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

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

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.

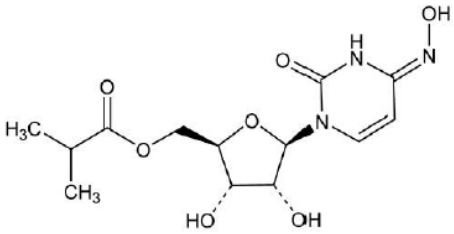
2.2. Quality aspects

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

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

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.

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

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.

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.

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

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

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).

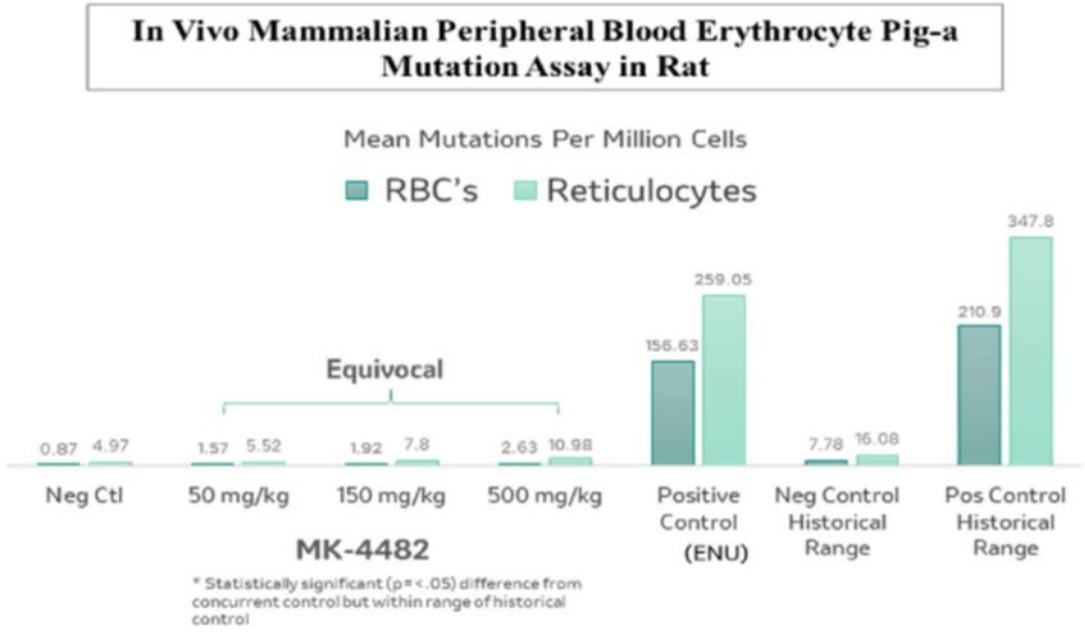
A non-GLP compliant Ames study was performed with NHC and a GLP compliant study with molnupiravir. With NHC in the E. coli WP2 *uvrA* strain all plates ≥5 µg with and without metabolic activation were positive for revertants. With molnupiravir mutagenic potential was also seen in the WP2 uvrA strain, 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

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 ≥ 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]
$AUC_{0\text{-}inf}$ (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]
$DAUC_{0\text{-}inf}$ (h*ng/mL/mg)	8.64 (26.5) [6]	9.32 (27.0) [6]	9.15 (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_R (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]

$AUC_{0\text{-}inf}$ = 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}); 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 $AUC_{0\text{-}inf}$ 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]
$AUC_{0\text{-}inf}$ (h*ng/mL)	13800 (11.8) [6]	20700 (31.4) [6]
$DAUC_{0\text{-}inf}$ (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_R (L/h)	3.90 (29.8) [6]	4.08 (18.5) [6]

$AUC_{0\text{-}inf}$ = 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}); 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 $AUC_{0\text{-}inf}$ 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 $AUC_{0\text{-}inf}$ 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 $AUC_{0\text{-}12}$, AUC_{last}, $AUC_{0\text{-}inf}$ 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)[#]	200 mg EIDD-2801 capsule (fasted)	10	1.00	
	200 mg EIDD-2801 capsule (fed)	10	3.00	1.75 (1.00, 2.50)

[#] 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]
$AUC_{0\text{-}inf}$ (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]
$DAUC_{0\text{-}inf}$ (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_τ (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]
$DAUC_\tau$ (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]
$\%AUC_{\tau,extrap}$ (%)	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_R (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]

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_{τ} (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]
$DAUC_{\tau}$ (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]
$\%AUC_{\tau,extrap}$ (%)	3.78 (50.8) [6]	1.82 (81.7) [6]	---	0.370 (NC) [6]	0.367 (NC) [6]	---	---
$RA_{AUC\tau}$	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_R (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_{τ} = area under the plasma concentration-time curve during a dosing interval hours postdose; 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; $RA_{AUC\tau}$ = 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 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 AUCτ. Between-subject variability, as assessed by geometric CV, was generally low (<25%) on Days 1 and 6 for AUCτ 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 ($Fe_{0-\tau}$). 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-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.

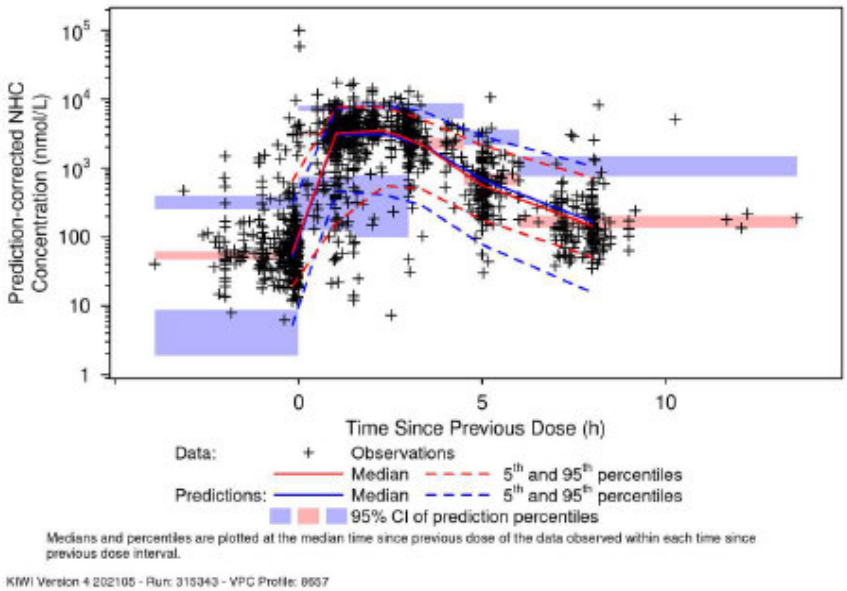
Table 13. Parameter Estimates and Standard Errors for the Final Plasma NHC Pharmacokinetic Model

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-lab_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[a]
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)	266 (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 (30100)	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, 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, x^{th} percentile; SD, standard deviation.

[a] 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[a]
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

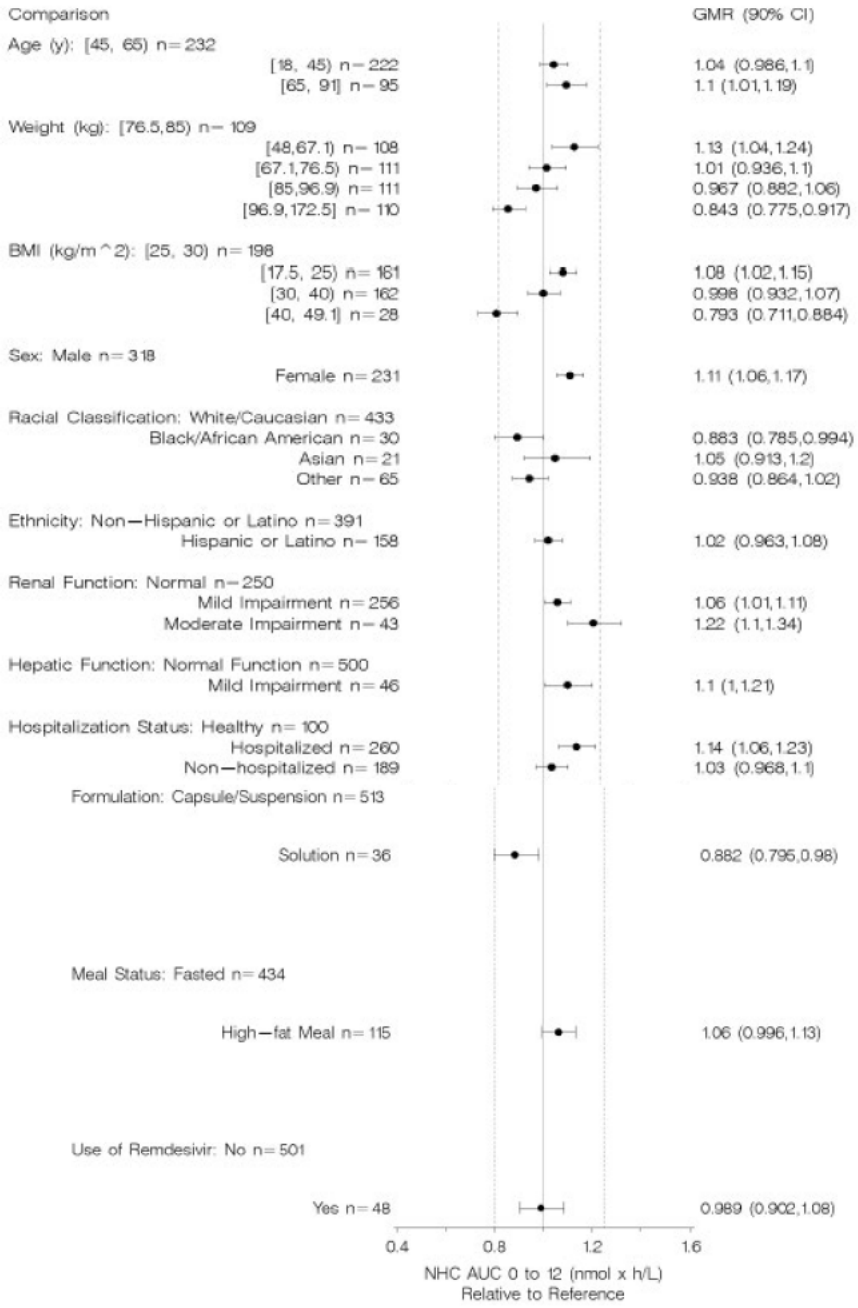
Abbreviations: AUC_{0-12}, area under the NHC concentration versus time curve from 0 to 12 h postdose; %CV, coefficient of variation expressed as a percent; Geom., geometric; n, number of individuals; NA, not applicable; NHC, β-d-N4-hydroxycytidine; Px, x^{th} percentile; SD, standard deviation.

[a] 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_{0-12} 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

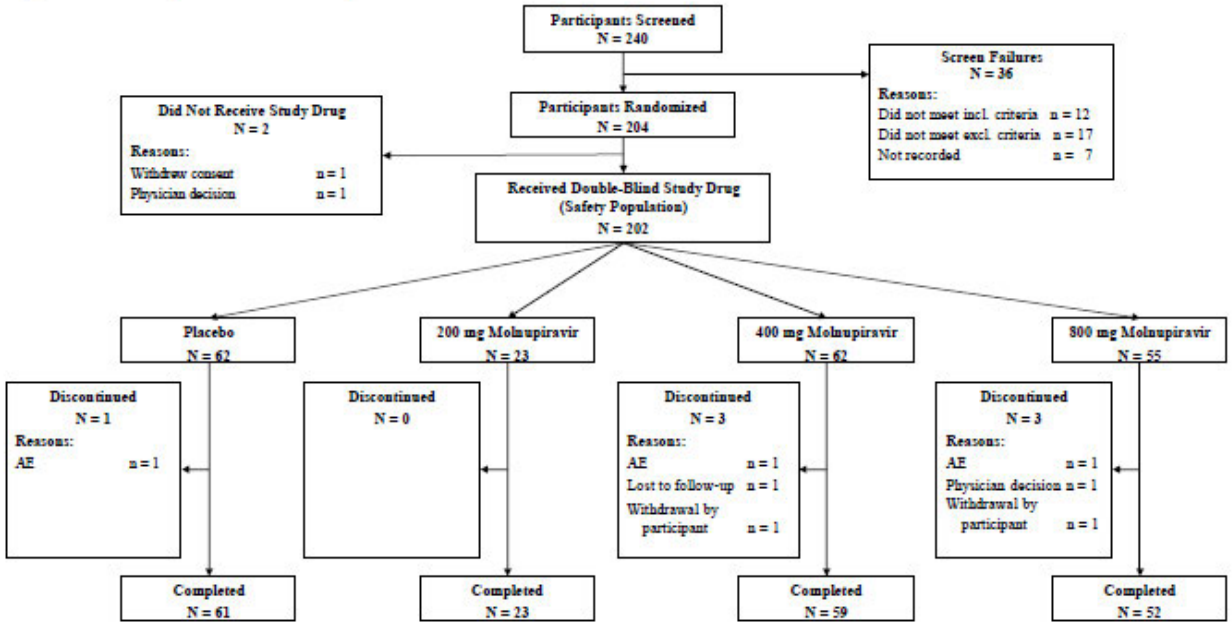


Table 2: Summary of Participant Populations (Randomized Participants)

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

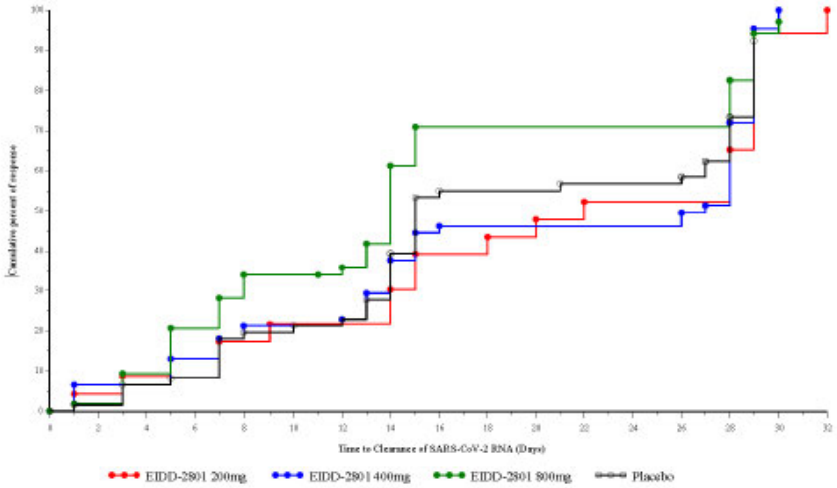
The majority had at least 1 risk factor for severe illness from COVID-19 (60.7% in the combined molnupiravir group and 57.7% in the placebo group). The most common risk factor for severe illness was smoking (30.7% molnupiravir and 32.3% placebo) while 39.3% and 40.3% in respective groups had no known 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	

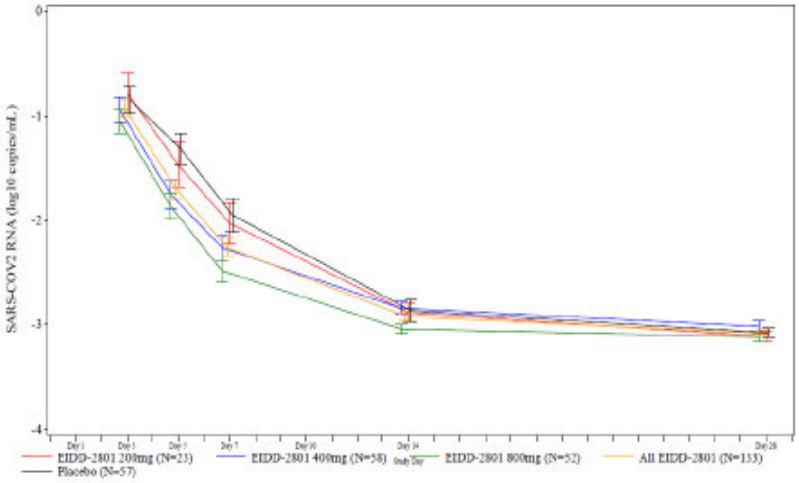


Source: [P006MK4482: adam-adsl; adtte]

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	0.4941	
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	

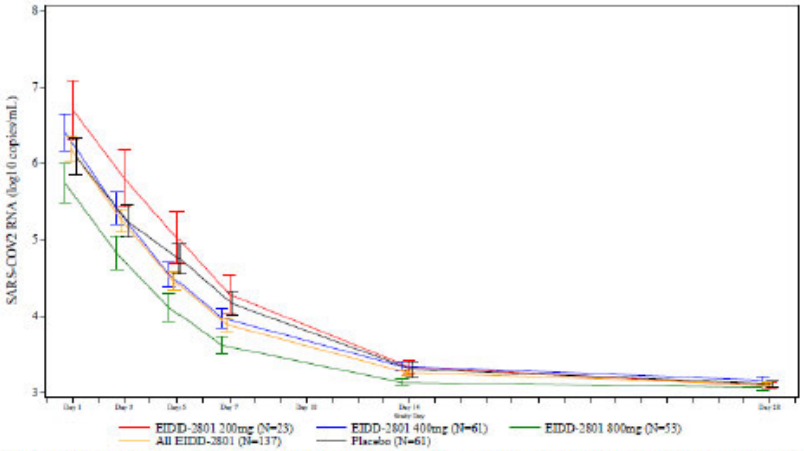


Analysis was based on MMRM including fixed effects of treatment, visit, days from COVID symptom onset, baseline SARS-COV-2 viral load and interaction terms of treatment by visit, days from COVID symptom onset by visit, and baseline SARS-COV-2 viral load by visit.

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.

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 Infectivity by RT-PCR	SARS-CoV-2 Viral Load		Kappa Statistic
	Negative (BLQ)	Positive	
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.

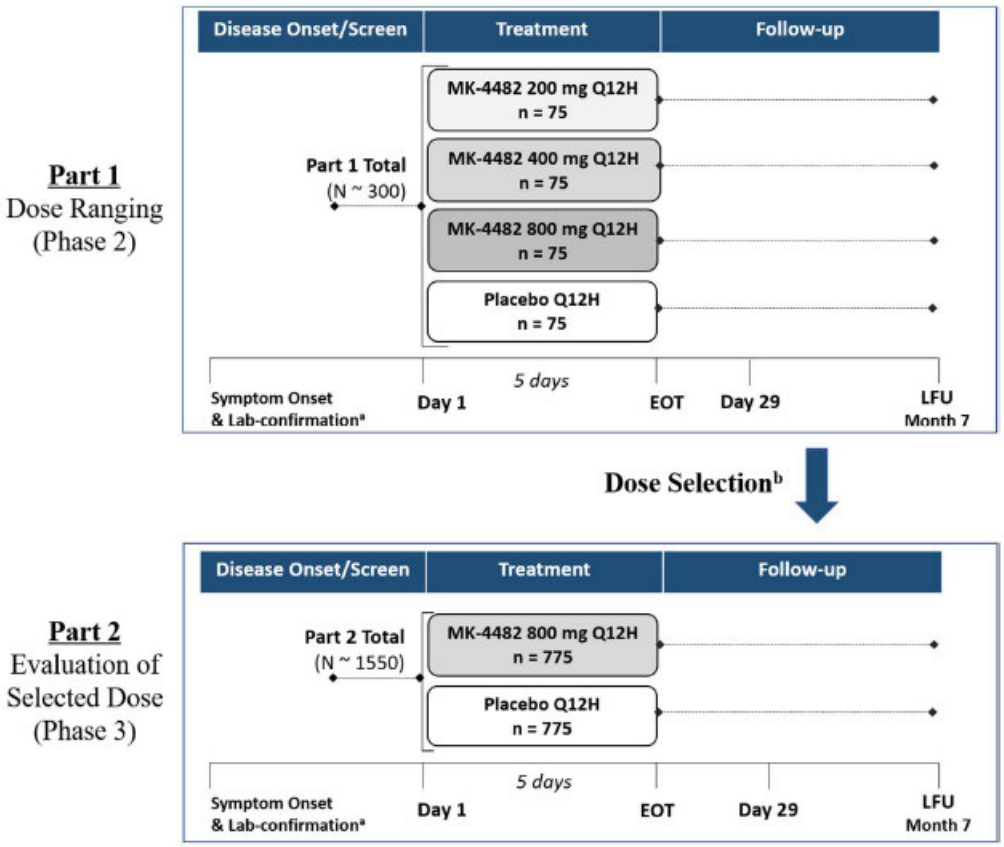
Overall, there was a high degree of variability between groups and over time in COVID-19 symptoms recorded in patient diaries. Among the summaries and analyses prepared, there were no consistent or meaningful differences between the treatment groups at any time during the study. There were 4 participants 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.

[a] 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 Therapeutics	• Sponsor-designated standard of care for treatment for COVID-19[a] 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:

Arm Name	Arm Type	Intervention Name	Inter-vention Type	Dose Formu-lation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
MK-4482	Experi-mental	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)	Experi-mental	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%

- **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.

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)[a]	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)[a]	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

[a] 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[a]						
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
[a] 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)
Unknowna	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		145		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	(3.4)	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)
Noa	2	(0.5)	11	(2.8)	13	(1.7)

a 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 % (95% CI)a	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)			

a 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 = -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%.).

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.

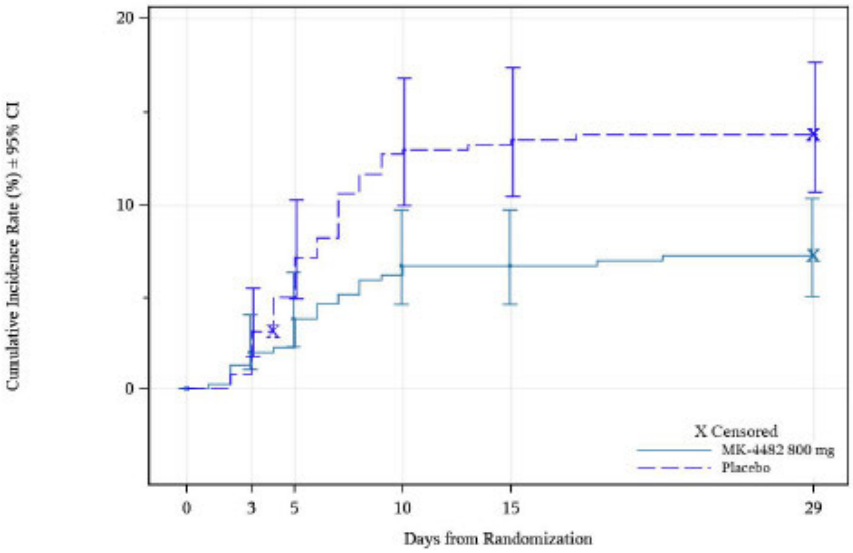
Results of time-to-event sensitivity analyses were consistent with the results of the primary analysis.

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 Ratiob (95% CI)[b]	p-Valuec
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 covariates 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:

- 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)[a]
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, -3.4)

[a] 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)[a]
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)

[a] 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)[a]
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)

[a] 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)[a]
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)

[a] 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	(-26.8, 1.5)
21A	5/33	(15.2)	9/29	(31.0)	-15.9	(-36.9, 5.3)
21H	3/41	(7.3)	6/55	(10.9)	-3.6	(-15.9, 10.0)

* The corresponding confidence interval is based on Miettinen & Nurminen method.
m= number of participants in the modified intent-to-treat population with the corresponding 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.
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.

- 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	1/15	(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.

- 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)[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)

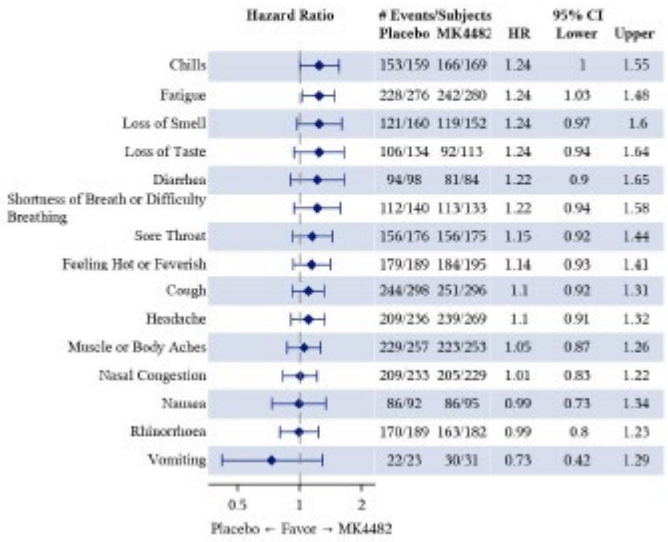
[a] The corresponding confidence interval is based on Miettinen & Nurminen method.
m= number of participants in the modified intent-to-treat population with the corresponding group.
n= number of participants died or hospitalized through Day 29.
Unknown survival status at Day 29 was counted as having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

- **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).

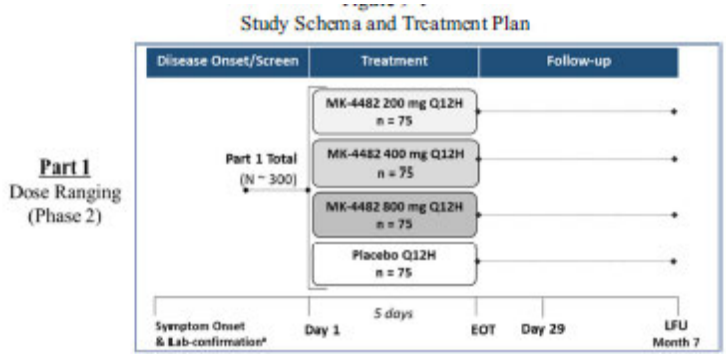
Molnupiravir was associated with a greater reduction in SARS-CoV-2 RNA from baseline compared with the placebo group at Days 3 and 5 but not at later time points. Results stratified by baseline SARS-CoV-2 RNA titre ($>10^6$ and $\leq 10^6$ copies/mL) were generally consistent with the overall results 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 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											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[a]												
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 IA2

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, 92.6)
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 Comparisons					Hazard Ratio[b] (95% CI)[b]	p-Value
MK-4482 200 mg vs. Placebo					0.99 (0.68, 1.45)	0.5620[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.

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	**75.9** (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, 83.2)	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.

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.

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) nS (%) [nE]	EIDD-2801 capsule BID (fasted) 50 mg (N = 6) nS (%) [nE]	100 mg (N = 6) nS (%) [nE]	200 mg (N = 6) nS (%) [nE]	300 mg (N = 6) nS (%) [nE]	400 mg (N = 6) nS (%) [nE]	600 mg (N = 6) nS (%) [nE]	800 mg (N = 6) nS (%) [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%)	---	---	---	---
Ageusia	---	---	---	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%)	---	---
Chromaturia	---	---	---	---	---	---	---	1 (16.7%)
Dizziness postural	---	---	---	1 (16.7%)	---	---	---	---
Epistaxis	---	---	---	---	---	1 (16.7%)	---	---
Gastrointestinal sounds abnormal	---	---	---	1 (16.7%)	---	---	---	---
Hot flush	1 (7.1%)	---	---	---	---	---	---	---
Hypersomnia	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 $<150 \times 10^9$/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) 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.

MK4482-006

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

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[a] 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)

[a] 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 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.

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

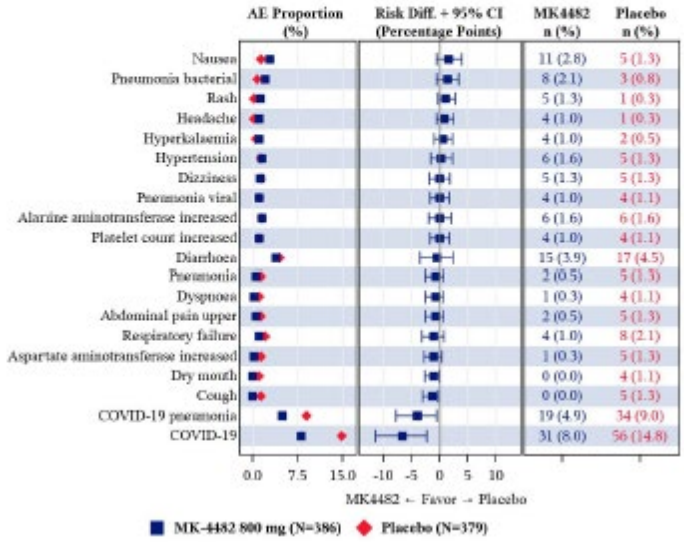
The table summarises the safety profile as reported at the time of the cut-off date applied to IA4.

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.

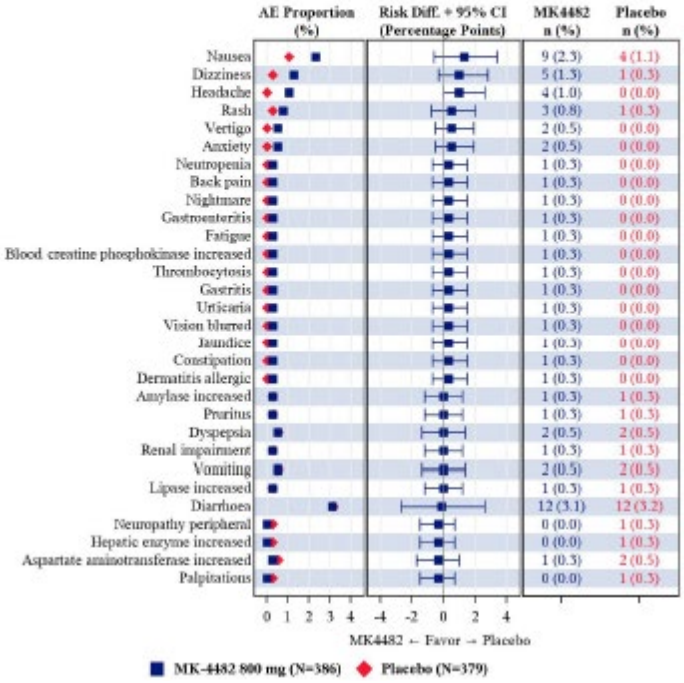
Rainfall Plot of Participants with Adverse Events During Treatment and 14-Day Follow-Up Period
(Incidence ≥ 4 Participants in One or More Treatment Groups)
All Participants as Treated Population
MK-4482-002 Combined IA3/IA4



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 IA3/IA4



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 IA3/IA4

	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 800 mg		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 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)
Grade 1	34	(8.8)	31	(8.2)	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.

Adverse Event 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[a] 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)

[a] 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.

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
PPD	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
	PPD	Placebo	2	PPD				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.

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.

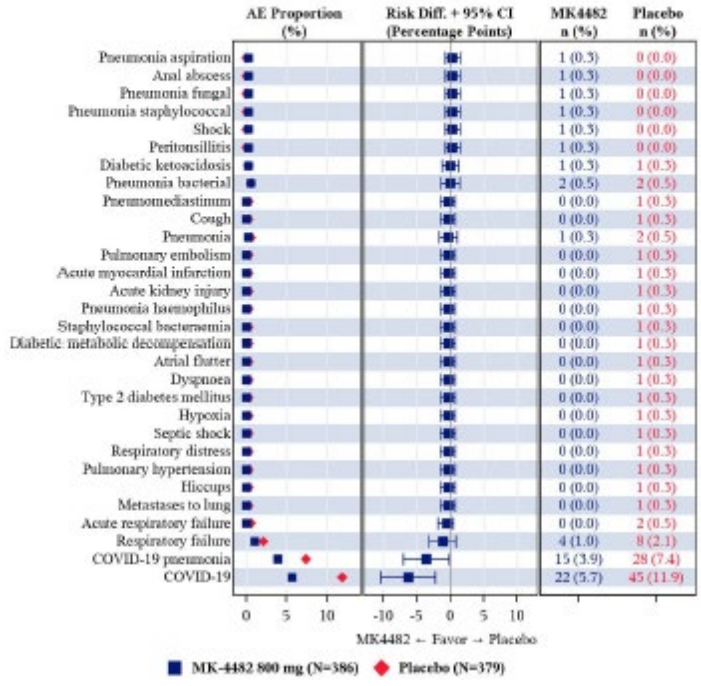
Participants With Adverse Events Resulting in Death During Treatment and 14-Day Follow-Up Period
(Incidence > 0% in One or More Treatment Groups)
All Participants as Treated Population
MK-4482-002 Combined IA3/IA4

	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



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 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

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 IA3/IA4

	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

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.