human data on the use of molnupiravir in pregnant individuals to evaluate the risk of major birth defects, miscarriage or adverse maternal or fetal outcomes; therefore, molnupiravir is not recommended for use during pregnancy. When considering molnupiravir for a pregnant individual, the prescribing healthcare provider must communicate the known and potential benefits and the potential risks of using molnupiravir during pregnancy to the pregnant individual. Molnupiravir is authorized to be prescribed to a pregnant individual only after the healthcare provider has determined that the benefits would outweigh the risks for that individual patient. If the decision is made to use molnupiravir during pregnancy, the prescribing healthcare provider must document that the known and potential benefits and the potential risks of using molnupiravir during pregnancy were communicated to the pregnant individual.

Advise individuals of childbearing potential of the potential risk to a fetus and to use an effective method of contraception correctly and consistently, as applicable, during treatment with molnupiravir and for 4 days after the final dose *[see Use in Specific Populations (8.1, 8.3 and Nonclinical Toxicology (13.1)]*.

Prior to initiating treatment with molnupiravir, assess whether an individual of childbearing potential is pregnant or not, if clinically indicated. Pregnancy status does not need to be confirmed in patients who have undergone permanent sterilization, are currently using an intrauterine system or contraceptive implant, or in whom pregnancy is not possible. In all other patients, assess whether the patient is pregnant based on the first day of last menstrual period in individuals who have regular menstrual cycles, is using a reliable method of contraception correctly and consistently or have had a negative pregnancy test. A pregnancy test is recommended if the individual has irregular menstrual cycles, is unsure of the first day of last menstrual period or is not using effective contraception correctly and consistently *[see Box]*.

5.2 Bone and Cartilage Toxicity

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Molnupiravir is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth. Bone and cartilage toxicity was observed in rats after repeated dosing *[see Nonclinical Toxicity (13.2)]*. The safety and efficacy of molnupiravir have not been established in pediatric patients *[see Use in Specific Populations (8.4)]*.

6 ADVERSE REACTIONS

6.1 Adverse Reactions from Clinical Studies

The following adverse reactions have been observed in the clinical study of molnupiravir that supported the EUA. The adverse reaction rates observed in these clinical trials cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Additional adverse events associated with molnupiravir may become apparent with more widespread use.

Overall, more than 900 subjects have been exposed to molnupiravir 800 mg twice daily in clinical trials. The safety assessment of molnupiravir is primarily based on an analysis from subjects followed through Day 29 in the Phase 3 study in non-hospitalized subjects with COVID-19 (MOVe-OUT) *[see Clinical Studies (14)]*.

The safety of molnupiravir was evaluated based on an analysis of a Phase 3 double-blind trial (MOVe-OUT) in which 1,411 non-hospitalized subjects with COVID-19 were randomized and treated with molnupiravir (N=710) or placebo (N=701) for up to 5 days. Adverse events were those reported while subjects were on study intervention or within 14 days of study intervention completion/discontinuation.

Discontinuation of study intervention due to an adverse event occurred in 1% of subjects receiving molnupiravir and 3% of subjects receiving placebo. Serious adverse events occurred in 7% of subjects receiving molnupiravir and 10% receiving placebo; most serious adverse events were COVID-19 related. Adverse events leading to death occurred in 2 (<1%) subjects receiving molnupiravir and 12 (2%) of subjects receiving placebo.

The most common adverse reactions in the molnupiravir treatment group in MOVe-OUT are presented in Table 1, all of which were Grade 1 (mild) or Grade 2 (moderate).

Table 1: Adverse Reactions Occurring in Greater Than or Equal to 1% of Subjects Receiving Molnupiravir in MOVe-OUT*

	Molnupiravir N=710	**Placebo N=701**
Diarrhea	2%	2%
Nausea	1%	1%
Dizziness	1%	1%
*Frequencies of adverse reactions are based on all adverse events attributed to study intervention by the investigator.		

Laboratory Abnormalities

Selected Grade 3 and 4 laboratory abnormalities in chemistry (alanine aminotransferase, aspartate aminotransferase, creatinine, and lipase) and hematology (hemoglobin, platelets, and leukocytes) parameters all occurred at a rate of less than or equal to 2% and occurred at a similar rate across arms in MOVe-OUT.

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 molnupiravir within 7 calendar days from the healthcare provider's awareness of the event, using

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FDA Form 3500 (for information on how to access 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 "*Molnupiravir* 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 preexisting 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: 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:
Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ USA
Fax: 215-616-5677
E-mail: dpoc.usa@msd.com

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 molnupiravir.

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.

7 DRUG INTERACTIONS

No drug interactions have been identified based on the limited available data on the emergency use of molnupiravir authorized under this EUA. No clinical drug-drug interaction trials of molnupiravir with concomitant medications, including other treatments for mild-to-moderate COVID-19, have been conducted *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Surveillance Program

There is a pregnancy surveillance program that monitors pregnancy outcomes in individuals exposed to molnupiravir during pregnancy. The prescribing healthcare provider must document

that a pregnant individual was made aware of Merck Sharp & Dohme's pregnancy surveillance program at 1-877-888-4231 or pregnancyreporting.msd.com. If the pregnant individual agrees to participate in the pregnancy surveillance program and allows the prescribing healthcare provider to disclose patient specific information to Merck Sharp & Dohme, the prescribing healthcare provider must provide the patient's name and contact information to Merck Sharp & Dohme. Pregnant individuals exposed to molnupiravir can also report the exposure by contacting Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ USA at 1-877-888-4231 or pregnancyreporting.msd.com.

Risk Summary

Based on animal data, molnupiravir may cause fetal harm when administered to pregnant individuals. There are no available human data on the use of molnupiravir in pregnant individuals to evaluate the risk of major birth defects, miscarriage or adverse maternal or fetal outcomes; therefore, molnupiravir is not recommended during pregnancy *[see Box and Warnings and Precautions (5.1)]*. In an animal reproduction study, oral administration of molnupiravir to pregnant rats during the period of organogenesis resulted in embryofetal lethality and teratogenicity at 8 times the human NHC (N4-hydroxycytidine) exposures at the recommended human dose (RHD) and reduced fetal growth at ≥ 3 times the human NHC exposure at the RHD. Oral administration of molnupiravir to pregnant rabbits during the period of organogenesis resulted in reduced fetal body weights at 18 times the human NHC exposure at the RHD (see *Data*). When considering molnupiravir for a pregnant individual, the prescribing healthcare provider must communicate the known and potential benefits and the potential risks of using molnupiravir during pregnancy to the pregnant individual. Molnupiravir may only be prescribed to a pregnant individual after the prescribing healthcare provider has determined that the benefits would outweigh the risks for that individual patient. If the decision is made to use molnupiravir during pregnancy, the prescribing healthcare provider must document that the known and potential benefits and potential risks of using molnupiravir during pregnancy were communicated to the pregnant individual *[see Box]*. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy *(see Clinical Considerations)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background 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.

Data

Animal Data

In an embryofetal development (EFD) study in rats, molnupiravir was administered orally to pregnant rats at 0, 100, 250, or 500 mg/kg/day from gestation days (GDs) 6 to 17. Molnupiravir was also administered orally to pregnant rats at up to 1,000 mg/kg/day from GDs 6 to 17 in a preliminary EFD study. Developmental toxicities included post-implantation losses, malformations of the eye, kidney, and axial skeleton, and rib variations at 1,000 mg/kg/day (8 times the human NHC exposure at the RHD) and decreased fetal body weights and delayed ossification at ≥500 mg/kg/day (3 times the human NHC exposure at the RHD). There were no developmental toxicities at ≤250 mg/kg/day (less than the human NHC exposure at the RHD). Maternal toxicities included decreased food consumption and body weight losses, resulting in the early sacrifice of two of sixteen animals at 1,000 mg/kg/day, and decreased body weight gain at 500 mg/kg/day.

In an EFD study in rabbits, molnupiravir was administered orally to pregnant rabbits at 0, 125, 400, or 750 mg/kg/day from GDs 7 to 19. Developmental toxicity was limited to reduced fetal

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body weights at 750 mg/kg/day (18 times the human NHC exposures at the RHD). There was no developmental toxicity at ≤400 mg/kg/day (7 times the human NHC exposures at the RHD). Maternal toxicities included reduced food consumption and body weight gains, and abnormal fecal output at 750 mg/kg/day.

In a pre- and post-natal developmental study, molnupiravir was administered orally to female rats at doses up to 500 mg/kg/day (similar to the human NHC exposure at the RHD) from GD6 through lactation day 20. No effects were observed in offspring.

8.2 Lactation

Risk Summary

There are no data on the presence of molnupiravir or its metabolites in human milk. NHC was detected in the plasma of nursing pups from lactating rats administered molnupiravir *(see Data)*. It is unknown whether molnupiravir has an effect on the breastfed infant or effects on milk production.

Based on the potential for adverse reactions in the infant from molnupiravir, breastfeeding is not recommended during treatment with molnupiravir and for 4 days after the final dose. A lactating individual may consider interrupting breastfeeding and may consider pumping and discarding breast milk during treatment and for 4 days after the last dose of molnupiravir *[see Warnings and Precautions (5.1, 5.2)].*

Data

When molnupiravir was administered to lactating rats at ≥250 mg/kg/day in the pre- and post-natal development study, NHC was detected in plasma of nursing pups.

8.3 Females and Males of Reproductive Potential

Based on animal studies, molnupiravir may cause fetal harm when administered to a pregnant individual.

Pregnancy Testing

Prior to initiating treatment with molnupiravir, assess whether an individual of childbearing potential is pregnant or not, if clinically indicated *[see Warnings and Precautions (5.1)].*

Contraception

Females

Advise individuals of childbearing potential to use a reliable method of contraception correctly and consistently, as applicable for the duration of treatment and for 4 days after the last dose of molnupiravir *[see Warnings and Precautions (5.1)].*

Males

While the risk is regarded as low, nonclinical studies to fully assess the potential for molnupiravir to affect offspring of treated males have not been completed. Advise sexually active individuals with partners of childbearing potential to use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose of molnupiravir. The risk beyond three months after the last dose of molnupiravir is unknown. Studies to understand the risk beyond three months are ongoing.

Molnupiravir was equivocal (neither clearly positive nor negative) in one *in vivo* mutagenicity assay of reticulocytes and RBCs which are used to reflect prior effects on hematopoietic stem cells in bone marrow. Molnupiravir was not mutagenic when assessed in a second *in vivo* assay of liver (somatic cells) and bone marrow (somatic cells and stem cells) from transgenic rats administered molnupiravir for 28 days. In contrast to somatic cells, germ cells (eggs and sperm) pass genetic information from generation to generation. A planned study of male testicular germ cells from transgenic rats will assess the potential for molnupiravir to affect offspring of treated males *[see Nonclinical Toxicology (13.1)].*

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8.4 Pediatric Use
Molnupiravir is not authorized for use in patients less than 18 years of age.
Bone and cartilage toxicity were observed in a 3-month, repeat-dose toxicology study in rats. The safety and efficacy of molnupiravir have not been established in pediatric patients *[see Warnings and Precautions (5.2) and Nonclinical Toxicology (13.2)]*.

8.5 Geriatric Use
In MOVe-OUT, there was no difference in safety and tolerability between patients ≥65 years of age and younger patients who were treated with molnupiravir. No dosage adjustment is recommended based on age. The PK of NHC was similar in geriatric patients compared to younger patients *[see Clinical Pharmacology (12.3)]*.

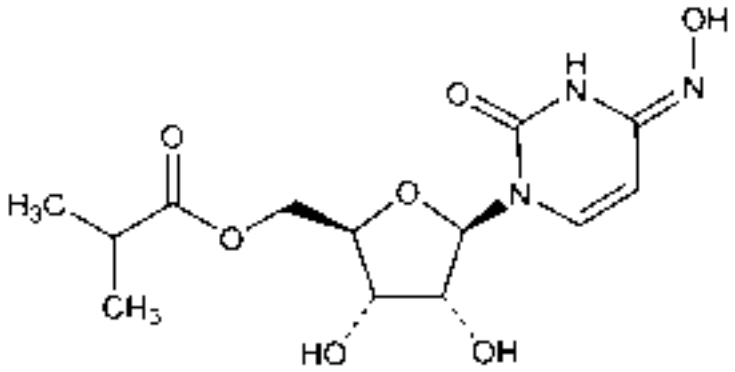
8.6 Renal Impairment
No dosage adjustment in patients with any degree of renal impairment is recommended. Renal clearance is not a meaningful route of elimination for NHC. Mild or moderate renal impairment did not have a meaningful impact on the PK of NHC. While the PK of NHC has not been evaluated in patients with eGFR less than 30 mL/min/1.73m^2 or on dialysis, severe renal impairment, and end-stage renal disease (ESRD) are not expected to have a significant effect on NHC exposure *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment
No dosage adjustment in patients with hepatic impairment is recommended. Preclinical data indicate that hepatic elimination is not expected to be a major route of NHC elimination therefore, hepatic impairment is unlikely to affect NHC exposure *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE
There is no human experience of overdosage with molnupiravir. Treatment of overdose with molnupiravir should consist of general supportive measures including the monitoring of the clinical status of the patient. Hemodialysis is not expected to result in effective elimination of NHC.

11 DESCRIPTION
Molnupiravir is a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis and is the 5´-isobutyrate ester of the ribonucleoside analog N4-hydroxycytidine (NHC).

The chemical name for molnupiravir is {(2R,3S,4R,5R)-3,4-Dihydroxy-5-[(4Z)-4-(hydroxyimino)-2-oxo-3,4-dihydropyrimidin-1(2H)-yl]oxolan-2-yl}methyl 2-methylpropanoate. It has an empirical formula of $C_{13}H_{19}N_3O_7$ and its molecular weight is 329.31 g/mol. Its structural formula is:



Molnupiravir is a white to off-white powder that is soluble in water.

Each molnupiravir capsule, for oral use, contains 200 mg of molnupiravir and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate and microcrystalline cellulose and purified water. The capsule shell is made of hypromellose, red iron oxide and titanium dioxide. The capsule is printed with white ink made of butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, purified water, shellac, strong ammonia solution and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Molnupiravir is a prodrug with antiviral activity against SARS-CoV-2. It is metabolized to the cytidine nucleoside analogue, NHC which distributes into cells where NHC is phosphorylated to form the pharmacologically active ribonucleoside triphosphate (NHC-TP). NHC-TP incorporation (as NHC-monophosphate [NHC-MP]) into SARS-CoV-2 RNA by the viral RNA polymerase (nsp12) results in an accumulation of errors in the viral genome leading to inhibition of replication. The mechanism of action (known as viral error catastrophe or viral lethal mutagenesis) is supported by biochemical and cell culture data, studies of SARS-CoV-2 infection in animal models, and analyses of SARS-CoV-2 genome sequences in human subjects treated with molnupiravir.

12.2 Pharmacodynamics

The relationship between NHC and intracellular NHC-TP with antiviral efficacy has not been evaluated clinically.

12.3 Pharmacokinetics

Molnupiravir is a 5´-isobutyrate prodrug of NHC that is hydrolyzed during or after absorption. NHC, the primary circulating analyte, is taken up by cells and anabolized to NHC-TP. NHC is eliminated by metabolism to uridine and/or cytidine through the same pathways involved in endogenous pyrimidine metabolism. NHC pharmacokinetics are shown in Table 2.

Table 2: Pharmacokinetics of NHC After Multiple Oral Administration of 800 mg Molnupiravir Every 12 Hours

	NHC Geometric Mean (%CV)
Pharmacokinetics in Patients	
$AUC_{0\text{-}12hr}$ (ng*hr/mL)*	8260 (41.0)
C_{max} (ng/mL)*	2330 (36.9)
C_{12hr} (ng/mL)*	31.1 (124)
Pharmacokinetics in Healthy Subjects	
$AUC_{0\text{-}12hr}$ (ng*hr/mL)	8330 (17.9)
C_{max} (ng/mL)	2970 (16.8)
C_{12hr} (ng/mL)	16.7 (42.8)
AUC Accumulation Ratio	1.09 (11.8)
Absorption	
T_{max} (hr)†	1.50 [1.00 – 2.02]
Effect of Food	35% reduction in C_{max}, no effect on AUC
Distribution	
Plasma Protein Binding (*in vitro*)	0%
Apparent Volume of Distribution (L)*	142
Elimination	
Effective $t_{1/2}$ (hr)	3.3
Apparent Clearance (L/hr)*	76.9
Fraction of dose excreted in urine over the time interval of 0-12 hours	3% (81.6%)
Values were obtained from a Phase 1 study of healthy subjects, unless otherwise indicated. *Values were obtained from population PK analysis.	

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†Median [min - max]

Specific Populations
Population PK analysis results indicated that age, sex, race, ethnicity, or disease severity do not meaningfully influence the PK of NHC.

Pediatric Patients
Molnupiravir has not been studied in pediatric patients.

Patients with Renal Impairment
Renal clearance is not a meaningful route of elimination for NHC. In a population PK analysis, mild or moderate renal impairment did not have a meaningful impact on the PK of NHC. The PK of molnupiravir and NHC has not been evaluated in patients with eGFR less than 30 mL/min/1.73m^2 or on dialysis.

Patients with Hepatic Impairment
The PK of molnupiravir and NHC has not been evaluated in patients with moderate and severe hepatic impairment. Preclinical data indicate that hepatic elimination is not expected to be a major route of NHC elimination; therefore, hepatic impairment is unlikely to affect NHC exposure.

Drug Interaction Studies
In vitro study results indicated that molnupiravir and NHC are not substrates of CYP enzymes or human P-gp and BCRP transporters. *In vitro* study results also indicated that molnupiravir and NHC are not inhibitors of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 or inhibitors of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2K, MRP2, MDR1 and BCRP or inducers of CYP1A2, 2B6, and 3A4. The interaction between molnupiravir with concomitant medications, including other treatments for mild-to-moderate COVID-19, has not been evaluated.

12.4 Microbiology
Antiviral Activity

NHC, the nucleoside analogue metabolite of molnupiravir, was active in cell culture assays against SARS-CoV-2 with 50% effective concentrations (EC_{50} values) ranging between 0.67 to 2.66 µM in A-549 cells and 0.32 to 2.03 µM in Vero E6 cells. NHC had similar activity against SARS-CoV-2 variants Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2) with EC_{50} values of 1.59, 1.77 and 1.32 and 1.68 µM, respectively. NHC had non-antagonistic antiviral activity with remdesivir against SARS-CoV-2 in cell culture.

Resistance
No amino acid substitutions in SARS-CoV-2 associated with resistance to NHC have been identified in Phase 2 clinical trials evaluating molnupiravir for the treatment of COVID-19. Studies to evaluate selection of resistance to NHC with SARS-CoV-2 in cell culture have not been completed. Resistance selection studies have been conducted with other coronaviruses (MHV and MERS-CoV) and showed a low likelihood of resistance development to NHC. Following 30 passages in cell culture, only a 2-fold decrease in susceptibility was observed and no NHC resistance-associated amino acid substitutions were identified. NHC retained activity in cell culture against virus with polymerase (nsp 12) substitutions (e.g., F480L, V557L and E802D) associated with decreased remdesivir sensitivity, indicating a lack of cross-resistance.

In clinical trials, encoded amino acid changes (substitutions, deletions or insertions) were more likely to be detected in viral sequences in subjects treated with molnupiravir compared to placebo. In a small number of subjects amino acid changes in the spike protein occurred at positions targeted by monoclonal antibodies and vaccines. The clinical and public health significance of these changes are unknown.

Activity against SARS-CoV-2 in animal models

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The antiviral activity of molnupiravir has been demonstrated in mouse, hamster, and ferret models of SARS-CoV-2 infection when dosing was administered prior to or within 1-2 days after viral challenge. In SARS-CoV-2 infected ferrets, molnupiravir significantly reduced SARS-CoV-2 viral titers in the upper respiratory tract and completely inhibited viral spread to untreated contact animals. In SARS-CoV-2 infected Syrian hamsters, molnupiravir reduced viral RNA and infectious virus titers in the lungs of animals. Histopathological analysis of lung tissue harvested after infection showed significantly reduced SARS-CoV-2 viral antigen levels and a lower abundance of pulmonary lesions in molnupiravir-treated animals compared with controls.

In Vitro Cytotoxicity
NHC, the nucleoside analogue metabolite of molnupiravir, had variable cytotoxicity against different mammalian cell types with CC_{50} values ranging from 7.5 µM (human lymphoid CEM cell line) to >100 µM, in 3-day exposure assays. Molnupiravir inhibited the proliferation of human bone marrow progenitor cells with CC_{50} values of 24.9 µM and 7.7 µM for erythroid and myeloid progenitor proliferation, respectively, in 14-day colony formation assays.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
A mouse carcinogenicity study with molnupiravir is ongoing.

Mutagenesis
Molnupiravir and NHC were positive in the *in vitro* bacterial reverse mutation assay (Ames assay) with and without metabolic activation. Molnupiravir was studied in two *in vivo* rodent mutagenicity models. The *in vivo* Pig-a mutagenicity assay gave equivocal results. Molnupiravir was negative in the *in vivo* Big Blue® (cII Locus) transgenic rodent mutagenicity assay. Molnupiravir was negative for induction of chromosomal damage in *in vitro* micronucleus (with and without metabolic activation) and *in vivo* rat micronucleus assays. To assess effects on germ cells, a transgenic rodent male germ cell mutagenicity assay is planned.

Based on the totality of the available genotoxicity data and the duration of treatment (5 days), molnupiravir is low risk for genotoxicity.

Impairment of Fertility
There were no effects on fertility, mating performance or early embryonic development when molnupiravir was administered to female or male rats at NHC exposures approximately 2 and 6 times, respectively, the human NHC exposure at the RHD.

13.2 Animal Toxicology and/or Pharmacology

Bone and cartilage toxicity changes resulting in impaired transformation of growth cartilage into new bone were observed in the femur and tibia of rats in a 3-month toxicity study at ≥ 500 mg/kg/day (5 times the human NHC exposure at the RHD). There was no bone or cartilage toxicity in a 1-month toxicity study in rats up to 500 mg/kg/day (4 and 8 times the human NHC exposure at the RHD in females and males, respectively), in dogs dosed for 14 days up to 50 mg/kg/day (similar to the human NHC exposure at the RHD), or in a 1-month toxicity study in mice up to 2,000 mg/kg/day (19 times the human NHC exposure at the RHD).

Growth cartilage is not present in mature skeletons, therefore the bone and cartilage findings are not relevant for adult humans but may be relevant for pediatric patients *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.4)]*.

Reversible, dose-related bone marrow toxicity affecting all hematopoietic cell lines was observed in dogs at ≥17 mg/kg/day (less than the human NHC exposure at the RHD). Mild decreases in peripheral blood cell and platelet counts were seen after 7 days of molnupiravir treatment progressing to more severe hematological changes after 14 days of treatment. Neither bone

marrow nor hematological toxicity was observed in a 1-month toxicity study in mice up to 2,000 mg/kg/day (19 times the human NHC exposure at the RHD) and a 3-month toxicity study in rats up to 1,000 mg/kg/day (9 and 15 times the human NHC exposure at the RHD in females and males, respectively).

14 CLINICAL STUDIES

Clinical data supporting this EUA are based on data from 1,433 randomized subjects in the Phase 3 MOVe-OUT trial (NCT04575597). MOVe-OUT is a randomized, placebo-controlled, double-blind clinical trial studying molnupiravir for the treatment of non-hospitalized patients with mild-to-moderate COVID-19 who are at risk for progressing to severe COVID-19 and/or hospitalization. Eligible subjects were 18 years of age and older and had one or more pre-defined risk factors for disease progression: over 60 years of age, diabetes, obesity (BMI ≥30), chronic kidney disease, serious heart conditions, chronic obstructive pulmonary disease, or active cancer. The study included symptomatic subjects not vaccinated against SARS-CoV-2 and who had laboratory confirmed SARS-CoV-2 infection and symptom onset within 5 days of randomization. Subjects were randomized 1:1 to receive 800 mg of molnupiravir or placebo orally twice daily for 5 days.

At baseline, in all randomized subjects, the median age was 43 years (range:18 to 90); 17% of subjects were over 60 years of age and 3% were 75 years of age or older; 49% of subjects were male; 57% were White, 5% Black or African American, 3% Asian, 50% Hispanic or Latino. The majority of subjects were enrolled from sites in Latin America (46%) and Europe (33%); 12% were enrolled in Africa, 6% were enrolled in North America and 3% were enrolled in Asia. Forty-eight percent of subjects received molnupiravir or placebo within 3 days of COVID-19 symptom onset. The most common risk factors were obesity (74%), over 60 years of age (17%), and diabetes (16%). Among 792 subjects (55% of total randomized population) with available baseline SARS-CoV-2 variant/clade identification results, 58% were infected with Delta (B.1.617.2 and AY lineages), 20% were infected with Mu (B.1.621), 11% were infected with Gamma (P.1), and the remainder were infected with other variants/clades. Overall, baseline demographic and disease characteristics were well balanced between the treatment arms.

Table 3 provides the results of the primary endpoint (the percentage of subjects who were hospitalized or died through Day 29 due to any cause). The efficacy results are based on unvaccinated adults who were 18 years of age and older and had one or more pre-defined risk factors for disease progression: over 60 years of age, diabetes, obesity (BMI ≥30), chronic kidney disease, serious heart conditions, chronic obstructive pulmonary disease, or active cancer. Please refer to Figure 1 for results by certain subgroups. These subgroup analyses are considered exploratory. Data are not available in certain subgroups of subjects who are at high risk for progression to severe COVID-19 as defined by CDC.

Table 3. Efficacy Results in Non-Hospitalized Adults with COVID-19*

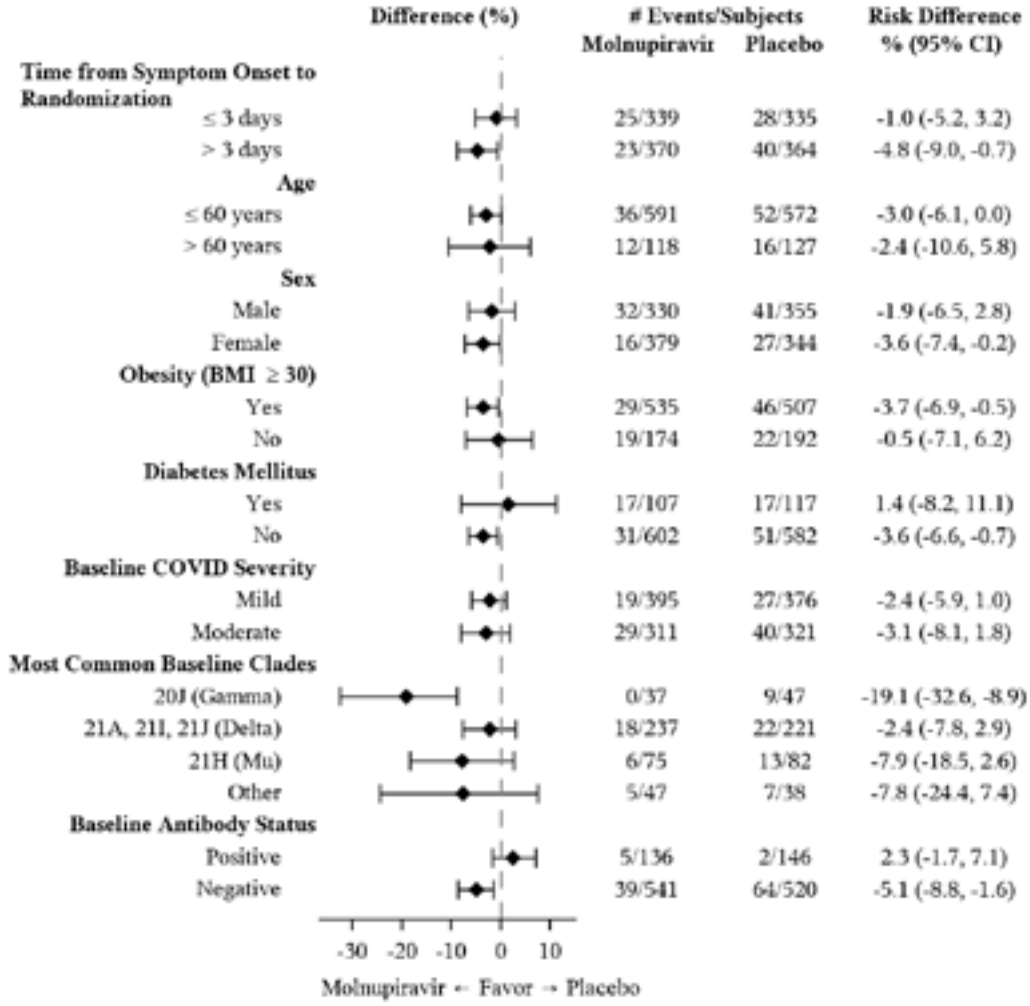
Molnupiravir (N=709) n (%)	**Placebo (N=699) n (%)**	**Adjusted Risk Difference % (95% CI)**
All-cause hospitalization ≥24 hours for acute care or death through Day 29		
48 (6.8%)	68 (9.7%)	-3.0% (-5.9%, -0.1%)
All-cause mortality through Day 29		
1 (0.1%)	9 (1.3%)	

*The determination of primary efficacy was based on a planned interim analysis of 762 subjects. At the interim analysis, 7.3% of patients who received molnupiravir were either hospitalized or died through Day 29 (28/385), compared with 14.1% of placebo-treated patients (53/377). The adjusted risk difference was -6.8% with a 95% CI of (-11.3%, -2.4%) and 2-sided p-value = 0.0024.

Adjusted relative risk reduction of molnupiravir compared to placebo for all randomized subjects was 30% (95% CI: 1%, 51%).

Analyses are adjusted by the stratification factor of time of COVID-19 symptom onset (≤3 days vs. >3 [4-5] days).

Figure 1. Subgroup Efficacy Results in Non-Hospitalized Adults with COVID-19 - All-Randomized Subjects



The corresponding confidence interval is based on Miettinen & Nurminen method.
The modified intent-to-treat population is the efficacy analysis population.
Baseline serum samples were evaluated with the Roche Elecsys anti-N assay to test for the presence of antibodies (IgM, IgG and IgA) against the SARS-CoV-2 nucleocapsid protein.
The findings of these subgroup analyses are considered exploratory.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Molnupiravir capsules are supplied as follows:

Contents	Description	How Supplied	NDC
200 mg molnupiravir	Swedish Orange opaque capsules with corporate logo and “82” printed in white ink	40 count bottles	NDC-0006-5055-06 NDC-0006-5055-07

Storage and Handling
Store molnupiravir capsules at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) *[see USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION
As a prescribing healthcare practitioner, you must communicate to the patient and/or caregiver information consistent with the "FACT SHEET FOR PATIENTS AND CAREGIVERS" and document that information was provided. A copy of this Fact Sheet should be provided to the patient and/or caregiver prior to receiving molnupiravir *[see Box]*.

Risk of Fetal Toxicity
Advise patients that molnupiravir is not recommended for use in pregnancy because it may cause fetal harm. Advise individuals of childbearing potential to inform their healthcare provider of a known or suspected pregnancy *[see Box, Warnings and Precautions (5.1) and Use in Specific Populations (8.1)].*

Advise individuals of childbearing potential to use effective contraception correctly and consistently while taking molnupiravir and for 4 days after the last dose.

While the risk is regarded as low, nonclinical studies to fully assess the potential for molnupiravir to affect offspring of treated males have not been completed. Advise sexually active individuals with partners of childbearing potential to use a reliable method of contraception consistently and correctly while taking molnupiravir and for at least 3 months after the last dose of molnupiravir. The risk beyond 3 months after the last dose of molnupiravir is unknown. Studies to understand the risk beyond three months are ongoing *[see Use in Specific Populations (8.3)].*

Risk of Bone and Cartilage Toxicity
Molnupiravir is not authorized for use in patients less than 18 year of age as it may affect bone growth and cartilage formation *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.4)].*

Pregnancy Surveillance Program
There is a pregnancy surveillance program that monitors pregnancy outcomes in individuals exposed to molnupiravir during pregnancy. Encourage participation and advise patients about how they may enroll in the pregnancy surveillance program. Advise patients who have taken molnupiravir during pregnancy to report their pregnancy to Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ USA at 1-877-888-4231 or pregnancyreporting.msd.com *[see Use in Specific Populations (8.1)]*.

Lactation
Breastfeeding is not recommended while taking molnupiravir and for 4 days after the last dose of molnupiravir. Advise lactating individuals to consider interrupting breastfeeding and to consider pumping and discarding breast milk during treatment and for 4 days after the last dose of molnupiravir *[see Use in Specific Populations (8.2)]*.

Administration Instructions
Inform patients to take molnupiravir with or without food. Advise patients to swallow molnupiravir capsules whole, and to not open, break, or crush the capsules. Instruct patients that if they miss a dose of molnupiravir and it is within 10 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 10 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. Advise the patient to not double the dose to make up for a missed dose *[see Dosage and Administration (2.2)]*.

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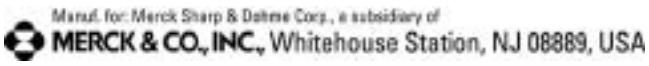
Alert the patient of the importance of completing the full 5-day treatment course and to continuing isolation in accordance with public health recommendations to maximize viral clearance and minimize transmission of SARS-CoV-2 *[see Dosage and Administration (2.2)]*.

18 MANUFACTURER INFORMATION
For additional information visit: www.molnupiravir.com

If you have questions, please contact
1-800-672-6372



For patent information: www.msd.com/research/patent

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Fact Sheet for Patients And Caregivers
Emergency Use Authorization (EUA) Of Molnupiravir For Coronavirus Disease 2019 (COVID-19)

What is the most important information I should know about molnupiravir?
Molnupiravir may cause serious side effects, including:

- **Molnupiravir may cause harm to your unborn baby. It is not known if molnupiravir will harm your baby if you take molnupiravir during pregnancy.**
  - Molnupiravir is not recommended for use in pregnancy.
  - Molnupiravir has not been studied in pregnancy. Molnupiravir was studied in pregnant animals only. When molnupiravir was given to pregnant animals, molnupiravir caused harm to their unborn babies.
  - You and your healthcare provider may decide that you should take molnupiravir during pregnancy if there are no other COVID-19 treatment options authorized by the FDA that are accessible or clinically appropriate for you.
  - If you and your healthcare provider decide that you should take molnupiravir during pregnancy, you and your healthcare provider should discuss the known and potential benefits and the potential risks of taking molnupiravir during pregnancy.

For individuals who are able to become pregnant:

- You should use a reliable method of birth control (contraception) consistently and correctly during treatment with molnupiravir and for 4 days after the last dose of molnupiravir. Talk to your healthcare provider about reliable birth control methods.
- Before starting treatment with molnupiravir your healthcare provider may do a pregnancy test to see if you are pregnant before starting treatment with molnupiravir.
- Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with molnupiravir.

Pregnancy Surveillance Program:

- There is a pregnancy surveillance program for individuals who take molnupiravir during pregnancy. The purpose of this program is to collect information about the health of you and your baby. Talk to your healthcare provider about how to take part in this program.
- If you take molnupiravir during pregnancy and you agree to participate in the pregnancy surveillance program and allow your healthcare provider to share your information with Merck Sharp & Dohme, then your healthcare provider will report your use of molnupiravir during pregnancy to Merck Sharp & Dohme Corp. by calling 1-877-888-4231 or pregnancyreporting.msd.com.

For individuals who are sexually active with partners who are able to become pregnant:

- It is not known if molnupiravir can affect sperm. While the risk is regarded as low, animal studies to fully assess the potential for molnupiravir to affect the babies of males treated with molnupiravir have not been completed. A reliable method of birth control (contraception) should be used consistently and correctly during treatment with molnupiravir and for at least 3 months after the last dose. The risk to sperm beyond 3 months is not known. Studies to understand the risk to sperm beyond 3 months are ongoing. Talk to your healthcare provider

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about reliable birth control methods. Talk to your healthcare provider if you have questions or concerns about how molnupiravir may affect sperm.

You are being given this fact sheet because your healthcare provider believes it is necessary to provide you with molnupiravir for the treatment of adults with mild-to-moderate coronavirus disease 2019 (COVID-19) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 including hospitalization or death, and for whom other COVID-19 treatment options authorized by the FDA are not accessible or clinically appropriate.

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to make molnupiravir 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). Molnupiravir is not an FDA-approved medicine in the United States. Read this Fact Sheet for information about molnupiravir. Talk to your healthcare provider about your options if you have any questions. It is your choice to take molnupiravir.

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 molnupiravir?
Molnupiravir is an investigational medicine used to treat mild-to-moderate COVID-19 in adults:

- with positive results of direct SARS-CoV-2 viral testing, and
- who are at high risk for progressing to severe COVID-19 including hospitalization or death, and for whom other COVID-19 treatment options authorized by the FDA are not accessible or clinically appropriate.

The FDA has authorized the emergency use of molnupiravir for the treatment of mild-to-moderate COVID-19 in adults under an EUA. For more information on EUA, see the **"What is an Emergency Use Authorization (EUA)?"** section at the end of this Fact Sheet.

Molnupiravir is not authorized:

- for use in people less than 18 years of age.
- for prevention of COVID-19.
- for people needing hospitalization for COVID-19.
- for use for longer than 5 consecutive days.

What should I tell my healthcare provider before I take molnupiravir?

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Tell your healthcare provider if you:

- Have any allergies
- Are breastfeeding or plan to breastfeed
- Have any serious illnesses
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products).

How do I take molnupiravir?

- Take molnupiravir exactly as your healthcare provider tells you to take it.
- Take 4 capsules of molnupiravir every 12 hours (for example, at 8 am and at 8 pm)
- **Take molnupiravir for 5 days**. It is important that you complete the full 5 days of treatment with molnupiravir. Do not stop taking molnupiravir before you complete the full 5 days of treatment, even if you feel better.
- Take molnupiravir with or without food.
- You should stay in isolation for as long as your healthcare provider tells you to. Talk to your healthcare provider if you are not sure about how to properly isolate while you have COVID-19.
- Swallow molnupiravir capsules whole. Do not open, break, or crush the capsules. If you cannot swallow capsules whole, tell your healthcare provider.
- **What to do if you miss a dose:**
    - If it has been **less than 10 hours** since the missed dose, take it as soon as you remember
    - If it has been **more than 10 hours** since the missed dose, skip the missed dose and take your dose at the next scheduled time.
- Do not double the dose of molnupiravir to make up for a missed dose.

What are the important possible side effects of molnupiravir?
Possible side effects of molnupiravir are:

- See, **"What is the most important information I should know about molnupiravir?"**
- diarrhea
- nausea
- dizziness

These are not all the possible side effects of molnupiravir. Not many people have taken molnupiravir. Serious and unexpected side effects may happen. This medicine 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 molnupiravir, 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 more information.

It is your choice to be treated or not to be treated with molnupiravir. Should you decide not to take it, it will not change your standard medical care.

What if I am breastfeeding?

Breastfeeding is not recommended during treatment with molnupiravir and for 4 days after the last dose of molnupiravir. If you are breastfeeding or plan to breastfeed, talk to your healthcare provider about your options and specific situation before taking molnupiravir.

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How do I report side effects with molnupiravir?
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 (1-800-332-1088).

How should I store molnupiravir?

- Store molnupiravir capsules at room temperature between 68°F to 77°F (20°C to 25°C).
- **Keep molnupiravir and all medicines out of the reach of children and pets.**

How can I learn more about COVID-19?

- Ask your healthcare provider.
- Visit www.cdc.gov/COVID19
- Contact your local or state public health department.
- Call Merck Sharp & Dohme at 1-800-672-6372 (toll free in the U.S.)
- Visit www.molnupiravir.com

What Is an Emergency Use Authorization (EUA)?

The United States FDA has made molnupiravir 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 emergency use of drugs and biological products during the COVID-19 pandemic. Molnupiravir for the treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing, who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate, 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 molnupiravir is in effect for the duration of the COVID-19 declaration justifying emergency use of molnupiravir, unless terminated or revoked (after which molnupiravir may no longer be used under the EUA).

Manuf. for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

For patent information: www.msd.com/research/patent

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KIMBERLY A STRUBLE
12/23/2021 07:17:04 AM

DEBRA B BIRNKRANT
12/23/2021 07:27:18 AM

JOHN J FARLEY
12/23/2021 08:15:19 AM

EMERGENCY USE AUTHORIZATION REVIEW
US FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF INFECTIOUS DISEASES
DIVISION OF ANTIVIRALS
ADDENDUM

EUA:	000108
Product:	Molnupiravir
Sponsor:	Merck Sharp & Dohme
Intended Population:	Adults who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.

This addendum is for corrections to the summary EUA review for molnupiravir for the treatment of mild-to-moderate COVID-19 dated December 23, 2021.

The corrections are as follows:

On Page 1, “Senior” should be added prior to “Director” for Dr. Kumar’s title on page 1.

On page 73, “mild” should be changed to “milk.”

On pages 69 and 94, the pharmacokinetic/distribution study in rats should be changed from “ongoing” to “planned.” The study is planned to be initiated in mid-January 2022.

On page 98, “pediatrics” should be removed from the Supply Information section as molnupiravir is not authorized for use in pediatric patients.

The corrections do not alter the conclusion of the review and do not alter the information presented in the authorized Facts Sheets for Healthcare Providers or for Patients and Caregivers.

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DEBRA B BIRNKRANT
01/05/2022 08:43:11 AM

JOHN J FARLEY
01/05/2022 09:52:38 AM

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Document 3A.7

U.S. FDA Emergency Use Authorization (EUA) for Molnupiravir 200 mg Capsules Center for Drug Evaluation and Research (CDER) Review Memorandum (February 17, 2023)

Document URL

https://www.fda.gov/media/165856/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

Non applicable

Emergency Use Authorization (EUA) for Molnupiravir 200 mg Capsules

Center for Drug Evaluation and Research Review Memorandum

Identifying Information

Application Type (EUA or Pre-EUA) If EUA, designate whether pre-event or intra-event EUA request.	EUA
EUA Application Number(s)	000108
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	Merck Sharp & Dohme., a subsidiary of Merck & Co., Inc. 1 Merck Drive PO Box 100 Whitehouse Station, NJ 08889-0100 908-423-1000 POC: Sushma Kumar, PhD, PMP Senior Director, Global Regulatory Affairs and Clinical Safety Merck Sharp & Dohme Corp. (b) (6)
OND Division / Office	Division of Antivirals (DAV)/Office of Infectious Diseases (OID)
Reviewer Name(s)/Discipline(s)	Clinical Reviewer: Aimee Hodowanec, MD Clinical Team Leader: Kimberly Struble, PharmD Clinical Virology Reviewer: Patrick Harrington, PhD Clinical Virology Team Leader: Jules O'Rear, PhD
Proprietary Name	Lagevrio
Established Name/Other names used during development	Molnupiravir (MK-4482; MOV; EIDD-2801)
Dosage Forms/Strengths	Oral capsule, 200 mg
Therapeutic Class	SARS-CoV-2 antiviral
Intended Use or Need for EUA	Treatment of mild-to-moderate coronavirus disease 2019 (COVID-19)
Intended Population(s)	Adults with a current diagnosis of mild-to-moderate 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.

Abbreviations: DAV, Division of Antivirals; EUA, emergency use authorization; OID, Office of Infectious Diseases; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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1. Background

Molnupiravir (MOV, EIDD-2801) is a 5' isobutyrate prodrug of a cytidine ribonucleoside analogue, β-D-N^4-hydroxycytidine (NHC, EIDD-1931), which inhibits SARS-CoV-2 replication by viral mutagenesis. MOV received Emergency Use Authorization (EUA) on 12/23/2021 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" (Molnupiravir Fact Sheet for Healthcare Providers).

A recently released preprint (i.e., not peer-reviewed) manuscript by Sanderson et al., 2023, titled "Identification of a molnupiravir-associated mutational signature in SARS-CoV-2 sequencing databases," has led to some concerns in the scientific and non-scientific press about the potential for MOV to contribute to enhanced SARS-CoV-2 evolution that could result in emergence and spread of novel variants (e.g., Service 2023; Callaway 2023; Lowe 2023; Lauerman 2023).

On January 31, 2023, Drs. Janet Woodcock and Patrizia Cavazzoni received an email from Michael Lin, MD, PhD from Stanford University noting this Sanderson et al., 2023 preprint article as well as another recent publication by Butler et. al., 2022 regarding the PANORAMIC clinical trial and expressing several concerns regarding the MOV EUA:

- **Comment #1: The UK PANORAMIC trial, published in late December 2022 in The Lancet, showed no benefit of MOV in preventing severe disease in a high-risk population with prior immunity (not even a nonsignificant trend in favor of drug, really 0 benefit):**

  https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)02597-1/fulltext

  As 95-100% of Americans now have prior immunity, this is the only study relevant to our current situation. The Phase 3 MOV trial showing 30% reduced risk of severe disease, which led to EUA, was in SARS2-immunonaive patients. UK NIHR press release at: https://www.nihr.ac.uk/news/molnupiravir-does-not-reduce-covid-19-hospitalisations-or-deaths-in-vaccinated-high-risk-people/32329

- **Comment #2: A survey of worldwide SARSCoV2 sequence databases showing widespread signatures of MOV-induced mutagenesis in patient samples, with some examples showing onward transmission:**

  https://www.medrxiv.org/content/10.1101/2023.01.26.23284998v2

  The expected pattern of MOV mutagenesis (increased G–>A mutations) was seen only after MOV approval and only in countries that approved it. Some mutant genomes with 31 mutations occurred in clusters, showing these mutated viruses are viable and can propagate. This mutation load is similar to that seen in Omicron BA.1 vs ancestral, which of course was associated

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with enhanced transmission and increased immunoevasion. Thus it is possible for MOV to produce in a single round of infection a virus with enhanced propagative abilities; the more patients who take MOV, the higher the probability such an event would actually happen.

Following the release of the Sanderson et al., 2023 preprint and receipt of Dr. Lin's inquiry, DAV requested on February 2, 2023 that the Sponsor (i.e., Merck) provide an assessment on the findings reported in the Sanderson et al., 2023 article; the Sponsor submitted their assessment on February 9, 2023 in EUA 108 SDN 161.

This review memo includes the following:

- Summary of available MOV efficacy data, including recently published data from the U.K. PANORAMIC trial (Butler et al., 2022)
- DAV's Clinical Virology assessment of the Sanderson et al., 2023 preprint article
- Summary of the Sponsor's assessment of the Sanderson et al., 2023 preprint article
- High-level perspective on how on the findings from U.K. PANORAMIC trial (Butler et al., 2022) and the Sanderson et al., 2023 preprint article factor into the overall risk-benefit assessment of MOV

2. Review of Human Clinical Efficacy: Trial MK-4482-002 and PANORAMIC Trial

The data in support of the MOV EUA came from trial MK-4482-002 ("MOVe-OUT"), a randomized, double-blind, placebo-controlled, trial in patients with mild-to-moderate COVID-19. The Phase 3 (Part 2) portion of this trial was conducted from May 2021 through October 2021 and patients who had undergone SARS-CoV-2 vaccination were excluded. Overall, MOV was associated with a 3.0% (-5.9%, -0.1%) adjusted risk difference in hospitalization or death through Day 29 (nominal p-value = 0.0436). However, as described in detail in the EUA 108 12/23/2021 multi-disciplinary review, there was marked decrease in the molnupiravir treatment effect between the first and second half of the trial, that appeared to be driven by a decrease in the rate of hospitalization and death in the placebo arm over time, while rates of hospitalization and death remained relatively stable in the MOV arm.

Based on the observed reduction in the rate of hospitalization and death in the full MK-4482-002 Part 2 population, the review team concluded that the known and potential benefits of MOV outweigh the known and potential risks of MOV 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. However, given the modest benefit and the inconsistencies between the first and second half of trial MK-4482-002, MOV is only authorized for use for adults for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

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More recently, MOV was studied in a large, randomized, controlled open-label, platform trial conducted in the UK, the PANORAMIC trial. The MOV portion of this trial was conducted from December 2021 to April 2022 and the trial enrolled a highly vaccinated patient population (98.9% had at least one dose of a SARS-CoV-2 vaccine and 94.4% had received at least three doses). This trial did not meet the pre-specified primary efficacy endpoint of hospitalization or death through Day 28 (103/12,516 [0.8%] in the MOV plus usual care group and 96/12,484 [0.8%] in the usual care group).

Molnupiravir did meet some of the secondary endpoints in PANORAMIC, including time to self-reported recovery [(9 days (range 5 to 23 days) in the MOV plus usual care group vs.15 days (range 7 days to not reached) in the usual care group]. However, the reliability of this symptom-based endpoint is uncertain, largely because of the trial's open-label design. (b) (4)

There are likely several factors that led to the low rates of hospitalization and death in the PANORAMIC trial. The PANORAMIC trial was conducted while the less virulent Omicron variant was circulating (whereas trial MK-4482-002 was conducted while the Delta variant was circulating). Further, in addition to enrolling a highly vaccinated population, the PANORAMIC trial also enrolled a less high-risk population. Individuals aged ≥ 50 years or aged 18-50 years with an underlying health conditions that made them "clinically vulnerable" were eligible for study participation. Approximately 17% of the study population consisted of persons aged 50-59 years without other risk factors for severe COVID-19. The patients at greatest risk for progression to severe COVID-19 had limited representation in the trial. For instance, <1% of study participants were transplant recipients. Further, patients at "very high risk" of severe COVID-19 (i.e., those with impaired immune systems or who are extremely clinically vulnerable) were eligible to receive monoclonal antibodies, intravenous antivirals (remdesivir), and oral antivirals (molnupiravir or nirmatrelvir–ritonavir) as "usual care."

Given the PANORAMIC trial design and study population, limited conclusions regarding the effectiveness of molnupiravir in treating mild-to-moderate COVID-19 can be drawn from this trial. Trial MK-4482-002 remains the primary source of data in support of the MOV EUA. (b) (4) . However, the results from MK-4482-002 are sufficient to fulfill the statutory requirements for an EUA (i.e., molnupiravir may be effective).

3. Overview of molnupiravir mechanism of action and impact on SARS-CoV-2 sequences and shedding

After oral administration, MOV is hydrolyzed by esterases to generate NHC, which circulates systemically. After cellular uptake, NHC is phosphorylated by host cell kinases to generate the active 5'-triphosphate, NHC-TP. The triphosphate acts as a

competitive alternative substrate by the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), nsp12, and the NHC-monophosphate (NHC-MP) is incorporated into negative- or positive-sense RNA in place of the monophosphates of C or U, which is attributed to the N4-hydroxycytosine base of NHC having two tautomeric forms allowing base pairing with either G or A. Over time, as NHC-MP is incorporated into viral RNA genomes and copied, changes accumulate in the viral genome, particularly G→A and C→U transition mutations, ultimately resulting in defective viral genomes. The mechanism of action of NHC as a viral RNA mutagen is well established and supported by data from several biochemical, cellular, and animal studies, as well as data showing increased numbers of nucleotide mutations in SARS-CoV-2 genome sequences from human participants treated with MOV in clinical trials (EUA 108 12/23/2021 multi-disciplinary review; EUA 000108 SDNs 98,100,101,104 clinical virology review).

As described in the EUA 108 reviews noted above, analyses conducted by FDA and the sponsor of SARS-CoV-2 sequences from MOV- and placebo-treated subjects in clinical trials showed higher frequencies of SARS-CoV-2 mutations in MOV-treated subjects. As an example, Table 1 (Merck Virology Report 07X2GY, pg. 88) shows an analysis conducted by Merck of nucleotide changes detected in SARS-CoV-2 sequences from subjects in the Phase 3 outpatient trial, MK-4482-002 Part 2 ("MOVe-OUT"). Consistent with the MOV mechanism of action, MOV treatment was primarily associated with elevated frequencies of transition mutations, i.e., G-to-A, C-to-U, A-to-G, and U-to-C mutations. Although less common, transversions and other (i.e., insertion/deletion) mutations also appeared to be enriched in MOV-treated subjects. It is unclear mechanistically how MOV would enrich for such changes, but this trend was also noted in the Phase 2 portion of the trial, MK-4482-002 Part 1.

Table 1. SARS-CoV-2 nucleotide mutations observed relative to baseline sequences in subjects enrolled in clinical trial MK-4482-002 Part 2 ("MOVe-OUT"). Source: Merck Virology Report 07X2GY.

			Transitions				Transversions								Other Nucleotide Changes
Visit	Treatment	N	C:U	U:C	G:A	A:G	C:A	C:G	U:A	U:G	G:U	G:C	A:C	A:U	
EOT (Day 5)	MK-4482 800 mg	205	6.6	1.9	4.2	1.7	0.1	0.1	0.1	0.1	1.2	0.1	0.1	0.3	1.9
	Placebo	233	2.4	0.6	0.2	0.3	0.1	0.0	0.0	0.0	0.6	0.0	0.1	0.2	1.5
Day 10	MK-4482 800 mg	31	10.2	2.8	8.8	2.8	0.1	0.0	0.0	0.0	0.2	0.0	0.0	0.1	1.1
	Placebo	41	2.0	0.4	0.5	0.4	0.1	0.0	0.1	0.0	0.6	0.0	0.1	0.1	1.4
Day 15	MK-4482 800 mg	15	3.0	1.1	2.5	0.6	0.1	0.0	0.0	0.1	0.3	0.0	0.0	0.1	0.5
	Placebo	14	6.4	1.3	2.5	1.1	0.1	0.1	0.1	0.1	1.5	0.1	0.0	0.1	1.5
Day 29	MK-4482 800 mg	1	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0	2.0
	Placebo	4	8.0	1.8	2.9	0.8	0.0	0.0	0.0	0.3	2.3	0.0	0.3	0.3	3.3

N = number of participants with both baseline and post-baseline SARS-CoV-2 gene sequencing data at the reported visit.
EOT (Day 5) includes post-baseline records from day 5 (relative to randomization) up to day 7.
Other Nucleotide Changes include insertions and deletions.

Viral genetic changes associated with MOV mutagenesis occur throughout the SARS-CoV-2 genome. Of particular interest, FDA and sponsor analyses of viral sequences from the MK-4482-002 Part 2 ("MOVe-OUT") trial identified a greater proportion of MOV-treated participants, compared to placebo-treated participants, had treatment-emergent amino acid substitutions detected in the viral spike (S) protein. Some of the S

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substitutions had been associated with antibody escape and/or observed in major SARS-CoV-2 variants.

While these observations raise concerns that MOV could increase the rate of SARS-CoV-2 evolution and contribute to the generation of novel viral variants, it must also be recognized that MOV-associated mutagenicity more often leads to impairment of virus replication and reduced viral shedding, which likely reduces the chance that viruses bearing MOV-associated mutations are transmitted to other individuals. Studies directly investigating virus transmission from MOV-treated patients have not been conducted, but the impact of MOV on virus shedding was observed based on analyses of viral RNA and cell culture infectious virus obtained from NP swab samples from subjects in MK-4482-002 Part 2 ("MOVe-OUT"). As shown in Figure 1 (FDA analysis; EUA 000108 SDNs 98,100,101,104 clinical virology review), MOV treatment was associated with a modestly greater decline in SARS-CoV-2 RNA shedding through Day 5 (i.e., end-of-treatment). However, the impact of MOV on virus shedding is likely better reflected by analyses of cell culture infectious virus. While the detection of cell culture infectious SARS-CoV-2 quickly declined in both MOV and placebo-treated subjects, a more pronounced decline was seen in MOV-treated subjects (Table 2, FDA analysis; EUA 000108 SDNs 98,100,101,104 clinical virology review). The cell culture assay provides a readout of MOV antiviral activity that is arguably more relevant to the mutagenic mechanism of MOV, as MOV is likely to exert an effect on viral infectivity and replication fitness prior to an effect on overall viral RNA levels. Of note, 4 of the MOV-treated subjects were immunocompromised and had culturable virus detected at baseline; no virus could be isolated from these subjects at any timepoint after initiation of MOV.

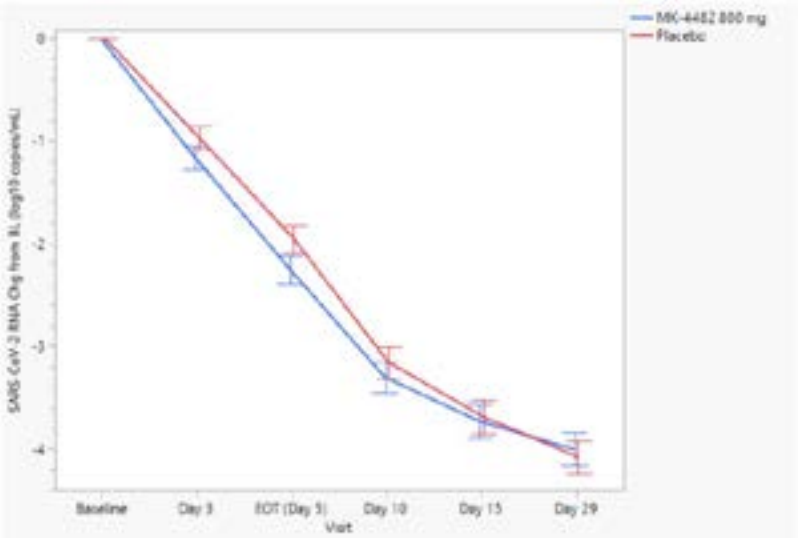

Figure 1. Change in SARS-CoV-2 RNA levels in NP samples from MK-4482-002, Part 2. Results show mean values and 95% confidence intervals. MK-4482, molnupiravir. Source: FDA analysis.

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Table 2. Detection of cell culture infectious SARS-CoV-2 in MK-4482-002, Part 2. Analyses were conducted only for those with baseline and post-baseline results. IA, interim analysis.

	All Subjects		Subjects with Positive Infectivity Result at Baseline	
	MOV 800 mg BID	Placebo	MOV 800 mg BID	Placebo
Baseline	14.3% (96/671)	14.5% (97/670)	100.0% (96/96)	100.0% (97/97)
Day 3	0.5% (3/637)	4.7% (30/643)	0.0% (0/92)[1]	20.8% (20/96)[2]
EOT (Day 5)	0.0% (0/623)	1.0% (6/616)	0.0% (0/91)	2.2% (2/89)[3]
Day 10	0.2% (1/583)	0.2% (1/582)	0.0% (0/82)	0.0% (0/86)
Day 15	0.0% (0/581)	0.0% (0/580)	0.0% (0/78)	0.0% (0/83)
Day 29	0.0% (0/577)	0.0% (0/590)	0.0% (0/77)	0.0% (0/89)

[1]All 92 negative results in subgroup were observed, not imputed. [2]15/69 in IA population, 5/27 in Post-IA population. [3]2/67 in IA population, 0/22 in Post-IA population.

As noted above, to our knowledge, clinical studies directly investigating transmission of SARS-CoV-2 from MOV-treated patients have not been conducted to assess and quantify the risk of transmission of MOV-mutagenized viruses to others. However, studies conducted in a ferret model of SARS-CoV-2 infection showed early MOV treatment was associated with reduced virus shedding and impairment of virus transmission to contact ferrets (cox et al., 2020; Lieber et al., 2022).

4. Summary of Sanderson et al., 2023 preprint publication

The referenced preprint manuscript identified a possible correlation between MOV availability and SARS-CoV-2 sequences/sequence clusters with mutational signatures claimed to be consistent with MOV-mediated mutagenesis, but a causal relationship has not yet been established.

In analyses of published SARS-CoV-2 sequences from the GISAID database, the authors identified viral sequences with long phylogenetic branches that contained what they viewed as higher-than-expected numbers of G-to-A mutations, and the authors hypothesized these sequences represent a mutational signature of MOV-mediated mutagenesis consistent with MOV-associated mutation patterns observed in the AGILE clinical trial.

These high G-to-A containing, long phylogenetic branches in the GISAID database were almost exclusively detected in sequences submitted in 2022, after the introduction of MOV in the U.S. and several other countries (Figure 2; from Sanderson et al., 2023). Furthermore, these branches appeared to be most common in the U.S., Australia and the U.K., where MOV is authorized, and less common in certain countries where MOV is not authorized, such as Canada and France. Considering viral sequences from the U.S. and Australia, the branches were also identified more commonly in sequences from older individuals, which the authors claimed was consistent with a “prioritized” use of MOV to treat older individuals. The authors also identified some examples of long SARS-CoV-2 phylogenetic branches with high numbers of G-to-A and other transition mutations that appeared to give rise to descendant sequences, leading the authors to

speculate that viruses with MOV-associated signature mutations were transmitted to others.

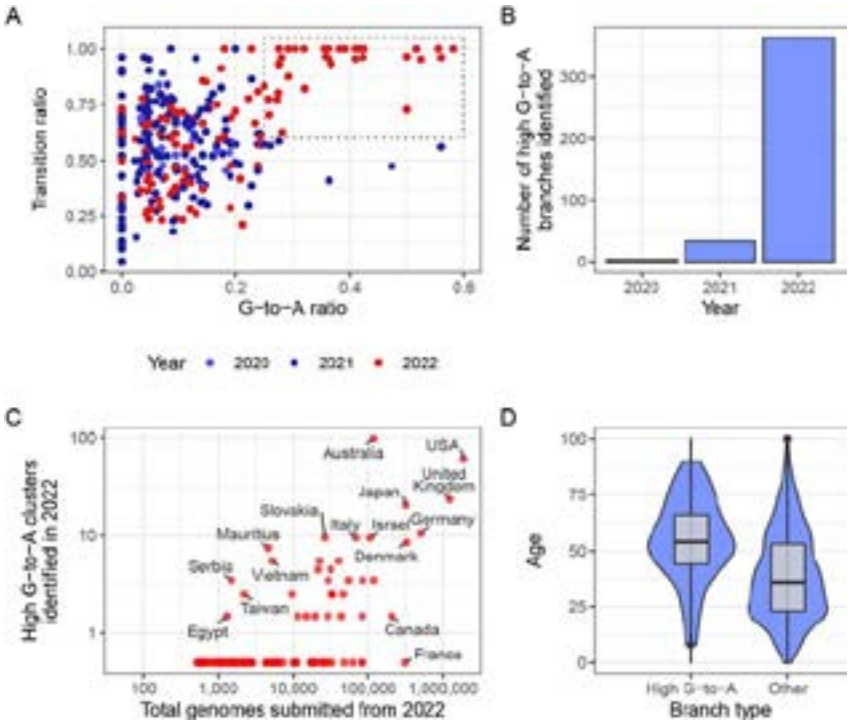

Figure 2. Identification of SARS-CoV-2 sequences in GISAID database with long branch lengths and high concentrations of G-to-A mutations. Source: preprint publication by Sanderson et al., 2023.

While it is plausible that MOV use could contribute to mutational patterns in SARS-CoV-2 sequences, there are some uncertainties regarding the authors claims and the public health implications of their results, including the following:

- Because the viral sequence data do not include information on the timing of virus sampling and whether the patients were even treated with MOV or any other agent, none of these findings can be directly attributed to MOV use. Therefore, the authors claim that these high G-to-A mutation, long phylogenetic branches are associated with MOV use is entirely hypothetical.
- The authors claim that the high G-to-A mutation, long phylogenetic branches primarily arose in 2022 following the introduction of MOV in the U.S. and several other countries (Fig. 1B). However, the numbers presented in this analysis are absolute numbers, and the denominators for the numbers of sequences analyzed were not reported so it is not possible to determine if this represents an increase in the frequencies of sequences with high G-to-A mutation, long phylogenetic branches, or if this can be attributed at least in part to an increasing number of viral sequences available for analysis.
- The high G-to-A mutation sequences identified by the authors represent a small fraction of the total genomes submitted to GISAID in 2022. For example, Australia had the highest numbers of such sequences but this reflected 0.08%

(97/119,194) of sequences. In the U.S., this frequency was 0.003% (60/1,911,997), and in the U.K., the country where MOV was first approved (Syed, 2022) the frequency was 0.002% (23/1,218,724). Thus, even if these sequences can be attributed directly to MOV mutagenesis, they do not contribute a substantial proportion of SARS-CoV-2 sequences in the GISAID database in 2022.

- It should also be noted that in the absence of MOV or any other antiviral agent, mutations arise throughout the SARS-CoV-2 genome through natural viral replication, and that transition mutations in general are more frequently introduced during replication than other types of changes (transversion mutations [i.e., purine↔pyrimidine], insertions, and deletions). Therefore, it is challenging to assert a precise "signature" mutational pattern to MOV use when it does not create novel mutations, but rather increases the frequencies of mutations that are already generated naturally.
- Long phylogenetic branches can also be a result of inconsistent SARS-CoV-2 genetic sampling in a particular sub-population. This could lead to collection of some genetically distant viral sequences without representation of other phylogenetically related sequences with intermediate numbers of mutations that were present in the population but were not adequately sampled.
- Technical issues could contribute to artifactual variability in mutational patterns in the database sequences, such as the specific next generation sequencing assay platform/chemistry, variability in clinical sampling and processing, and variability in viral RNA concentrations in clinical specimens (e.g., low viral RNA concentrations could contribute to a higher rate of mutations detected).

5. Sponsor's assessment of Sanderson et al., 2023 preprint publication

The sponsor has reviewed the preprint publication and noted that there are "gaps in the analyses done by the authors to draw their conclusions." Some of the concerns and uncertainties highlighted by the sponsor are the same as those independently identified in DAV's review of the article. Specific points raised in the sponsor's assessment include the following (paraphrased):

- The authors assume that the observed SARS-CoV-2 mutations are associated with MOV treatment, relying on circumstantial associations between viral sequence origin and timeframe of sequence collection in countries where MOV is available, with no direct evidence that the viral sequences arose from MOV use.
- In the analyses of high G-to-A, long phylogenetic branch sequences by year, the authors did not normalize the number of long branches identified to the total number of sequences analyzed each year. It is possible that an increase in high G-to-A, long branch sequences was a function of the increased number of sequences analyzed in 2022. This is supported by the plot of the number of high G-to-A branches identified by the total number of sequences submitted by

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country (referring to Figure 2C above), showing that the number of high G-to-A branches generally increases with greater number of available sequences.

- Given that high G-to-A branches represent only approximately 4.5% of the total long branches observed, similar analyses should have been conducted to evaluate other types of transitions (e.g., T-to-C and A-to-G) and other types of mutations (e.g., G-to-T) to determine whether these patterns were also observed during the evaluation period.
- The authors do not consider alternative scenarios for the existence of long phylogenetic branches, such as gaps in the database due to unavailability of intermediate genomes at the time of analysis. For example, sparse sampling, delays in sequencing, or data submission to the GISAID database, could all contribute to an incomplete phylogenetic tree, resulting in generation of sporadic long branch arms.
- In India, a country where generic versions of MOV are available, only 3 high G-to-A branches were identified, despite having a similar number of submitted sequences as Australia.
- The noted genetic mutations can also occur as a result of normal viral evolution. Of the 25 mutations identified in the Australian cohort, all 25 have been previously observed in SARS-CoV-2 genomes isolated prior to the authorization of MOV, confirming that all individual errors attributed to MOV use in this example occur through normal viral evolution.
- The authors describe a single sequence containing over 130 mutations and speculate, without evidence, that this highly mutated virus may have arisen as a result of multiple courses of MOV treatment in a chronically infected individual. Administration of multiple courses of MOV should be an uncommon clinical scenario as chronic infection with SARS-CoV-2 is rare, and treatment with MOV for longer than 5 days would not be consistent with prescribing information.
- Statistical analyses of the of data to support the author's conclusions are not provided.
- Data from clinical trials have demonstrated that MOV use results in a rapid decline in viral infectivity. The authors acknowledge that the mutations are likely deleterious or neutral, in which case the virus would likely become less fit.
- There is no known impact of MOV-associated transition mutations on MOV resistance or transmission of novel variants of concern.

6. Review Team's Perspectives and Conclusions

- The data available regarding efficacy in the Omicron era and in vaccinated individuals are limited for all approved and authorized SARS-CoV-2 antivirals. This is not unique to MOV. High rates of SARS-CoV-2 seropositivity (from vaccination or natural infection) combined with the predominance of the less

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virulent Omicron variant make it more difficult to show an effect on hospitalization and death given the low background rate of these outcomes.

- MOV was not shown to be associated with a reduction in the rate of hospitalization or death in the PANORAMIC trial. We believe that this is largely attributable to the enrollment of a less high-risk population, as evidenced by a hospitalization/death rate of < 2% in both the molnupiravir arm and the usual care arm.
- MOV was associated with a modest decrease in hospitalization and death in the Phase 3 trial, MK-4482-002. This "modest efficacy" is accounted for in the second-line authorized use statement, whereby MOV is only authorized for use in patients for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.
- While a large portion of the U.S. population has now been previously infected with SARS-CoV-2 and/or vaccinated against COVID-19, the most immunosuppressed patients may not have developed effective immunity following infection and/or vaccination. These patients may be closer to the "immunonaive" MK-4482-002 study population than the PANORAMIC study population.
- Now that EVUSHELD is no longer an effective means of preventing COVID-19 in the most vulnerable patients, the availability of multiple effective antiviral treatments is more important than ever. Many of these highly immunosuppressed patients also take concomitant medications that prevent them from being able to safely take PAXLOVID.
- The Sanderson et al., 2023 preprint manuscript identified a possible correlation between MOV availability and SARS-CoV-2 sequences/sequence clusters with mutational signatures claimed to be consistent with MOV-mediated mutagenesis. While it is plausible that MOV use could contribute to mutational patterns in SARS-CoV-2 sequences, there are some uncertainties regarding the authors claims and the public health implications of their results, and a causal relationship between MOV use and the noted SARS-CoV-2 sequence patterns has not yet been established.
- The potential for MOV-induced mutations to affect SARS-CoV-2 evolution was acknowledged prior to the EUA for MOV, and this concern was addressed in the EUA 108 12/23/2021 multi-disciplinary review and discussed at the November 30, 2021 Advisory Committee meeting on the EUA for MOv (meeting transcript).
- Nonclinical and clinical virology studies have shown that MOV-associated mutagenicity leads to impairment of virus replication and reduced viral shedding, which is expected to reduce the risk of transmission of viruses bearing MOV-associated mutations to other individuals.

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- The theoretical potential for an antiviral agent to contribute to SARS-CoV-2 evolution is not unique to MOV. The selective evolutionary pressures conferred by other agents, including small molecule antiviral drugs and virus Spike protein-targeting monoclonal antibodies, can contribute to the emergence or enrichment of SARS-CoV-2 variants with reduced susceptibilities to these agents.
- The preprint publication by Sanderson et al., 2023 does not change the review team's overall risk assessment of MOV. The risk that MOV use could contribute to SARS-CoV-2 genetic changes that are transmissible remains challenging to quantify, and DAV will continue to closely monitor the scientific literature for related preprints and published papers. We also look forward to the broader scientific community's assessment of this work. Ultimately, any risk of MOV-associated SARS-CoV-2 mutagenicity must be considered in the context of other risks and benefits of MOV.
- The evidentiary standard for an EUA is different than that for an NDA. The criteria for issuing an EUA include a requirement that it be reasonable to believe that the product *may be* effective in treating a serious or life-threatening disease. We continue to believe that molnupiravir meets this requirement. Further, it is the review team's current position that the risk-benefit assessment of MOV as a second-line therapy remains acceptable. We will continue evaluating data, including new real world data and any clinical trial data as they become available, noting the many limitations of real world data.

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KIMBERLY A STRUBLE
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Document 3A.8

U.S. FDA Fact Sheet for Patients and Caregivers Emergency Use Authorization (EUA) of Lagevrio (molnupiravir) capsules for Coronavirus Disease 2019 (COVID-19)

Document URL

https://www.fda.gov/media/155055/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 HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR LAGEVRIO™ (molnupiravir) CAPSULES

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)
These highlights of the EUA do not include all the information needed to use LAGEVRIO under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for LAGEVRIO.

LAGEVRIO™ (molnupiravir) capsules, for oral use
Original EUA Authorized Date: 12/23/2021
Revised EUA Authorized Date: 07/2023

MANDATORY REQUIREMENTS FOR ADMINISTRATION OF LAGEVRIO UNDER EMERGENCY USE AUTHORIZATION

Refer to FULL FACTSHEET for details.

----------RECENT MAJOR CHANGES----------

Adverse Reactions (Section 6.2): update to post-authorization experience section	07/2023
Mandatory Requirements Box, Use in Specific Populations (Section 8.1): Updates to pregnancy registry information	02/2023
Emergency Use Authorization (Section 1): Removal of requirement of SARS-CoV-2 viral testing	02/2023
Dosage and Administration (Section 2.3): Addition of preparation and administration instructions via nasogastric and orogastric tube.	02/2023
Microbiology (Section 12.4): Addition of Omicron subvariants	02/2023
Nonclinical Toxicology (Section 13.1): Updated carcinogenicity data	02/2023
Microbiology (Section 12.4): addition of viral RNA rebound	08/2022
Mandatory Requirements Box: Revised requirements pertaining to other therapeutics	02/2022
Emergency Use Authorization (Section 1): Updates on available alternatives to LAGEVRIO	02/2022
Warnings and Precautions (Sections 5.2 and 17): addition of hypersensitivity including anaphylaxis	02/2022
Adverse Reactions (Section 6.2): addition of post-authorization experience section	02/2022

----------EUA FOR LAGEVRIO----------

The U.S. Food and Drug Administration (FDA) has issued an EUA for the emergency use of the unapproved LAGEVRIO, a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis 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.

LAGEVRIO is not FDA-approved for any use including for use for the treatment of COVID-19. Prior to initiating treatment with LAGEVRIO, carefully consider the known and potential risks and benefits. (1)

LIMITATIONS OF AUTHORIZED USE (1)

- LAGEVRIO is not authorized
  - for use in patients less than 18 years of age (5.3)
  - for initiation of treatment in patients requiring hospitalization due to COVID-19. Benefit of treatment with LAGEVRIO has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19. (2.1)
  - for use for longer than 5 consecutive days.
  - for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

LAGEVRIO 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 LAGEVRIO belongs (i.e., anti-infectives).

LAGEVRIO is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of LAGEVRIO 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 the box in the beginning of the Full Fact Sheet for details on mandatory requirements for administration of LAGEVRIO under emergency use authorization.

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----------

- 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food. (2.1, 2.3)
- Take LAGEVRIO as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset. (2.1)
- 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. (2.1)
- LAGEVRIO is not authorized for use for longer than 5 consecutive days because the safety and efficacy have not been established. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 200 mg (3)

----------CONTRAINDICATIONS----------

No contraindications have been identified based on the limited available data on the emergency use of LAGEVRIO authorized under this EUA. (4)

----------WARNINGS AND PRECAUTIONS----------

- Embryo-Fetal Toxicity: LAGEVRIO is not recommended for use during pregnancy. (5.1, 8.1, 8.3)
- Hypersensitivity reactions, including anaphylaxis have been reported with LAGEVRIO. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue LAGEVRIO. (5.2)
- Bone and Cartilage Toxicity: LAGEVRIO is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth. (5.3, 8.4, 13.2)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥ 1%) are diarrhea, nausea, and dizziness. (6.1)

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to LAGEVRIO (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 Merck Sharp & Dohme LLC, Rahway, NJ USA at 1-800-672-6372 or Fax 215-616-5677 (6.4)

----------DRUG INTERACTIONS----------

No drug interactions have been identified based on the limited available data on the emergency use of LAGEVRIO authorized under this EUA. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: The use of LAGEVRIO is not recommended during pregnancy. Advise individuals of childbearing potential to use effective contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of LAGEVRIO. (8.1, 8.3)
- Lactation: Breastfeeding is not recommended during treatment and for 4 days after the last dose of LAGEVRIO. A lactating individual

may consider interrupting breastfeeding and may consider pumping and discarding breast milk during treatment and for 4 days after the last dose of LAGEVRIO. (8.2)

See FACT SHEET FOR PATIENTS 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

MANDATORY REQUIREMENTS FOR ADMINISTRATION OF LAGEVRIO UNDER EMERGENCY USE AUTHORIZATION

In order to mitigate the risks of using this unapproved product under the EUA and to optimize the potential benefit of LAGEVRIO, the following steps are required. Use of LAGEVRIO under this EUA is limited to the following (all requirements must be met):

1. Treatment of adults with a current diagnosis of mild-to-moderate 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 *[see Limitations of Authorized Use (1)]*.

2. As the prescribing healthcare provider, review the information contained within the "Fact Sheet for Patients and Caregivers" with your patient or caregiver prior to the patient receiving LAGEVRIO. Healthcare providers must provide the patient/caregiver with an electronic or hard copy of the "Fact Sheet for Patients and Caregivers" prior to the patient receiving LAGEVRIO and must document that the patient/caregiver has been given an electronic or hard copy of the "Fact Sheet for Patients and Caregivers".

3. The prescribing healthcare providers must inform the patient/caregiver that:
    i. LAGEVRIO is an unapproved drug that is authorized for use under this Emergency Use Authorization.
    ii. Other therapeutics are currently approved or authorized for the same use as LAGEVRIO *[*see *Emergency Use Authorization (1) - Information Regarding Available Alternatives for the EUA Authorized Use].*
    iii. There are benefits and risks of taking LAGEVRIO as outlined in the "Fact Sheet for Patients and Caregivers."
    iv. There is a pregnancy registry.
    v. Females of childbearing potential should use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of LAGEVRIO.
    vi. Males of reproductive potential who are sexually active with females of childbearing potential should use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose.

4. The prescribing healthcare provider must assess whether a female of childbearing potential is pregnant or not, if clinically indicated *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.3)].*

5. Based on findings from animal reproduction studies, LAGEVRIO may cause fetal harm when administered to pregnant individuals. If LAGEVRIO is used during pregnancy, prescribing healthcare providers must communicate to the patient the known and potential benefits and the potential risks of LAGEVRIO use during pregnancy, as outlined in the "Fact Sheet for Patients and Caregivers" *[see Warnings and Precautions (5.1, 5.3), Use in Specific Populations (8.1, 8.3) and Nonclinical Toxicology (13.1)].*

6. If the decision is made to use LAGEVRIO during pregnancy, the prescriber must document that the known and potential benefits and the potential risks of LAGEVRIO use during pregnancy, as outlined in the "Fact Sheet for Patients and Caregivers," were discussed with the patient.

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7. The prescribing healthcare provider must document that a pregnant individual was made aware of the pregnancy registry at https://covid-pr.pregistry.com or 1-800-616-3791.

8. The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all medication errors and serious adverse events potentially related to LAGEVRIO within 7 calendar days from the healthcare provider's awareness of the event *[see Adverse Reactions (6.4)]*.

For information on clinical studies of LAGEVRIO and other therapies for the treatment of COVID-19, see www.clinicaltrials.gov .

1 EMERGENCY USE AUTHORIZATION

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product LAGEVRIO™ for 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. Refer to CDC website[1] for additional details, and for
- whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

LIMITATIONS OF AUTHORIZED USE

- LAGEVRIO is not authorized for use in patients who are less than 18 years of age *[see Warnings and Precautions (5.3)]*.
- LAGEVRIO is not authorized for initiation of treatment in patients hospitalized due to COVID-19[2]. Benefit of treatment with LAGEVRIO has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19 *[see Dosing and Administration (2.1)]*.
- LAGEVRIO is not authorized for use for longer than 5 consecutive days.
- LAGEVRIO is not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

LAGEVRIO 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 LAGEVRIO belongs (i.e., anti-infectives).

LAGEVRIO is not approved for any use, including for use for the treatment of COVID-19.

Prior to initiating treatment with LAGEVRIO, carefully consider the known and potential risks and benefits *[see Warnings and Precautions (5.1, 5.3), Use in Specific Populations (8.1, 8.3) and Nonclinical Toxicology (13.1)]*.

LAGEVRIO is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of LAGEVRIO 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 Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2, a novel coronavirus. The Secretary of HHS has declared that:

- A public health emergency related to COVID-19 has existed since January 27, 2020.

[1] https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html . Healthcare providers should consider the benefit-risk for an individual patient.

[2] Should a patient require hospitalization after starting treatment with LAGEVRIO, the patient may complete the full 5 day treatment course per the healthcare provider's discretion.

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- 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 FDA 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:

- 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.

APPROVED AVAILABLE ALTERNATIVES

Veklury (remdesivir) is FDA-approved for the treatment of COVID-19 in adults and pediatric patients (at least 28 days old and weighing at least 3 kg) who are not hospitalized and have mild-to-moderate COVID-19, and 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 approved alternative treatment of mild-to-moderate COVID-19 in adults and who are at high risk for progression to severe COVID-19, including hospitalization or death, FDA does not consider Veklury to be an adequate alternative to LAGEVRIO for this authorized use because it may not be feasible or clinically appropriate for certain patients.

Other therapeutics are currently authorized for the same use as LAGEVRIO. 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 of LAGEVRIO and other therapies for the treatment of COVID-19, see www.clinicaltrials.gov.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Emergency Use of LAGEVRIO in Adult Patients

The dosage in adult patients is 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food *[see Clinical Pharmacology (12.3)]*. Take LAGEVRIO as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset *[see Emergency Use Authorization (1) and Clinical Studies (14)]*.

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 *[see Patient Counseling Information (17)]*.

LAGEVRIO is not authorized for use for longer than 5 consecutive days because the safety and efficacy have not been established.

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If the patient misses a dose of LAGEVRIO within 10 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 10 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.

Should a patient require hospitalization after starting treatment with LAGEVRIO, the patient may complete the full 5 day treatment course per the healthcare provider's discretion.

2.2 Dosage Adjustments in Specific Populations
No dosage adjustment is recommended based on renal or hepatic impairment or in geriatric patients *[see Use in Specific Populations (8.5, 8.6, 8.7)]*.

2.3 Administration via Nasogastric (NG) or Orogastric (OG) Tube (12F or Larger)

1. Open four (4) capsules and transfer contents into a clean container with a lid.
2. Add 40 mL of water to the container.
3. Put the lid on the container and shake to mix the capsule contents and water thoroughly for 3 minutes.
    - **NOTE**: Capsule contents may not dissolve completely.
    - The prepared mixture may have visible undissolved particulates and are acceptable for administration.
4. Flush NG/OG tube with 5 mL of water prior to administration.
5. Using a catheter tip syringe, draw up the entire contents from the container and administer immediately through the NG/OG tube (12F or larger). Do not keep the mixture for future use.
6. If any portion of the capsule contents are left in the container, add 10 mL of water to the container, mix, and using the same syringe draw up the entire contents of the container and administer through the NG/OG (12F or larger). Repeat as needed until no capsule contents are left in the container or syringe.
7. Flush the NG/OG tube with 5 mL of water twice (10 mL total) after administration of the mixture.

3 DOSAGE FORMS AND STRENGTHS
Capsules: 200 mg, Swedish Orange opaque size 0 capsules. The capsules have the corporate logo and "82" printed in white ink.

4 CONTRAINDICATIONS
No contraindications have been identified based on the limited available data on the emergency use of LAGEVRIO authorized under this EUA.

5 WARNINGS AND PRECAUTIONS
There are limited clinical data available for LAGEVRIO. Serious and unexpected adverse events may occur that have not been previously reported with LAGEVRIO use.

5.1 Embryo-Fetal Toxicity
Based on findings from animal reproduction studies, LAGEVRIO may cause fetal harm when administered to pregnant individuals. There are no available human data on the use of LAGEVRIO in pregnant individuals to evaluate the risk of major birth defects, miscarriage or adverse maternal or fetal outcomes; therefore, LAGEVRIO is not recommended for use during pregnancy. When considering LAGEVRIO for a pregnant individual, the prescribing healthcare provider must communicate the known and potential benefits and the potential risks of using LAGEVRIO during pregnancy to the pregnant individual. LAGEVRIO is authorized to be prescribed to a pregnant individual only after the healthcare provider has determined that the benefits would outweigh the risks for that individual patient. If the decision is made to use LAGEVRIO during pregnancy, the prescribing healthcare provider must document that the known

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and potential benefits and the potential risks of using LAGEVRIO during pregnancy were communicated to the pregnant individual.

Advise individuals of childbearing potential of the potential risk to a fetus and to use an effective method of contraception correctly and consistently, as applicable, during treatment with LAGEVRIO and for 4 days after the final dose *[see Use in Specific Populations (8.1, 8.3 and Nonclinical Toxicology (13.1)]*.

Prior to initiating treatment with LAGEVRIO, assess whether an individual of childbearing potential is pregnant or not, if clinically indicated. Pregnancy status does not need to be confirmed in patients who have undergone permanent sterilization, are currently using an intrauterine system or contraceptive implant, or in whom pregnancy is not possible. In all other patients, assess whether the patient is pregnant based on the first day of last menstrual period in individuals who have regular menstrual cycles, is using a reliable method of contraception correctly and consistently or have had a negative pregnancy test. A pregnancy test is recommended if the individual has irregular menstrual cycles, is unsure of the first day of last menstrual period or is not using effective contraception correctly and consistently *[see Box]*.

5.2 Hypersensitivity Including Anaphylaxis
Hypersensitivity reactions, including anaphylaxis, have been reported with LAGEVRIO. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue LAGEVRIO and initiate appropriate medications and/or supportive care.

5.3 Bone and Cartilage Toxicity
LAGEVRIO is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth. Bone and cartilage toxicity was observed in rats after repeated dosing *[see Nonclinical Toxicity (13.2)]*. The safety and efficacy of LAGEVRIO have not been established in pediatric patients *[see Use in Specific Populations (8.4)]*.

6 ADVERSE REACTIONS
6.1 Adverse Reactions from Clinical Studies
The following adverse reactions have been observed in the clinical study of LAGEVRIO that supported the EUA. The adverse reaction rates observed in these clinical trials cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Additional adverse events associated with LAGEVRIO may become apparent with more widespread use.

Overall, more than 900 subjects have been exposed to LAGEVRIO 800 mg twice daily in clinical trials. The safety assessment of LAGEVRIO is primarily based on an analysis from subjects followed through Day 29 in the Phase 3 study in non-hospitalized subjects with COVID-19 (MOVe-OUT) *[see Clinical Studies (14)]*.

The safety of LAGEVRIO was evaluated based on an analysis of a Phase 3 double-blind trial (MOVe-OUT) in which 1,411 non-hospitalized subjects with COVID-19 were randomized and treated with LAGEVRIO (N=710) or placebo (N=701) for up to 5 days. Adverse events were those reported while subjects were on study intervention or within 14 days of study intervention completion/discontinuation.

Discontinuation of study intervention due to an adverse event occurred in 1% of subjects receiving LAGEVRIO and 3% of subjects receiving placebo. Serious adverse events occurred in 7% of subjects receiving LAGEVRIO and 10% receiving placebo; most serious adverse events were COVID-19 related. Adverse events leading to death occurred in 2 (<1%) subjects receiving LAGEVRIO and 12 (2%) of subjects receiving placebo.

The most common adverse reactions in the LAGEVRIO treatment group in MOVe-OUT are presented in Table 1, all of which were Grade 1 (mild) or Grade 2 (moderate).

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Table 1: Adverse Reactions Occurring in Greater Than or Equal to 1% of Subjects Receiving LAGEVRIO in MOVe-OUT*

	LAGEVRIO N=710	**Placebo N=701**
Diarrhea	2%	2%
Nausea	1%	1%
Dizziness	1%	1%
*Frequencies of adverse reactions are based on all adverse events attributed to study intervention by the investigator.		

Laboratory Abnormalities
Selected Grade 3 and 4 laboratory abnormalities in chemistry (alanine aminotransferase, aspartate aminotransferase, creatinine, and lipase) and hematology (hemoglobin, platelets, and leukocytes) parameters all occurred at a rate of less than or equal to 2% and occurred at a similar rate across arms in MOVe-OUT.

6.2 Post-Authorization Experience
The following adverse reactions have been identified during post-authorization use of LAGEVRIO. 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.

Gastrointestinal Disorders
vomiting

Immune System Disorders
hypersensitivity, anaphylaxis, angioedema *[see Warnings and Precautions (5.2)]*

Skin and Subcutaneous Tissue Disorders
erythema, pruritus, rash, urticaria

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 LAGEVRIO 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 "*LAGEVRIO* 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 preexisting 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:

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- Complete and submit the report online: 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:
Merck Sharp & Dohme LLC, Rahway, NJ USA
Fax: 215-616-5677
E-mail: dpoc.usa@msd.com

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 LAGEVRIO.

*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
No drug interactions have been identified based on the limited available data on the emergency use of LAGEVRIO authorized under this EUA. No clinical drug-drug interaction trials of LAGEVRIO with concomitant medications, including other treatments for mild-to-moderate COVID-19, have been conducted *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Registry
There is a pregnancy registry that monitors pregnancy outcomes in individuals exposed to LAGEVRIO during pregnancy. The prescribing healthcare provider must document that a pregnant individual was made aware of the pregnancy registry at https://covid-pr.pregistry.com or 1-800-616-3791. Pregnant individuals exposed to LAGEVRIO or their healthcare providers can also report the exposure by contacting Merck Sharp & Dohme LLC, Rahway, NJ USA at 1-877-888-4231.

Risk Summary
Based on animal data, LAGEVRIO may cause fetal harm when administered to pregnant individuals. There are no available human data on the use of LAGEVRIO in pregnant individuals to evaluate the risk of major birth defects, miscarriage or adverse maternal or fetal outcomes; therefore, LAGEVRIO is not recommended during pregnancy *[see Box and Warnings and Precautions (5.1)]*. In an animal reproduction study, oral administration of molnupiravir to pregnant rats during the period of organogenesis resulted in embryofetal lethality and teratogenicity at 8 times the human NHC (N4-hydroxycytidine) exposures at the recommended

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human dose (RHD) and reduced fetal growth at ≥ 3 times the human NHC exposure at the RHD. Oral administration of molnupiravir to pregnant rabbits during the period of organogenesis resulted in reduced fetal body weights at 18 times the human NHC exposure at the RHD (see *Data*). When considering LAGEVRIO for a pregnant individual, the prescribing healthcare provider must communicate the known and potential benefits and the potential risks of using LAGEVRIO during pregnancy to the pregnant individual. LAGEVRIO may only be prescribed to a pregnant individual after the prescribing healthcare provider has determined that the benefits would outweigh the risks for that individual patient. If the decision is made to use LAGEVRIO during pregnancy, the prescribing healthcare provider must document that the known and potential benefits and potential risks of using LAGEVRIO during pregnancy were communicated to the pregnant individual *[see Box]*. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy *(see Clinical Considerations)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background 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.

Data

Animal Data

In an embryofetal development (EFD) study in rats, molnupiravir was administered orally to pregnant rats at 0, 100, 250, or 500 mg/kg/day from gestation days (GDs) 6 to 17. Molnupiravir was also administered orally to pregnant rats at up to 1,000 mg/kg/day from GDs 6 to 17 in a preliminary EFD study. Developmental toxicities included post-implantation losses, malformations of the eye, kidney, and axial skeleton, and rib variations at 1,000 mg/kg/day (8 times the human NHC exposure at the RHD) and decreased fetal body weights and delayed ossification at ≥500 mg/kg/day (3 times the human NHC exposure at the RHD). There were no developmental toxicities at ≤250 mg/kg/day (less than the human NHC exposure at the RHD). Maternal toxicities included decreased food consumption and body weight losses, resulting in the early sacrifice of two of sixteen animals at 1,000 mg/kg/day, and decreased body weight gain at 500 mg/kg/day.

In an EFD study in rabbits, molnupiravir was administered orally to pregnant rabbits at 0, 125, 400, or 750 mg/kg/day from GDs 7 to 19. Developmental toxicity was limited to reduced fetal body weights at 750 mg/kg/day (18 times the human NHC exposures at the RHD). There was no developmental toxicity at ≤400 mg/kg/day (7 times the human NHC exposures at the RHD). Maternal toxicities included reduced food consumption and body weight gains, and abnormal fecal output at 750 mg/kg/day.

In a pre- and post-natal developmental study, molnupiravir was administered orally to female rats at doses up to 500 mg/kg/day (similar to the human NHC exposure at the RHD) from GD6 through lactation day 20. No effects were observed in offspring.

8.2 Lactation

Risk Summary

There are no data on the presence of molnupiravir or its metabolites in human milk. NHC was detected in the plasma of nursing pups from lactating rats administered molnupiravir *(see Data)*. It is unknown whether molnupiravir has an effect on the breastfed infant or effects on milk production.

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Based on the potential for adverse reactions in the infant from LAGEVRIO, breastfeeding is not recommended during treatment with LAGEVRIO and for 4 days after the final dose. A lactating individual may consider interrupting breastfeeding and may consider pumping and discarding breast milk during treatment and for 4 days after the last dose of LAGEVRIO *[see Warnings and Precautions (5.1, 5.3)].*

Data
When molnupiravir was administered to lactating rats at ≥250 mg/kg/day in the pre- and post-natal development study, NHC was detected in plasma of nursing pups.

8.3 Females and Males of Reproductive Potential
Based on animal studies, LAGEVRIO may cause fetal harm when administered to a pregnant individual.

Pregnancy Testing
Prior to initiating treatment with LAGEVRIO, assess whether an individual of childbearing potential is pregnant or not, if clinically indicated *[see Warnings and Precautions (5.1)].*

Contraception
Females
Advise individuals of childbearing potential to use a reliable method of contraception correctly and consistently, as applicable for the duration of treatment and for 4 days after the last dose of LAGEVRIO *[see Warnings and Precautions (5.1)].*

Males
While the risk is regarded as low, nonclinical studies to fully assess the potential for LAGEVRIO to affect offspring of treated males have not been completed. Advise sexually active individuals with partners of childbearing potential to use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose of LAGEVRIO.
The risk beyond three months after the last dose of LAGEVRIO is unknown. Studies to understand the risk beyond three months are ongoing.

Molnupiravir was equivocal (neither clearly positive nor negative) in one *in vivo* mutagenicity assay of reticulocytes and RBCs which are used to reflect prior effects on hematopoietic stem cells in bone marrow. Molnupiravir was not mutagenic when assessed in a second *in vivo* assay of liver (somatic cells) and bone marrow (somatic cells and stem cells) from transgenic rats administered molnupiravir for 28 days. In contrast to somatic cells, germ cells (eggs and sperm) pass genetic information from generation to generation. A planned study of male testicular germ cells from transgenic rats will assess the potential for molnupiravir to affect offspring of treated males *[see Nonclinical Toxicology (13.1)].*

8.4 Pediatric Use
LAGEVRIO is not authorized for use in patients less than 18 years of age.
Bone and cartilage toxicity were observed in a 3-month, repeat-dose toxicology study in rats. The safety and efficacy of LAGEVRIO have not been established in pediatric patients *[see Warnings and Precautions (5.3) and Nonclinical Toxicology (13.2)]*.

8.5 Geriatric Use
In MOVe-OUT, there was no difference in safety and tolerability between patients ≥65 years of age and younger patients who were treated with LAGEVRIO. No dosage adjustment is recommended based on age. The PK of NHC was similar in geriatric patients compared to younger patients *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment
No dosage adjustment in patients with any degree of renal impairment is recommended. Renal clearance is not a meaningful route of elimination for NHC. Mild or moderate renal impairment did

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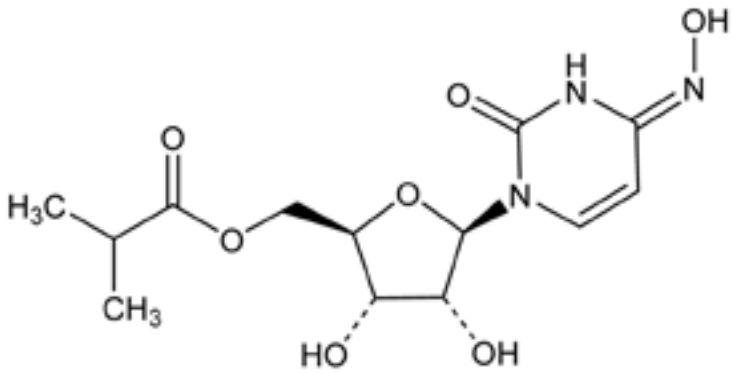
not have a meaningful impact on the PK of NHC. While the PK of NHC has not been evaluated in patients with eGFR less than 30 mL/min/1.73m^2 or on dialysis, severe renal impairment, and end-stage renal disease (ESRD) are not expected to have a significant effect on NHC exposure *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment
No dosage adjustment in patients with hepatic impairment is recommended. Preclinical data indicate that hepatic elimination is not expected to be a major route of NHC elimination therefore, hepatic impairment is unlikely to affect NHC exposure *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE
There is no human experience of overdosage with LAGEVRIO. Treatment of overdose with LAGEVRIO should consist of general supportive measures including the monitoring of the clinical status of the patient. Hemodialysis is not expected to result in effective elimination of NHC.

11 DESCRIPTION
LAGEVRIO capsules contain molnupiravir, a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis and is the 5´-isobutyrate ester of the ribonucleoside analog N4-hydroxycytidine (NHC).

The chemical name for molnupiravir is {(2R,3S,4R,5R)-3,4-Dihydroxy-5-[(4Z)-4-(hydroxyimino)-2-oxo-3,4-dihydropyrimidin-1(2H)-yl]oxolan-2-yl}methyl 2-methylpropanoate. It has an empirical formula of $C_{13}H_{19}N_3O_7$ and its molecular weight is 329.31 g/mol. Its structural formula is:



Molnupiravir is a white to off-white powder that is soluble in water.

Each LAGEVRIO capsule, for oral use, contains 200 mg of molnupiravir and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate and microcrystalline cellulose and purified water. The capsule shell is made of hypromellose, red iron oxide and titanium dioxide. The capsule is printed with white ink made of butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, purified water, shellac, strong ammonia solution and titanium dioxide.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Molnupiravir is a prodrug with antiviral activity against SARS-CoV-2. It is metabolized to the cytidine nucleoside analogue, NHC which distributes into cells where NHC is phosphorylated to form the pharmacologically active ribonucleoside triphosphate (NHC-TP). NHC-TP incorporation (as NHC-monophosphate [NHC-MP]) into SARS-CoV-2 RNA by the viral RNA polymerase (nsp12) results in an accumulation of errors in the viral genome leading to inhibition of replication. The mechanism of action (known as viral error catastrophe or viral lethal mutagenesis) is supported by biochemical and cell culture data, studies of SARS-CoV-2

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infection in animal models, and analyses of SARS-CoV-2 genome sequences in human subjects treated with LAGEVRIO.

12.2 Pharmacodynamics

The relationship between NHC and intracellular NHC-TP with antiviral efficacy has not been evaluated clinically.

12.3 Pharmacokinetics

Molnupiravir is a 5´-isobutyrate prodrug of NHC that is hydrolyzed during or after absorption. NHC, the primary circulating analyte, is taken up by cells and anabolized to NHC-TP. NHC is eliminated by metabolism to uridine and/or cytidine through the same pathways involved in endogenous pyrimidine metabolism. NHC pharmacokinetics are shown in Table 2.

Plasma NHC concentrations in patients (N=5) following administration of molnupiravir via nasogastric or orogastric tube fell within the range of NHC concentrations following oral molnupiravir capsule administration under the same dosing regimen.

Table 2: Pharmacokinetics of NHC After Multiple Oral Administration of 800 mg LAGEVRIO Every 12 Hours

	NHC Geometric Mean (%CV)
Pharmacokinetics in Patients	
$AUC_{0\text{-}12hr}$ (ng*hr/mL)*	8260 (41.0)
C_{max} (ng/mL)*	2330 (36.9)
C_{12hr} (ng/mL)*	31.1 (124)
Pharmacokinetics in Healthy Subjects	
$AUC_{0\text{-}12hr}$ (ng*hr/mL)	8330 (17.9)
C_{max} (ng/mL)	2970 (16.8)
C_{12hr} (ng/mL)	16.7 (42.8)
AUC Accumulation Ratio	1.09 (11.8)
Absorption	
T_{max} (hr)†	1.50 [1.00 – 2.02]
Effect of Food	35% reduction in C_{max}, no effect on AUC
Distribution	
Plasma Protein Binding (*in vitro*)	0%
Apparent Volume of Distribution (L)*	142
Elimination	
Effective $t_{1/2}$ (hr)	3.3
Apparent Clearance (L/hr)*	76.9
Fraction of dose excreted in urine over the time interval of 0-12 hours	3% (81.6%)
Values were obtained from a Phase 1 study of healthy subjects, unless otherwise indicated. *Values were obtained from population PK analysis. †Median [min - max]	

Specific Populations

Population PK analysis results indicated that age, sex, race, ethnicity, or disease severity do not meaningfully influence the PK of NHC.

Pediatric Patients

LAGEVRIO has not been studied in pediatric patients.

Patients with Renal Impairment

Renal clearance is not a meaningful route of elimination for NHC. In a population PK analysis, mild or moderate renal impairment did not have a meaningful impact on the PK of NHC. The PK

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of molnupiravir and NHC has not been evaluated in patients with eGFR less than 30 mL/min/1.73m^2 or on dialysis.

Patients with Hepatic Impairment
The PK of molnupiravir and NHC has not been evaluated in patients with moderate and severe hepatic impairment. Preclinical data indicate that hepatic elimination is not expected to be a major route of NHC elimination; therefore, hepatic impairment is unlikely to affect NHC exposure.

Drug Interaction Studies
In vitro study results indicated that molnupiravir and NHC are not substrates of CYP enzymes or human P-gp and BCRP transporters. *In vitro* study results also indicated that molnupiravir and NHC are not inhibitors of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 or inhibitors of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2K, MRP2, MDR1 and BCRP or inducers of CYP1A2, 2B6, and 3A4. The interaction between molnupiravir with concomitant medications, including other treatments for mild-to-moderate COVID-19, has not been evaluated.

12.4 Microbiology
Antiviral Activity
NHC, the nucleoside analogue metabolite of molnupiravir, was active in cell culture assays against SARS-CoV-2 (USA-WA1/2020 isolate) with 50% effective concentrations (EC_{50} values) ranging between 0.67 to 2.7 µM in A-549 cells and 0.32 to 2.0 µM in Vero E6 cells. NHC had similar antiviral activity against SARS-CoV-2 variants Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), Lambda (C.37), Mu (B.1.621) and Omicron (B.1.1.529/BA.1, BA.1.1, BA.2, BA.4 and BA.5), with mean EC_{50} values of 0.55-3.0 µM. NHC had non-antagonistic antiviral activity with remdesivir against SARS-CoV-2 in cell culture.

Resistance
No amino acid substitutions in SARS-CoV-2 associated with resistance to NHC have been identified in Phase 2 clinical trials evaluating LAGEVRIO for the treatment of COVID-19. Studies to evaluate selection of resistance to NHC with SARS-CoV-2 in cell culture have not been completed. Resistance selection studies have been conducted with other coronaviruses (MHV and MERS-CoV) and showed a low likelihood of resistance development to NHC. Following 30 passages in cell culture, only a 2-fold decrease in susceptibility was observed and no NHC resistance-associated amino acid substitutions were identified.

In clinical trials, encoded amino acid changes (substitutions, deletions or insertions) were more likely to be detected in viral sequences in subjects treated with LAGEVRIO compared to placebo. In a small number of subjects amino acid changes in the spike protein occurred at positions targeted by monoclonal antibodies and vaccines. The clinical and public health significance of these changes are unknown.

Cross-Resistance
NHC retained activity in cell culture against virus with polymerase (nsp 12) substitutions (e.g., F480L, V557L and E802D) associated with decreased remdesivir susceptibility, indicating a lack of cross-resistance.

Activity against SARS-CoV-2 in animal models
The antiviral activity of molnupiravir has been demonstrated in mouse, hamster, and ferret models of SARS-CoV-2 infection when dosing was administered prior to or within 1-2 days after viral challenge. In SARS-CoV-2 infected ferrets, molnupiravir significantly reduced SARS-CoV-2 viral titers in the upper respiratory tract and completely inhibited viral spread to untreated contact animals. In SARS-CoV-2 infected Syrian hamsters, molnupiravir reduced viral RNA and infectious virus titers in the lungs of animals. Histopathological analysis of lung tissue harvested after infection showed significantly reduced SARS-CoV-2 viral antigen levels and a lower abundance of pulmonary lesions in molnupiravir-treated animals compared with controls.

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In Vitro Cytotoxicity
NHC, the nucleoside analogue metabolite of molnupiravir, had variable cytotoxicity against different mammalian cell types with CC_{50} values ranging from 7.5 µM (human lymphoid CEM cell line) to >100 µM, in 3-day exposure assays. Molnupiravir inhibited the proliferation of human bone marrow progenitor cells with CC_{50} values of 24.9 µM and 7.7 µM for erythroid and myeloid progenitor proliferation, respectively, in 14-day colony formation assays.

Viral RNA Rebound
Post-treatment increases in SARS-CoV-2 RNA shedding levels (i.e., viral RNA rebound) in nasopharyngeal samples were observed on Day 10, Day 15, and/or Day 29 in a subset of LAGEVRIO and placebo recipients in the Phase 3 MOVe-OUT trial. Approximately 1% of both LAGEVRIO and placebo recipients had evidence of recurrent COVID-19 symptoms coinciding with a rebound in viral RNA levels in nasopharyngeal samples.

Post-treatment viral RNA rebound was not associated with the primary clinical outcome of hospitalization or death through Day 29 following the single 5-day course of LAGEVRIO treatment. Post-treatment viral RNA rebound also was not associated with the detection of cell culture infectious virus in nasopharyngeal swab samples.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Molnupiravir was not carcinogenic in a 6-month oral carcinogenicity study in RasH2 transgenic (Tg.RasH2) mice at any dose tested (30, 100 or 300 mg/kg/day).

Mutagenesis
Molnupiravir and NHC were positive in the *in vitro* bacterial reverse mutation assay (Ames assay) with and without metabolic activation. Molnupiravir was studied in two *in vivo* rodent mutagenicity models. The *in vivo* Pig-a mutagenicity assay gave equivocal results. Molnupiravir was negative in the *in vivo* Big Blue® (cII Locus) transgenic rodent mutagenicity assay. Molnupiravir was negative for induction of chromosomal damage in *in vitro* micronucleus (with and without metabolic activation) and *in vivo* rat micronucleus assays. To assess effects on germ cells, a transgenic rodent male germ cell mutagenicity assay is planned.

Based on the totality of the available genotoxicity data and the duration of treatment (5 days), molnupiravir is low risk for genotoxicity.

Impairment of Fertility
There were no effects on fertility, mating performance or early embryonic development when molnupiravir was administered to female or male rats at NHC exposures approximately 2 and 6 times, respectively, the human NHC exposure at the RHD.

13.2 Animal Toxicology and/or Pharmacology

Bone and cartilage toxicity changes resulting in impaired transformation of growth cartilage into new bone were observed in the femur and tibia of rats in a 3-month toxicity study at ≥ 500 mg/kg/day (5 times the human NHC exposure at the RHD). There was no bone or cartilage toxicity in a 1-month toxicity study in rats up to 500 mg/kg/day (4 and 8 times the human NHC exposure at the RHD in females and males, respectively), in dogs dosed for 14 days up to 50 mg/kg/day (similar to the human NHC exposure at the RHD), or in a 1-month toxicity study in mice up to 2,000 mg/kg/day (19 times the human NHC exposure at the RHD).

Growth cartilage is not present in mature skeletons, therefore the bone and cartilage findings are not relevant for adult humans but may be relevant for pediatric patients *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.4)]*.

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Reversible, dose-related bone marrow toxicity affecting all hematopoietic cell lines was observed in dogs at ≥17 mg/kg/day (less than the human NHC exposure at the RHD). Mild decreases in peripheral blood cell and platelet counts were seen after 7 days of molnupiravir treatment progressing to more severe hematological changes after 14 days of treatment. Neither bone marrow nor hematological toxicity was observed in a 1-month toxicity study in mice up to 2,000 mg/kg/day (19 times the human NHC exposure at the RHD) and a 3-month toxicity study in rats up to 1,000 mg/kg/day (9 and 15 times the human NHC exposure at the RHD in females and males, respectively).

14 CLINICAL STUDIES

Clinical data supporting this EUA are based on data from 1,433 randomized subjects in the Phase 3 MOVe-OUT trial (NCT04575597). MOVe-OUT is a randomized, placebo-controlled, double-blind clinical trial studying LAGEVRIO for the treatment of non-hospitalized patients with mild-to-moderate COVID-19 who are at risk for progressing to severe COVID-19 and/or hospitalization. Eligible subjects were 18 years of age and older and had one or more pre-defined risk factors for disease progression: over 60 years of age, diabetes, obesity (BMI ≥30), chronic kidney disease, serious heart conditions, chronic obstructive pulmonary disease, or active cancer. The study included symptomatic subjects not vaccinated against SARS-CoV-2 and who had laboratory confirmed SARS-CoV-2 infection and symptom onset within 5 days of randomization. Subjects were randomized 1:1 to receive 800 mg of LAGEVRIO or placebo orally twice daily for 5 days.

At baseline, in all randomized subjects, the median age was 43 years (range:18 to 90); 17% of subjects were over 60 years of age and 3% were 75 years of age or older; 49% of subjects were male; 57% were White, 5% Black or African American, 3% Asian, 50% Hispanic or Latino. The majority of subjects were enrolled from sites in Latin America (46%) and Europe (33%); 12% were enrolled in Africa, 6% were enrolled in North America and 3% were enrolled in Asia. Forty-eight percent of subjects received LAGEVRIO or placebo within 3 days of COVID-19 symptom onset. The most common risk factors were obesity (74%), over 60 years of age (17%), and diabetes (16%). Among 792 subjects (55% of total randomized population) with available baseline SARS-CoV-2 variant/clade identification results, 58% were infected with Delta (B.1.617.2 and AY lineages), 20% were infected with Mu (B.1.621), 11% were infected with Gamma (P.1), and the remainder were infected with other variants/clades. Overall, baseline demographic and disease characteristics were well balanced between the treatment arms.

Table 3 provides the results of the primary endpoint (the percentage of subjects who were hospitalized or died through Day 29 due to any cause). The efficacy results are based on unvaccinated adults who were 18 years of age and older and had one or more pre-defined risk factors for disease progression: over 60 years of age, diabetes, obesity (BMI ≥30), chronic kidney disease, serious heart conditions, chronic obstructive pulmonary disease, or active cancer. Please refer to Figure 1 for results by certain subgroups. These subgroup analyses are considered exploratory. Data are not available in certain subgroups of subjects who are at high risk for progression to severe COVID-19 as defined by CDC.

Table 3. Efficacy Results in Non-Hospitalized Adults with COVID-19*

LAGEVRIO (N=709) n (%)	Placebo (N=699) n (%)	Adjusted Risk Difference % (95% CI)
All-cause hospitalization ≥24 hours for acute care or death through Day 29		
48 (6.8%)	68 (9.7%)	-3.0% (-5.9%, -0.1%)
All-cause mortality through Day 29		
1 (0.1%)	9 (1.3%)	

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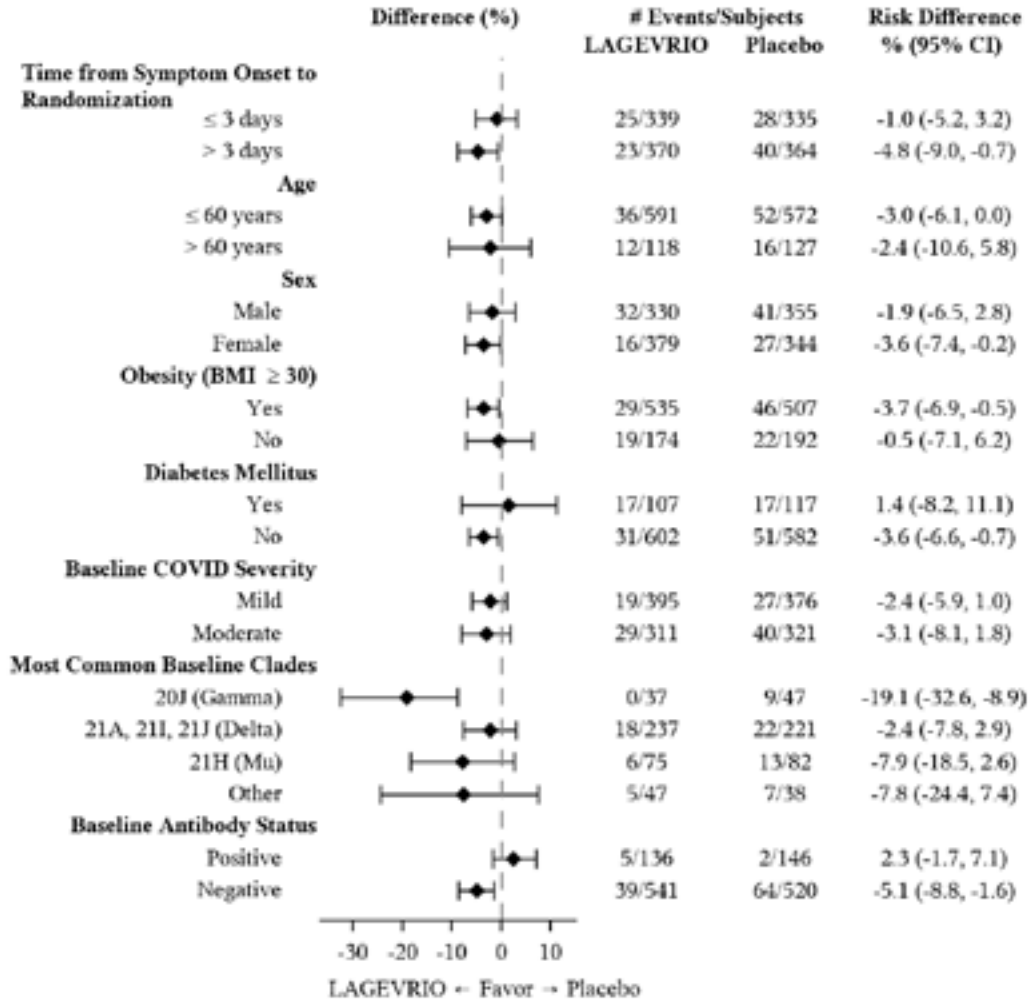
*The determination of primary efficacy was based on a planned interim analysis of 762 subjects. At the interim analysis, 7.3% of patients who received LAGEVRIO were either hospitalized or died through Day 29 (28/385), compared with 14.1% of placebo-treated patients (53/377). The adjusted risk difference was -6.8% with a 95% CI of (-11.3%, -2.4%) and 2-sided p-value = 0.0024.

Adjusted relative risk reduction of LAGEVRIO compared to placebo for all randomized subjects was 30% (95% CI: 1%, 51%).

Analyses are adjusted by the stratification factor of time of COVID-19 symptom onset (≤3 days vs. >3 [4-5] days).

Figure 1. Subgroup Efficacy Results in Non-Hospitalized Adults with COVID-19 - All-Randomized Subjects



The corresponding confidence interval is based on Miettinen & Nurminen method.
The modified intent-to-treat population is the efficacy analysis population.
Baseline serum samples were evaluated with the Roche Elecsys anti-N assay to test for the presence of antibodies (IgM, IgG and IgA) against the SARS-CoV-2 nucleocapsid protein.
The findings of these subgroup analyses are considered exploratory.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

LAGEVRIO capsules are supplied as follows:

Contents	Description	How Supplied	NDC

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200 mg molnupiravir	Swedish Orange opaque capsules with corporate logo and "82" printed in white ink	40 count bottles	NDC-0006-5055-06 NDC-0006-5055-07 NDC-0006-5055-09

Storage and Handling
Store LAGEVRIO capsules at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) *[see USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION
As a prescribing healthcare practitioner, you must communicate to the patient and/or caregiver information consistent with the "FACT SHEET FOR PATIENTS AND CAREGIVERS" and document that information was provided. A copy of this Fact Sheet should be provided to the patient and/or caregiver prior to receiving LAGEVRIO *[see Box]*.

Hypersensitivity Reactions
Inform patients that hypersensitivity reactions have been reported, even following a single dose of LAGEVRIO, and to discontinue the drug and to inform their healthcare provider at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, 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)]*.

Risk of Fetal Toxicity
Advise patients that LAGEVRIO is not recommended for use in pregnancy because it may cause fetal harm. Advise individuals of childbearing potential to inform their healthcare provider of a known or suspected pregnancy *[see Box, Warnings and Precautions (5.1) and Use in Specific Populations (8.1)].*

Advise individuals of childbearing potential to use effective contraception correctly and consistently while taking LAGEVRIO and for 4 days after the last dose.

While the risk is regarded as low, nonclinical studies to fully assess the potential for LAGEVRIO to affect offspring of treated males have not been completed. Advise sexually active individuals with partners of childbearing potential to use a reliable method of contraception consistently and correctly while taking LAGEVRIO and for at least 3 months after the last dose of LAGEVRIO. The risk beyond 3 months after the last dose of LAGEVRIO is unknown. Studies to understand the risk beyond three months are ongoing *[see Use in Specific Populations (8.3)].*

Risk of Bone and Cartilage Toxicity
LAGEVRIO is not authorized for use in patients less than 18 year of age as it may affect bone growth and cartilage formation *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.4)].*

Pregnancy Registry
There is a pregnancy registry that monitors pregnancy outcomes in individuals exposed to LAGEVRIO during pregnancy. Encourage participation and advise patients about how they may enroll in the pregnancy registry at https://covid-pr.pregistry.com or 1-800-616-3791 *[see Use in Specific Populations (8.1)]*.

Lactation
Breastfeeding is not recommended while taking LAGEVRIO and for 4 days after the last dose of LAGEVRIO. Advise lactating individuals to consider interrupting breastfeeding and to consider

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pumping and discarding breast milk during treatment and for 4 days after the last dose of LAGEVRIO *[see Use in Specific Populations (8.2)]*.

Administration Instructions
Inform patients to take LAGEVRIO with or without food. Advise patients to swallow LAGEVRIO capsules whole, and to not open, break, or crush the capsules. Instruct patients that if they miss a dose of LAGEVRIO and it is within 10 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 10 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. Advise the patient to not double the dose to make up for a missed dose *[see Dosage and Administration (2.2)]*.

LAGEVRIO capsule contents can be mixed with water and given via NG/OG tube. Inform patients to follow the instructions as described in the fact sheet for patients and caregivers *[see Dosage and Administration (2.3)]*.

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 *[see Dosage and Administration (2.1)]*.

18 MANUFACTURER INFORMATION
For additional information visit: www.molnupiravir.com

If you have questions, please contact
1-800-672-6372

Manuf. for: Merck Sharp & Dohme LLC
Rahway, NJ 07065, USA

For patent information: www.msd.com/research/patent

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Document 3A.9

U.S. FDA Fact Sheet for Healthcare Providers: Emergency Use Authorization for Lagevrio (molnupiravir) Capsules

Document URL

https://www.fda.gov/media/155054/download

Reference website URL

https://www.fda.gov/drugs/emergency-preparedness-drugs/emergency-use-authorizations-drugs-and-non-vaccine-biological-products

License

Non applicable

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FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR LAGEVRIO™ (molnupiravir) CAPSULES

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)
These highlights of the EUA do not include all the information needed to use LAGEVRIO under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for LAGEVRIO.

LAGEVRIO™ (molnupiravir) capsules, for oral use
Original EUA Authorized Date: 12/23/2021
Revised EUA Authorized Date: 02/2023

MANDATORY REQUIREMENTS FOR ADMINISTRATION OF LAGEVRIO UNDER EMERGENCY USE AUTHORIZATION

Refer to FULL FACTSHEET for details.

----------RECENT MAJOR CHANGES----------

Mandatory Requirements Box, Use in Specific Populations (Section 8.1): Updates to pregnancy registry information	02/2023
Emergency Use Authorization (Section 1): Removal of requirement of SARS-CoV-2 viral testing	02/2023
Dosage and Administration (Section 2.3): Addition of preparation and administration instructions via nasogastric and orogastric tube.	02/2023
Microbiology (Section 12.4): Addition of Omicron subvariants	02/2023
Nonclinical Toxicology (Section 13.1): Updated carcinogenicity data	02/2023
Microbiology (Section 12.4): addition of viral RNA rebound	08/2022
Mandatory Requirements Box: Revised requirements pertaining to other therapeutics	02/2022
Emergency Use Authorization (Section 1): Updates on available alternatives to LAGEVRIO	02/2022
Warnings and Precautions (Sections 5.2 and 17): addition of hypersensitivity including anaphylaxis	02/2022
Adverse Reactions (Section 6.2): addition of post-authorization experience section	02/2022

----------EUA FOR LAGEVRIO----------

The U.S. Food and Drug Administration (FDA) has issued an EUA for the emergency use of the unapproved LAGEVRIO, a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis 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.

LAGEVRIO is not FDA-approved for any use including for use for the treatment of COVID-19. Prior to initiating treatment with LAGEVRIO, carefully consider the known and potential risks and benefits. (1)

LIMITATIONS OF AUTHORIZED USE (1)

- LAGEVRIO is not authorized
  - for use in patients less than 18 years of age (5.3)
  - for initiation of treatment in patients requiring hospitalization due to COVID-19. Benefit of treatment with LAGEVRIO has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19. (2.1)
  - for use for longer than 5 consecutive days.
  - for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

LAGEVRIO 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 LAGEVRIO belongs (i.e., anti-infectives).

LAGEVRIO is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of LAGEVRIO 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 the box in the beginning of the Full Fact Sheet for details on mandatory requirements for administration of LAGEVRIO under emergency use authorization.

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----------

- 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food. (2.1, 2.3)
- Take LAGEVRIO as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset. (2.1)
- 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. (2.1)
- LAGEVRIO is not authorized for use for longer than 5 consecutive days because the safety and efficacy have not been established. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 200 mg (3)

----------CONTRAINDICATIONS----------

No contraindications have been identified based on the limited available data on the emergency use of LAGEVRIO authorized under this EUA. (4)

----------WARNINGS AND PRECAUTIONS----------

- Embryo-Fetal Toxicity: LAGEVRIO is not recommended for use during pregnancy. (5.1, 8.1, 8.3)
- Hypersensitivity reactions, including anaphylaxis have been reported with LAGEVRIO. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue LAGEVRIO. (5.2)
- Bone and Cartilage Toxicity: LAGEVRIO is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth. (5.3, 8.4, 13.2)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥ 1%) are diarrhea, nausea, and dizziness. (6.1)

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to LAGEVRIO (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 Merck Sharp & Dohme LLC, Rahway, NJ USA at 1-800-672-6372 or Fax 215-616-5677 (6.4)

----------DRUG INTERACTIONS----------

No drug interactions have been identified based on the limited available data on the emergency use of LAGEVRIO authorized under this EUA. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: The use of LAGEVRIO is not recommended during pregnancy. Advise individuals of childbearing potential to use effective contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of LAGEVRIO. (8.1, 8.3)
- Lactation: Breastfeeding is not recommended during treatment and for 4 days after the last dose of LAGEVRIO. A lactating individual may consider interrupting breastfeeding and may consider pumping and discarding breast milk during treatment and for 4 days after the last dose of LAGEVRIO. (8.2)

See FACT SHEET FOR PATIENTS 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

MANDATORY REQUIREMENTS FOR ADMINISTRATION OF LAGEVRIO UNDER EMERGENCY USE AUTHORIZATION

In order to mitigate the risks of using this unapproved product under the EUA and to optimize the potential benefit of LAGEVRIO, the following steps are required. Use of LAGEVRIO under this EUA is limited to the following (all requirements must be met):

1. Treatment of adults with a current diagnosis of mild-to-moderate 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 *[see Limitations of Authorized Use (1)]*.

2. As the prescribing healthcare provider, review the information contained within the "Fact Sheet for Patients and Caregivers" with your patient or caregiver prior to the patient receiving LAGEVRIO. Healthcare providers must provide the patient/caregiver with an electronic or hard copy of the "Fact Sheet for Patients and Caregivers" prior to the patient receiving LAGEVRIO and must document that the patient/caregiver has been given an electronic or hard copy of the "Fact Sheet for Patients and Caregivers".

3. The prescribing healthcare providers must inform the patient/caregiver that:
    i. LAGEVRIO is an unapproved drug that is authorized for use under this Emergency Use Authorization.
    ii. Other therapeutics are currently approved or authorized for the same use as LAGEVRIO *[*see *Emergency Use Authorization (1) - Information Regarding Available Alternatives for the EUA Authorized Use].*
    iii. There are benefits and risks of taking LAGEVRIO as outlined in the "Fact Sheet for Patients and Caregivers."
    iv. There is a pregnancy registry.
    v. Females of childbearing potential should use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of LAGEVRIO.
    vi. Males of reproductive potential who are sexually active with females of childbearing potential should use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose.

4. The prescribing healthcare provider must assess whether a female of childbearing potential is pregnant or not, if clinically indicated *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.3)].*

5. Based on findings from animal reproduction studies, LAGEVRIO may cause fetal harm when administered to pregnant individuals. If LAGEVRIO is used during pregnancy, prescribing healthcare providers must communicate to the patient the known and potential benefits and the potential risks of LAGEVRIO use during pregnancy, as outlined in the "Fact Sheet for Patients and Caregivers" *[see Warnings and Precautions (5.1, 5.3), Use in Specific Populations (8.1, 8.3) and Nonclinical Toxicology (13.1)].*

6. If the decision is made to use LAGEVRIO during pregnancy, the prescriber must document that the known and potential benefits and the potential risks of LAGEVRIO use during pregnancy, as outlined in the "Fact Sheet for Patients and Caregivers," were discussed with the patient.

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7. The prescribing healthcare provider must document that a pregnant individual was made aware of the pregnancy registry at https://covid-pr.pregistry.com or 1-800-616-3791.

8. The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all medication errors and serious adverse events potentially related to LAGEVRIO within 7 calendar days from the healthcare provider's awareness of the event *[see Adverse Reactions (6.4)]*.

For information on clinical studies of LAGEVRIO and other therapies for the treatment of COVID-19, see www.clinicaltrials.gov .

1 EMERGENCY USE AUTHORIZATION

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product LAGEVRIO™ for 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. Refer to CDC website[1] for additional details, and for
- whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

LIMITATIONS OF AUTHORIZED USE

- LAGEVRIO is not authorized for use in patients who are less than 18 years of age *[see Warnings and Precautions (5.3)]*.
- LAGEVRIO is not authorized for initiation of treatment in patients hospitalized due to COVID-19[2]. Benefit of treatment with LAGEVRIO has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19 *[see Dosing and Administration (2.1)]*.
- LAGEVRIO is not authorized for use for longer than 5 consecutive days.
- LAGEVRIO is not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

LAGEVRIO may only be prescribed for anindividual 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 LAGEVRIO belongs (i.e., anti-infectives).

LAGEVRIO is not approved for anyuse, including for use for the treatment of COVID-19.

Prior to initiating treatment with LAGEVRIO, carefully consider the known and potential risks and benefits *[see Warnings and Precautions (5.1, 5.3), Use in Specific Populations (8.1, 8.3) and Nonclinical Toxicology (13.1)]*.

LAGEVRIO is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of LAGEVRIO 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 Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2, a novel coronavirus. The Secretary of HHS has declared that:

- A public health emergency related to COVID-19 has existed since January 27, 2020.

[1] https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html . Healthcare providers should consider the benefit-risk for an individual patient.

[2] Should a patient require hospitalization after starting treatment with LAGEVRIO, the patient may complete the full 5 day treatment course per the healthcare provider's discretion.

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- 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 FDA 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:

- 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.

APPROVED AVAILABLE ALTERNATIVES

Veklury (remdesivir) is FDA-approved for the treatment of COVID-19 in adults and pediatric patients (at least 28 days old and weighing at least 3 kg) who are not hospitalized and have mild-to-moderate COVID-19, and 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 approved alternative treatment of mild-to-moderate COVID-19 in adults and who are at high risk for progression to severe COVID-19, including hospitalization or death, FDA does not consider Veklury to be an adequate alternative to LAGEVRIO for this authorized use because it may not be feasible or clinically appropriate for certain patients.

Other therapeutics are currently authorized for the same use as LAGEVRIO. 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 of LAGEVRIO and other therapies for the treatment of COVID-19, see www.clinicaltrials.gov.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Emergency Use of LAGEVRIO in Adult Patients

The dosage in adult patients is 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food *[see Clinical Pharmacology (12.3)]*. Take LAGEVRIO as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset *[see Emergency Use Authorization (1) and Clinical Studies (14)]*.

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 *[see Patient Counseling Information (17)]*.

LAGEVRIO is not authorized for use for longer than 5 consecutive days because the safety and efficacy have not been established.

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If the patient misses a dose of LAGEVRIO within 10 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 10 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.

Should a patient require hospitalization after starting treatment with LAGEVRIO, the patient may complete the full 5 day treatment course per the healthcare provider's discretion.

2.2 Dosage Adjustments in Specific Populations
No dosage adjustment is recommended based on renal or hepatic impairment or in geriatric patients *[see Use in Specific Populations (8.5, 8.6, 8.7)]*.

2.3 Administration via Nasogastric (NG) or Orogastric (OG) Tube (12F or Larger)

1. Open four (4) capsules and transfer contents into a clean container with a lid.
2. Add 40 mL of water to the container.
3. Put the lid on the container and shake to mix the capsule contents and water thoroughly for 3 minutes.
    - **NOTE**: Capsule contents may not dissolve completely.
    - The prepared mixture may have visible undissolved particulates and are acceptable for administration.
4. Flush NG/OG tube with 5 mL of water prior to administration.
5. Using a catheter tip syringe, draw up the entire contents from the container and administer immediately through the NG/OG tube (12F or larger). Do not keep the mixture for future use.
6. If any portion of the capsule contents are left in the container, add 10 mL of water to the container, mix, and using the same syringe draw up the entire contents of the container and administer through the NG/OG (12F or larger). Repeat as needed until no capsule contents are left in the container orsyringe.
7. Flush the NG/OG tube with 5 mL of water twice (10 mL total) after administration of the mixture.

3 DOSAGE FORMS AND STRENGTHS
Capsules: 200 mg, Swedish Orange opaque size 0 capsules. The capsules have the corporate logo and "82" printed in white ink.

4 CONTRAINDICATIONS
No contraindications have been identified based on the limited available data on the emergency use of LAGEVRIO authorized under this EUA.

5 WARNINGS AND PRECAUTIONS
There are limited clinical data available for LAGEVRIO. Serious and unexpected adverse events may occur that have not been previously reported with LAGEVRIO use.

5.1 Embryo-Fetal Toxicity
Based on findings from animal reproduction studies, LAGEVRIO may cause fetal harm when administered to pregnant individuals. There are no available human data on the use of LAGEVRIO in pregnant individuals to evaluate the risk of major birth defects, miscarriage or adverse maternal or fetal outcomes; therefore, LAGEVRIO is not recommended for use during pregnancy. When considering LAGEVRIO for a pregnant individual, the prescribing healthcare provider must communicate the known and potential benefits and the potential risks of using LAGEVRIO during pregnancy to the pregnant individual. LAGEVRIO is authorized to be prescribed to a pregnant individual only after the healthcare provider has determined that the benefits would outweigh the risks for that individual patient. If the decision is made to use LAGEVRIO during pregnancy, the prescribing healthcare provider must document that the known

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and potential benefits and the potential risks of using LAGEVRIO during pregnancy were communicated to the pregnant individual.

Advise individuals of childbearing potential of the potential risk to a fetus and to use an effective method of contraception correctly and consistently, as applicable, during treatment with LAGEVRIO and for 4 days after the final dose *[see Use in Specific Populations (8.1, 8.3 and Nonclinical Toxicology (13.1)]*.

Prior to initiating treatment with LAGEVRIO, assess whether an individual of childbearing potential is pregnant or not, if clinically indicated. Pregnancy status does not need to be confirmed in patients who have undergone permanent sterilization, are currently using an intrauterine system or contraceptive implant, or in whom pregnancy is not possible. In all other patients, assess whether the patient is pregnant based on the first day of last menstrual period in individuals who have regular menstrual cycles, is using a reliable method of contraception correctly and consistently or have had a negative pregnancy test. A pregnancy test is recommended if the individual has irregular menstrual cycles, is unsure of the first day of last menstrual period or is not using effective contraception correctly and consistently *[see Box]*.

5.2 Hypersensitivity Including Anaphylaxis
Hypersensitivity reactions, including anaphylaxis, have been reported with LAGEVRIO. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue LAGEVRIO and initiate appropriate medications and/or supportive care.

5.3 Bone and Cartilage Toxicity
LAGEVRIO is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth. Bone and cartilage toxicity was observed in rats after repeated dosing *[see Nonclinical Toxicity (13.2)]*. The safety and efficacy of LAGEVRIO have not been established in pediatric patients *[see Use in Specific Populations (8.4)]*.

6 ADVERSE REACTIONS
6.1 Adverse Reactions from Clinical Studies
The following adverse reactions have been observed in the clinical study of LAGEVRIO that supported the EUA. The adverse reaction rates observed in these clinical trials cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Additional adverse events associated with LAGEVRIO may become apparent with more widespread use.

Overall, more than 900 subjects have been exposed to LAGEVRIO 800 mg twice daily in clinical trials. The safety assessment of LAGEVRIO is primarily based on an analysis from subjects followed through Day 29 in the Phase 3 study in non-hospitalized subjects with COVID-19 (MOVe-OUT) *[see Clinical Studies (14)]*.

The safety of LAGEVRIO was evaluated based on an analysis of a Phase 3 double-blind trial (MOVe-OUT) in which 1,411 non-hospitalized subjects with COVID-19 were randomized and treated with LAGEVRIO (N=710) or placebo (N=701) for up to 5 days. Adverse events were those reported while subjects were on study intervention or within 14 days of study intervention completion/discontinuation.

Discontinuation of study intervention due to an adverse event occurred in 1% of subjects receiving LAGEVRIO and 3% of subjects receiving placebo. Serious adverse events occurred in 7% of subjects receiving LAGEVRIO and 10% receiving placebo; most serious adverse events were COVID-19 related. Adverse events leading to death occurred in 2 (<1%) subjects receiving LAGEVRIO and 12 (2%) of subjects receiving placebo.

The most common adverse reactions in the LAGEVRIO treatment group in MOVe-OUT are presented in Table 1, all of which were Grade 1 (mild) or Grade 2 (moderate).

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Table 1: Adverse Reactions Occurring in Greater Than or Equal to 1% of Subjects Receiving LAGEVRIO in MOVe-OUT*

	LAGEVRIO N=710	Placebo N=701
Diarrhea	2%	2%
Nausea	1%	1%
Dizziness	1%	1%
*Frequencies of adverse reactions are based on all adverse events attributed to study intervention by the investigator.		

Laboratory Abnormalities
Selected Grade 3 and 4 laboratory abnormalities in chemistry (alanine aminotransferase, aspartate aminotransferase, creatinine, and lipase) and hematology (hemoglobin, platelets, and leukocytes) parameters all occurred at arate of less than or equal to 2% and occurred at asimilar rate across arms in MOVe-OUT.

6.2 Post-Authorization Experience
The following adverse reactions have been identified during post-authorization use of LAGEVRIO. 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.

Immune System Disorders
hypersensitivity, anaphylaxis, angioedema *[see Warnings and Precautions (5.2)]*

Skin and Subcutaneous Tissue Disorders
erythema, rash, urticaria

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 LAGEVRIO 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 "*LAGEVRIO* 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 ormedication 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 preexisting 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: 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:

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  - 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 areporting form

In addition, please provide a copy of all FDA MedWatch forms to:
Merck Sharp & Dohme LLC, Rahway, NJ USA
Fax: 215-616-5677
E-mail: dpoc.usa@msd.com

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 LAGEVRIO.

*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
No drug interactions have been identified based on the limited available data on the emergency use of LAGEVRIO authorized under this EUA. No clinical drug-drug interaction trials of LAGEVRIO with concomitant medications, including other treatments for mild-to-moderate COVID-19, have been conducted *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Registry
There is a pregnancy registry that monitors pregnancy outcomes in individuals exposed to LAGEVRIO during pregnancy. The prescribing healthcare provider must document that a pregnant individual was made aware of the pregnancy registry at https://covid-pr.pregistry.com or 1-800-616-3791. Pregnant individuals exposed to LAGEVRIO or their healthcare providers can also report the exposure by contacting Merck Sharp & Dohme LLC, Rahway, NJ USA at 1-877-888-4231.

Risk Summary
Based on animal data, LAGEVRIO may cause fetal harm when administered to pregnant individuals. There are no available human data on the use of LAGEVRIO in pregnant individuals to evaluate the risk of major birth defects, miscarriage or adverse maternal or fetal outcomes; therefore, LAGEVRIO is not recommended during pregnancy *[see Box and Warnings and Precautions (5.1)]*. In an animal reproduction study, oral administration of molnupiravir to pregnant rats during the period of organogenesis resulted in embryofetal lethality and teratogenicity at 8 times the human NHC (N4-hydroxycytidine) exposures at the recommended human dose (RHD) and reduced fetal growth at ≥ 3 times the human NHC exposure at the RHD. Oral administration of molnupiravir to pregnant rabbits during the period of organogenesis resulted in reduced fetal body weights at 18 times the human NHC exposure at the RHD (see

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Data). When considering LAGEVRIO for a pregnant individual, the prescribing healthcare provider must communicate the known and potential benefits and the potential risks of using LAGEVRIO during pregnancy to the pregnant individual. LAGEVRIO may only be prescribed to a pregnant individual after the prescribing healthcare provider has determined that the benefits would outweigh the risks for that individual patient. If the decision is made to use LAGEVRIO during pregnancy, the prescribing healthcare provider must document that the known and potential benefits and potential risks of using LAGEVRIO during pregnancy were communicated to the pregnant individual *[see Box]*. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy *(see Clinical Considerations)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background 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.

Data

Animal Data

In an embryofetal development (EFD) study in rats, molnupiravir was administered orally to pregnant rats at 0, 100, 250, or 500 mg/kg/day from gestation days (GDs) 6 to 17. Molnupiravir was also administered orally to pregnant rats at up to 1,000 mg/kg/day from GDs 6 to 17 in a preliminary EFD study. Developmental toxicities included post-implantation losses, malformations of the eye, kidney, and axial skeleton, and rib variations at 1,000 mg/kg/day (8 times the human NHC exposure at the RHD) and decreased fetal body weights and delayed ossification at ≥500 mg/kg/day (3 times the human NHC exposure at the RHD). There were no developmental toxicities at ≤250 mg/kg/day (less than the human NHC exposure at the RHD). Maternal toxicities included decreased food consumption and body weight losses, resulting in the early sacrifice of two of sixteen animals at 1,000 mg/kg/day, and decreased body weight gain at 500 mg/kg/day.

In an EFD study in rabbits, molnupiravir was administered orally to pregnant rabbits at 0, 125, 400, or 750 mg/kg/day from GDs 7 to 19. Developmental toxicity was limited to reduced fetal body weights at 750 mg/kg/day (18 times the human NHC exposures at the RHD). There was no developmental toxicity at ≤400 mg/kg/day (7 times the human NHC exposures at the RHD). Maternal toxicities included reduced food consumption and body weight gains, and abnormal fecal output at 750 mg/kg/day.

In a pre- and post-natal developmental study, molnupiravir was administered orally to female rats at doses up to 500 mg/kg/day (similar to the human NHC exposure at the RHD) from GD6 through lactation day 20. No effects were observed in offspring.

8.2 Lactation

Risk Summary

There are no data on the presence of molnupiravir orits metabolites in human milk. NHC was detected in the plasma of nursing pups from lactating rats administered molnupiravir *(see Data)*. It is unknown whether molnupiravir has an effect on the breastfed infant or effects on milk production.

Based on the potential for adverse reactions in the infant from LAGEVRIO, breastfeeding is not recommended during treatment with LAGEVRIO and for 4 days after the final dose. A lactating individual may consider interrupting breastfeeding and may consider pumping and discarding

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breast milk during treatment and for 4 days after the last dose of LAGEVRIO *[see Warnings and Precautions (5.1, 5.3)].*

Data
When molnupiravir was administered to lactating rats at ≥250 mg/kg/day in the pre- and post-natal development study, NHC was detected in plasma of nursing pups.

8.3 Females and Males of Reproductive Potential
Based on animal studies, LAGEVRIO may cause fetal harm when administered to a pregnant individual.

Pregnancy Testing
Prior to initiating treatment with LAGEVRIO, assess whether an individual of childbearing potential is pregnant or not, if clinically indicated *[see Warnings and Precautions (5.1)].*

Contraception
Females
Advise individuals of childbearing potential to use a reliable method of contraception correctly and consistently, as applicable for the duration of treatment and for 4 days after the last dose of LAGEVRIO *[see Warnings and Precautions (5.1)]*.

Males
While the risk is regarded as low, nonclinical studies to fully assess the potential for LAGEVRIO to affect offspring of treated males have not been completed. Advise sexually active individuals with partners of childbearing potential to use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose of LAGEVRIO.
The risk beyond three months after the last dose of LAGEVRIO is unknown. Studies to understand the risk beyond three months are ongoing.

Molnupiravir was equivocal (neither clearly positive nor negative) in one *in vivo* mutagenicity assay of reticulocytes and RBCs which are used to reflect prior effects on hematopoietic stem cells in bone marrow. Molnupiravir was not mutagenic when assessed in a second *in vivo* assay of liver (somatic cells) and bone marrow (somatic cells and stem cells) from transgenic rats administered molnupiravir for 28 days. In contrast to somatic cells, germ cells (eggs and sperm) pass genetic information from generation to generation. A planned study of male testicular germ cells from transgenic rats will assess the potential for molnupiravir to affect offspring of treated males *[see Nonclinical Toxicology (13.1)].*

8.4 Pediatric Use
LAGEVRIO is not authorized for use in patients less than 18 years of age.
Bone and cartilage toxicity were observed in a 3-month, repeat-dose toxicology study in rats. The safety and efficacy of LAGEVRIO have not been established in pediatric patients *[see Warnings and Precautions (5.3) and Nonclinical Toxicology (13.2)]*.

8.5 Geriatric Use
In MOVe-OUT, there was no difference in safety and tolerability between patients ≥65 years of age and younger patients who were treated with LAGEVRIO. No dosage adjustment is recommended based on age. The PK of NHC was similar in geriatric patients compared to younger patients *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment
No dosage adjustment in patients with any degree of renal impairment is recommended. Renal clearance is not a meaningful route of elimination for NHC. Mild or moderate renal impairment did not have a meaningful impact on the PK of NHC. While the PK of NHC has not been evaluated in patients with eGFR less than 30 mL/min/1.73m^2 or ondialysis, severe renal impairment, and end-

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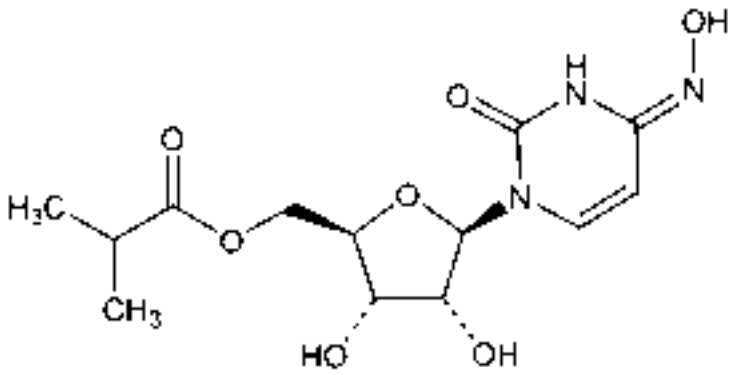
stage renal disease (ESRD) are not expected to have a significant effect on NHC exposure *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment
No dosage adjustment in patients with hepatic impairment is recommended. Preclinical data indicate that hepatic elimination is not expected to be a major route of NHC elimination therefore, hepatic impairment is unlikely to affect NHC exposure *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE
There is no human experience of overdosage with LAGEVRIO. Treatment of overdose with LAGEVRIO should consist of general supportive measures including the monitoring of the clinical status of the patient. Hemodialysis is not expected to result in effective elimination of NHC.

11 DESCRIPTION
LAGEVRIO capsules contain molnupiravir, a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis and is the 5´-isobutyrate ester of the ribonucleoside analog N4-hydroxycytidine (NHC).

The chemical name for molnupiravir is {(2R,3S,4R,5R)-3,4-Dihydroxy-5-[(4Z)-4-(hydroxyimino)-2-oxo-3,4-dihydropyrimidin-1(2H)-yl]oxolan-2-yl}methyl 2-methylpropanoate. It has an empirical formula of $C_{13}H_{19}N_3O_7$ and its molecular weight is 329.31 g/mol. Its structural formula is:



Molnupiravir is a white to off-white powder that is soluble in water.

Each LAGEVRIO capsule, for oral use, contains 200 mg of molnupiravir and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate and microcrystalline cellulose and purified water. The capsule shell is made of hypromellose, red iron oxide and titanium dioxide. The capsule is printed with white ink made of butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, purified water, shellac, strong ammonia solution and titanium dioxide.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Molnupiravir is a prodrug with antiviral activity against SARS-CoV-2. It is metabolized to the cytidine nucleoside analogue, NHC which distributes into cells where NHC is phosphorylated to form the pharmacologically active ribonucleoside triphosphate (NHC-TP). NHC-TP incorporation (as NHC-monophosphate [NHC-MP]) into SARS-CoV-2 RNA by the viral RNA polymerase (nsp12) results in an accumulation of errors in the viral genome leading to inhibition of replication. The mechanism of action (known as viral error catastrophe or viral lethal mutagenesis) is supported by biochemical and cell culture data, studies of SARS-CoV-2 infection in animal models, and analyses of SARS-CoV-2 genome sequences in human subjects treated with LAGEVRIO.

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12.2 Pharmacodynamics
The relationship between NHC and intracellular NHC-TP with antiviral efficacy has not been evaluated clinically.

12.3 Pharmacokinetics
Molnupiravir is a 5´-isobutyrate prodrug of NHC that is hydrolyzed during or after absorption. NHC, the primary circulating analyte, is taken up by cells and anabolized to NHC-TP. NHC is eliminated by metabolism to uridine and/or cytidine through the same pathways involved in endogenous pyrimidine metabolism. NHC pharmacokinetics are shown in Table 2.

Plasma NHC concentrations in patients (N=5) following administration of molnupiravir via nasogastric ororogastric tube fell within the range of NHC concentrations following oral molnupiravir capsule administration under the same dosing regimen.

Table 2: Pharmacokinetics of NHC After Multiple Oral Administration of 800 mg LAGEVRIO Every 12 Hours

	NHC Geometric Mean (%CV)
Pharmacokinetics in Patients	
$AUC_{0\text{-}12hr}$ (ng*hr/mL)*	8260 (41.0)
C_{max} (ng/mL)*	2330 (36.9)
C_{12hr} (ng/mL)*	31.1 (124)
Pharmacokinetics in Healthy Subjects	
$AUC_{0\text{-}12hr}$ (ng*hr/mL)	8330 (17.9)
C_{max} (ng/mL)	2970 (16.8)
C_{12hr} (ng/mL)	16.7 (42.8)
AUC Accumulation Ratio	1.09 (11.8)
Absorption	
T_{max} (hr)†	1.50 [1.00 – 2.02]
Effect of Food	35% reduction in C_{max}, no effect on AUC
Distribution	
Plasma Protein Binding (*in vitro*)	0%
Apparent Volume of Distribution (L)*	142
Elimination	
Effective $t_{1/2}$ (hr)	3.3
Apparent Clearance (L/hr)*	76.9
Fraction of dose excreted in urine over the time interval of 0-12 hours	3% (81.6%)
Values were obtained from a Phase 1 study of healthy subjects, unless otherwise indicated. *Values were obtained from population PK analysis. †Median [min - max]	

Specific Populations
Population PK analysis results indicated that age, sex, race, ethnicity, or disease severity do not meaningfully influence the PK of NHC.

Pediatric Patients
LAGEVRIO has not been studied in pediatric patients.

Patients with Renal Impairment
Renal clearance is not a meaningful route of elimination for NHC. In a population PK analysis, mild or moderate renal impairment did not have a meaningful impact on the PK of NHC. The PK of molnupiravir and NHC has not been evaluated in patients with eGFR less than 30 mL/min/1.73m^2 or on dialysis.

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Patients with Hepatic Impairment
The PK of molnupiravir and NHC has not been evaluated in patients with moderate and severe hepatic impairment. Preclinical data indicate that hepatic elimination is not expected to be a major route of NHC elimination; therefore, hepatic impairment is unlikely to affect NHC exposure.

Drug Interaction Studies
In vitro study results indicated that molnupiravir and NHC are not substrates of CYP enzymes or human P-gp and BCRP transporters. *In vitro* study results also indicated that molnupiravir and NHC are not inhibitors of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 or inhibitors of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2K, MRP2, MDR1 and BCRP or inducers of CYP1A2, 2B6, and 3A4. The interaction between molnupiravir with concomitant medications, including other treatments for mild-to-moderate COVID-19, has not been evaluated.

12.4 Microbiology
Antiviral Activity
NHC, the nucleoside analogue metabolite of molnupiravir, was active in cell culture assays against SARS-CoV-2 (USA-WA1/2020 isolate) with 50% effective concentrations (EC_{50} values) ranging between 0.67 to 2.7 μM in A-549 cells and 0.32 to 2.0 μM in Vero E6 cells. NHC had similar antiviral activity against SARS-CoV-2 variants Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), Lambda (C.37), Mu (B.1.621) and Omicron (B.1.1.529/BA.1, BA.1.1, BA.2, BA.4 and BA.5), with mean EC_{50} values of 0.55-3.0 μM. NHC had non-antagonistic antiviral activity with remdesivir against SARS-CoV-2 in cell culture.

Resistance
No amino acid substitutions in SARS-CoV-2 associated with resistance to NHC have been identified in Phase 2 clinical trials evaluating LAGEVRIO for the treatment of COVID-19. Studies to evaluate selection of resistance to NHC with SARS-CoV-2 in cell culture have not been completed. Resistance selection studies have been conducted with other coronaviruses (MHV and MERS-CoV) and showed a low likelihood of resistance development to NHC. Following 30 passages in cell culture, only a 2-fold decrease in susceptibility was observed and no NHC resistance-associated amino acid substitutions were identified.

In clinical trials, encoded amino acid changes (substitutions, deletions or insertions) were more likely to be detected in viral sequences in subjects treated with LAGEVRIO compared to placebo. In a small number of subjects amino acid changes in the spike protein occurred at positions targeted by monoclonal antibodies and vaccines. The clinical and public health significance of these changes are unknown.

Cross-Resistance
NHC retained activity in cell culture against virus with polymerase (nsp 12) substitutions (e.g., F480L, V557L and E802D) associated with decreased remdesivir susceptibility, indicating a lack of cross-resistance.

Activity against SARS-CoV-2 in animal models
The antiviral activity of molnupiravir has been demonstrated in mouse, hamster, and ferret models of SARS-CoV-2 infection when dosing was administered prior to or within 1-2 days after viral challenge. In SARS-CoV-2 infected ferrets, molnupiravir significantly reduced SARS-CoV-2 viral titers in the upper respiratory tract and completely inhibited viral spread to untreated contact animals. In SARS-CoV-2 infected Syrian hamsters, molnupiravir reduced viral RNA and infectious virus titers in the lungs of animals. Histopathological analysis of lung tissue harvested after infection showed significantly reduced SARS-CoV-2 viral antigen levels and a lower abundance of pulmonary lesions in molnupiravir-treated animals compared with controls.

In Vitro Cytotoxicity

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NHC, the nucleoside analogue metabolite of molnupiravir, had variable cytotoxicity against different mammalian cell types with CC_{50} values ranging from 7.5 µM (human lymphoid CEM cell line) to >100 µM, in 3-day exposure assays. Molnupiravir inhibited the proliferation of human bone marrow progenitor cells with CC_{50} values of 24.9 µM and 7.7 µM for erythroid and myeloid progenitor proliferation, respectively, in 14-day colony formation assays.

Viral RNA Rebound
Post-treatment increases in SARS-CoV-2 RNA shedding levels (i.e., viral RNA rebound) in nasopharyngeal samples were observed on Day 10, Day 15, and/or Day 29 in a subset of LAGEVRIO and placebo recipients in the Phase 3 MOVe-OUT trial. Approximately 1% of both LAGEVRIO and placebo recipients had evidence of recurrent COVID-19 symptoms coinciding with a rebound in viral RNA levels in nasopharyngeal samples.

Post-treatment viral RNA rebound was not associated with the primary clinical outcome of hospitalization or death through Day 29 following the single 5-day course of LAGEVRIO treatment. Post-treatment viral RNA rebound also was not associated with the detection of cell culture infectious virus in nasopharyngeal swab samples.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Molnupiravir was not carcinogenic in a 6-month oral carcinogenicity study in RasH2 transgenic (Tg.RasH2) mice at any dose tested (30, 100 or 300 mg/kg/day).

Mutagenesis
Molnupiravir and NHC were positive in the *in vitro* bacterial reverse mutation assay (Ames assay) with and without metabolic activation. Molnupiravir was studied in two *in vivo* rodent mutagenicity models. The *in vivo* Pig-a mutagenicity assay gave equivocal results. Molnupiravir was negative in the *in vivo* Big Blue® (cII Locus) transgenic rodent mutagenicity assay. Molnupiravir was negative for induction of chromosomal damage in *in vitro* micronucleus (with and without metabolic activation) and *in vivo* rat micronucleus assays. To assess effects on germ cells, a transgenic rodent male germ cell mutagenicity assay is planned.

Based on the totality of the available genotoxicity data and the duration of treatment (5 days), molnupiravir is low risk for genotoxicity.

Impairment of Fertility
There were no effects on fertility, mating performance or early embryonic development when molnupiravir was administered to female or male rats at NHC exposures approximately 2 and 6 times, respectively, the human NHC exposure at the RHD.

13.2 Animal Toxicology and/or Pharmacology

Bone and cartilage toxicity changes resulting in impaired transformation of growth cartilage into new bone were observed in the femur and tibia of rats in a 3-month toxicity study at ≥ 500 mg/kg/day (5 times the human NHC exposure at the RHD). There was no bone or cartilage toxicity in a 1-month toxicity study in rats up to 500 mg/kg/day (4 and 8 times the human NHC exposure at the RHD in females and males, respectively), in dogs dosed for 14 days up to 50 mg/kg/day (similar to the human NHC exposure at the RHD), or in a 1-month toxicity study in mice up to 2,000 mg/kg/day (19 times the human NHC exposure at the RHD).

Growth cartilage is not present in mature skeletons, therefore the bone and cartilage findings are not relevant for adult humans but may be relevant for pediatric patients *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.4)]*.

Reversible, dose-related bone marrow toxicity affecting all hematopoietic cell lines was observed in dogs at ≥17 mg/kg/day (less than the human NHC exposure at the RHD). Mild decreases in

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peripheral blood cell and platelet counts were seen after 7 days of molnupiravir treatment progressing to more severe hematological changes after 14 days of treatment. Neither bone marrow nor hematological toxicity was observed in a 1-month toxicity study in mice up to 2,000 mg/kg/day (19 times the human NHC exposure at the RHD) and a 3-month toxicity study in rats up to 1,000 mg/kg/day (9 and 15 times the human NHC exposure at the RHD in females and males, respectively).

14 CLINICAL STUDIES

Clinical data supporting this EUA are based on data from 1,433 randomized subjects in the Phase 3 MOVe-OUT trial (NCT04575597). MOVe-OUT is a randomized, placebo-controlled, double-blind clinical trial studying LAGEVRIO for the treatment of non-hospitalized patients with mild-to-moderate COVID-19 who are at risk for progressing to severe COVID-19 and/or hospitalization. Eligible subjects were 18 years of age and older and had one or more pre-defined risk factors for disease progression: over 60 years of age, diabetes, obesity (BMI ≥30), chronic kidney disease, serious heart conditions, chronic obstructive pulmonary disease, or active cancer. The study included symptomatic subjects not vaccinated against SARS-CoV-2 and who had laboratory confirmed SARS-CoV-2 infection and symptom onset within 5 days of randomization. Subjects were randomized 1:1 to receive 800 mg of LAGEVRIO or placebo orally twice daily for 5 days.

At baseline, in all randomized subjects, the median age was 43 years (range:18 to 90); 17% of subjects were over 60 years of age and 3% were 75 years of age or older; 49% of subjects were male; 57% were White, 5% Black or African American, 3% Asian, 50% Hispanic or Latino. The majority of subjects were enrolled from sites in Latin America (46%) and Europe (33%); 12% were enrolled in Africa, 6% were enrolled in North America and 3% were enrolled in Asia. Forty-eight percent of subjects received LAGEVRIO or placebo within 3 days of COVID-19 symptom onset. The most common risk factors were obesity (74%), over 60 years of age (17%), and diabetes (16%). Among 792 subjects (55% of total randomized population) with available baseline SARS-CoV-2 variant/clade identification results, 58% were infected with Delta (B.1.617.2 and AY lineages), 20% were infected with Mu (B.1.621), 11% were infected with Gamma (P.1), and the remainder were infected with other variants/clades. Overall, baseline demographic and disease characteristics were well balanced between the treatment arms.

Table 3 provides the results of the primary endpoint (the percentage of subjects who were hospitalized or died through Day 29 due to any cause). The efficacy results are based on unvaccinated adults who were 18 years of age and older and had one or more pre-defined risk factors for disease progression: over 60 years of age, diabetes, obesity (BMI ≥30), chronic kidney disease, serious heart conditions, chronic obstructive pulmonary disease, or active cancer. Please refer to Figure 1 for results by certain subgroups. These subgroup analyses are considered exploratory. Data are not available in certain subgroups of subjects who are at high risk for progression to severe COVID-19 as defined by CDC.

Table 3. Efficacy Results in Non-Hospitalized Adults with COVID-19*

LAGEVRIO (N=709) n (%)	Placebo (N=699) n (%)	Adjusted Risk Difference % (95% CI)
All-cause hospitalization ≥24 hours for acute care or death through Day 29		
48 (6.8%)	68 (9.7%)	-3.0% (-5.9%, -0.1%)
All-cause mortality through Day 29		
1 (0.1%)	9 (1.3%)	

*The determination of primary efficacy was based on a planned interim analysis of 762 subjects. At the interim analysis, 7.3% of patients who received LAGEVRIO were either hospitalized or died through Day

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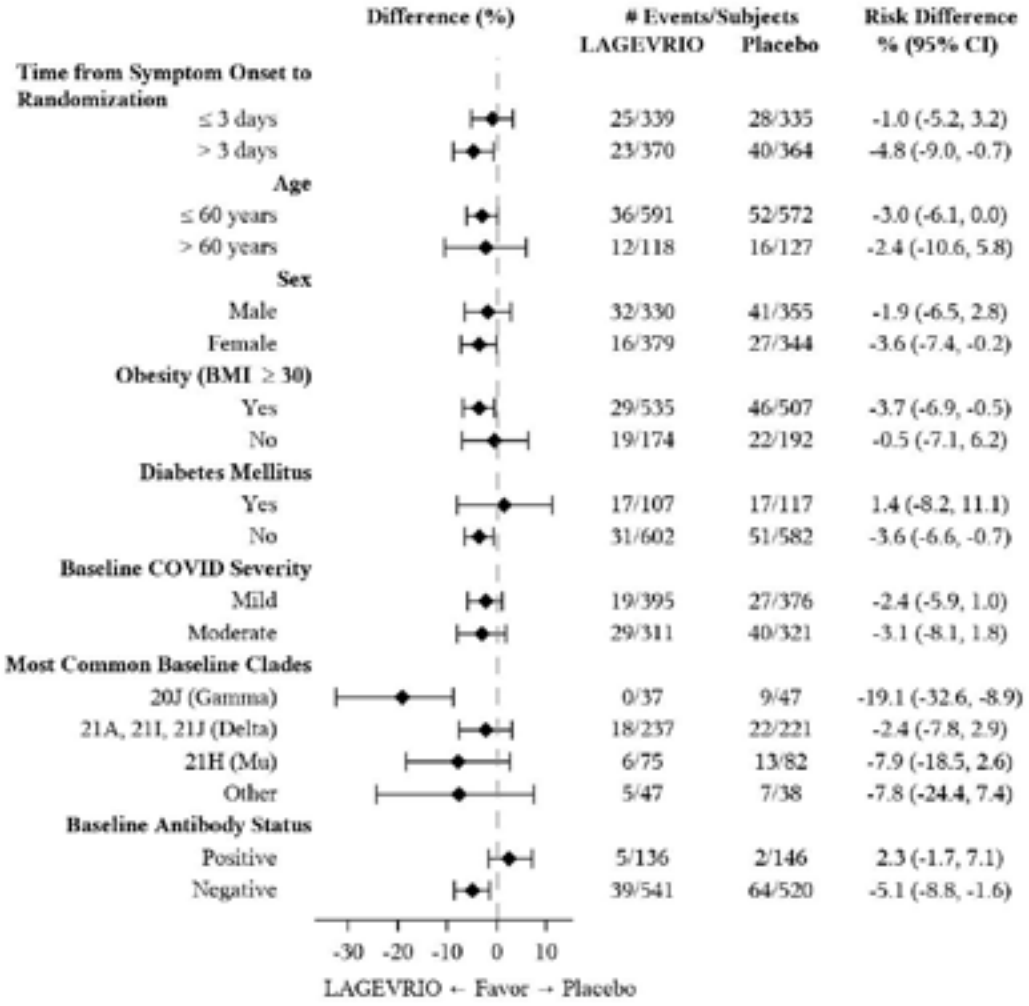
29 (28/385), compared with 14.1% of placebo-treated patients (53/377). The adjusted risk difference was -6.8% with a 95% CI of (-11.3%, -2.4%) and 2-sided p-value = 0.0024.

Adjusted relative risk reduction of LAGEVRIO compared to placebo for all randomized subjects was 30% (95% CI: 1%, 51%).

Analyses are adjusted by the stratification factor of time of COVID-19 symptom onset (≤3 days vs. >3 [4-5] days).

Figure 1. Subgroup Efficacy Results in Non-Hospitalized Adults with COVID-19 - All-Randomized Subjects



The corresponding confidence interval is based on Miettinen & Nurminen method.
The modified intent-to-treat population is the efficacy analysis population.
Baseline serum samples were evaluated with the Roche Elecsys anti-N assay to test for the presence of antibodies (IgM, IgG and IgA) against the SARS-CoV-2 nucleocapsid protein.
The findings of these subgroup analyses are considered exploratory.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

LAGEVRIO capsules are supplied as follows:

Contents	Description	How Supplied	NDC

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200 mg molnupiravir	Swedish Orange opaque capsules with corporate logo and "82" printed in white ink	40 count bottles	NDC-0006-5055-06 NDC-0006-5055-07 NDC-0006-5055-09

Storage and Handling
Store LAGEVRIO capsules at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) *[see USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION
As a prescribing healthcare practitioner, you must communicate to the patient and/or caregiver information consistent with the "FACT SHEET FOR PATIENTS AND CAREGIVERS" and document that information was provided. A copy of this Fact Sheet should be provided to the patient and/or caregiver prior to receiving LAGEVRIO *[see Box]*.

Hypersensitivity Reactions
Inform patients that hypersensitivity reactions have been reported, even following a single dose of LAGEVRIO, and to discontinue the drug and to inform their healthcare provider at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, 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 anallergic reaction *[see Warnings and Precautions (5.2)]*.

Risk of Fetal Toxicity
Advise patients that LAGEVRIO is not recommended for use in pregnancy because it may cause fetal harm. Advise individuals of childbearing potential to inform their healthcare provider of a known or suspected pregnancy *[see Box, Warnings and Precautions (5.1) and Use in Specific Populations (8.1)].*

Advise individuals of childbearing potential to use effective contraception correctly and consistently while taking LAGEVRIO and for 4 days after the last dose.

While the risk is regarded as low, nonclinical studies to fully assess the potential for LAGEVRIO to affect offspring of treated males have not been completed. Advise sexually active individuals with partners of childbearing potential to use a reliable method of contraception consistently and correctly while taking LAGEVRIO and for atleast 3 months after the last dose of LAGEVRIO. The risk beyond 3 months after the last dose of LAGEVRIO is unknown. Studies to understand the risk beyond three months are ongoing *[see Use in Specific Populations (8.3)].*

Risk of Bone and Cartilage Toxicity
LAGEVRIO is not authorized for use in patients less than 18 year of age as it may affect bone growth and cartilage formation *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.4)].*

Pregnancy Registry
There is a pregnancy registry that monitors pregnancy outcomes in individuals exposed to LAGEVRIO during pregnancy. Encourage participation and advise patients about how they may enroll in the pregnancy registry at https://covid-pr.pregistry.com or 1-800-616-3791 *[see Use in Specific Populations (8.1)]*.

Lactation
Breastfeeding is not recommended while taking LAGEVRIO and for 4 days after the last dose of LAGEVRIO. Advise lactating individuals to consider interrupting breastfeeding and to consider

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pumping and discarding breast milk during treatment and for 4 days after the last dose of LAGEVRIO *[see Use in Specific Populations (8.2)]*.

Administration Instructions
Inform patients to take LAGEVRIO with or without food. Advise patients to swallow LAGEVRIO capsules whole, and to not open, break, or crush the capsules. Instruct patients that if they miss a dose of LAGEVRIO and it is within 10 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 10 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. Advise the patient to not double the dose to make up for a missed dose *[see Dosage and Administration (2.2)]*.

LAGEVRIO capsule contents can be mixed with water and given via NG/OG tube. Inform patients to follow the instructions as described in the fact sheet for patients and caregivers *[see Dosage and Administration (2.3)]*.

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 *[see Dosage and Administration (2.1)]*.

18 MANUFACTURER INFORMATION
For additional information visit: www.molnupiravir.com

If you have questions, please contact
1-800-672-6372

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For patent information: www.msd.com/research/patent

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