Center for Drug Evaluation and Research

Antimicrobial Drugs Advisory Committee Meeting Briefing Document

Molnupiravir

Oral Treatment of COVID-19

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ADVISORY COMMITTEE BRIEFING MATERIALS:
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LIST OF ABBREVIATIONS

Abbreviation/Term	Definition
3TC	Lamivudine
AE	Adverse event
AGILE-ACCORD	Agile-sponsored Accelerating COVID-19 dRug Development
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APaT	All participants as treated
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC0-24 or AUC0-12	Area under the concentration-time curve from 0 to 24 (or 0 to 12) hours
AUC0-inf	Area under the concentration-time curve extrapolated to infinity
AUC0-last	Area under the concentration-time curve from 0 through the last measurable concentration
BID	Twice a day
BLOQ	Below the limit of quantitation
BMI	Body mass index
CC_{50}	Half-maximal cytotoxicity concentration
CHO	Chinese hamster ovary
CI	Confidence interval
Cmax	Maximum concentration
COV	Coronavirus
COVID-19	Coronavirus disease 2019
CTP	Cytosine triphosphate cytidine triphosphate
CYP	Cytochrome P450
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EFD	Embryo-fetal developmental
eGFR	Estimated glomerular filtration rate
EIDD	Emory Institute for Drug Development
Emax	Maximum Effect
ENU	N-ethyl-N-nitrosourea
EOT	End of treatment
ESRD	End-stage renal disease
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FTC	Emtricitabine
GD	Gestation day
hr	Hour
IAV	Influenza A virus
IA	Interim Analysis
IC_{50}	Half-maximal inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
IPCS	International Programme on Chemical Safety
IV	Intravenous
LFU	Late Follow-up Visit

Abbreviation/Term	Definition
LoM	Lung only mice
LOQ	Limit of quantitation
mAbs	Monoclonal antibodies
MERS	Middle east respiratory syndrome
MERS-CoV	MERS-associated coronavirus
MDRD	Modification of Diet in Renal Disease
MHV	Mouse hepatitis virus
MITT	Modified Intent to Treat
MOA	Mechanism of action
MOV	Molnupiravir (MK-4482)
NGS	Next generation sequencing
NHC	N-hydroxycytidine
NHC-TP	N-hydroxycytidine-5′-triphosphate
NOEL	No-observed effect level
NOAEL	No-observed-adverse-effect level
NP	Nasopharyngeal
NSP	Nonstructural protein
OECD	Organisation for Economic Co-operation and Development
OP	Oropharyngeal
PCR	Polymerase chain reaction
PK	Pharmacokinetic(s)
PO	Oral administration
PopPK	Population PK
PPND	Pre- and postnatal developmental
Q12H	Every 12 hours
RdRp	RNA-dependent RNA polymerase
RET	Reticulocyte(s)
RNA	Ribonucleic acid
RT-PCR	Reverse-transcriptase polymerase chain reaction
SAE	Serious adverse event
SARS	Severe acute respiratory syndrome
SARS-CoV	SARS-associated coronavirus
SARS-CoV-2	SARS-associated coronavirus-2
SD	Standard deviation
t1/2	Apparent terminal half-life
TK(6)	Toxicokinetic(s)(6)
Tmax	Time of maximum concentration
TSSO	Time since symptom onset
ULN	Upper limit of normal
US	United States of America
UTP	Uridine 5′-triphosphate
VEEV	Venezuelan equine encephalitis virus
vs.	Versus
WHO	World Health Organization
WOCBP	Women of childbearing potential

1 EXECUTIVE SUMMARY

This document provides a summary of the results of the development program conducted to support the use of molnupiravir (MOV, MK-4482) for the treatment of mild to moderate COVID-19 in adults who are at risk for progressing to severe COVID-19 and/or hospitalization.

MOV is an orally administered antiviral for the treatment of COVID-19. MOV inhibits the replication of SARS-CoV-2, with similar activity across variants of concern. It has a high barrier to resistance, with no evidence of resistance development to MOV in nonclinical or clinical studies to date. The proposed dosing regimen is MOV 800 mg (administered as four 200 mg capsules) taken every 12 hours (Q12H) with or without food for 5 days. Treatment should be started as soon as possible after a diagnosis of COVID-19, and within 5 days of symptom onset.

Treatment with MOV significantly reduces the risk of hospitalization or death through Day 29 by approximately 50%. The efficacy of MOV was demonstrated in a Phase 2/3 clinical study (MK-4482 Protocol 002 (P002), also known as the MOVe-OUT study) in non-hospitalized adults with mild to moderate COVID-19, at least 1 risk factor for severe illness, and symptom onset within 5 days prior to initiating treatment. In the planned interim analysis (IA), 7.3% of participants who received MOV were hospitalized or died through Day 29 (28/385) compared with 14.1% of participants who received placebo (53/377) (p=0.0012). No deaths were reported for participants who received MOV compared with 8 deaths (through Day 29) reported for participants who received placebo.

The safety of MOV was evaluated in approximately 600 participants who received the proposed dose and duration of treatment (MOV 800 mg Q12H for 5 days) across the comprehensive clinical development program. MOV was well tolerated with an acceptable safety profile and no organ toxicities observed in clinical studies.

The nonclinical (ie, pharmacology, metabolism, and toxicity) and clinical (ie, safety, efficacy, and virology) assessments summarized in this document demonstrate that MOV addresses a significant unmet medical need for safe and effective oral agents to treat COVID-19. The totality of data to date supports the favorable benefit/risk profile of MOV for the proposed authorized use under Emergency Use Authorization (EUA).

2 BACKGROUND

2.1 Unmet Medical Need

On 04-FEB-2020, the Secretary of Health and Human Services issued a public health emergency declaration in response to the COVID-19 pandemic in the United States (US). As of mid-October 2021, over 240 million cases and 4.94 million deaths have been reported globally, with more than 45 million cases of SARS-CoV-2 infection and over 725,000 COVID-19-related deaths reported in the US [1] [2] [3] [4].

There continues to be a significant unmet medical need for safe and effective treatments for COVID-19 in the postvaccine rollout setting. Earlier in 2021, there was a steep decline in

incidence of COVID-19 cases primarily due to global vaccination rollout programs. However, the number of cases has fluctuated with the most recent peak occurring in SEP-2021, after steadily increasing since JUN-2021 [1] [2] [3] [4] [5]. The latest increase has been attributed to the emergence of the Delta variant; surveillance data have shown that this variant has become the predominant strain in most countries worldwide, including the US [6] [7] [8] [9] [10]. Global surveillance and observation data have reported that the Delta variant is 40% to 60% more transmissible than the Alpha variant and 2-times more infectious than the original strain of the SARS-CoV-2 virus [6] [11] [9] [10].

The previously observed age-risk gradient for SARS-CoV-2 infections shifted mid-2021 such that the highest proportion of new cases is now being reported in younger adults, which comprise most of the unvaccinated population [10]. Among the unvaccinated population infected with the SARS-CoV-2 Delta variant, a 2-fold risk of hospitalization has been observed compared to individuals infected with Alpha or the original virus strains [6] [12] [9] [10]. In addition, vaccine breakthrough infections are being reported especially in individuals who have suboptimal vaccine responses and/or waning immunity over time.

2.2 Alternative Therapies

There are no oral antiviral agents, either approved or under EUA, for the treatment of mild to moderate COVID-19 in the US.

The FDA has issued EUAs for 3 monoclonal antibody (mAb) therapies: casirivimab/imdevimab (REGEN-COV™; 21-NOV-2020) [13], bamlanivimab/etesevimab (09-FEB-2021) [14], and sotrovimab (26-MAY-2021) [15]. These EUAs are for the treatment of mild to moderate COVID-19 in patients ≥12 years of age (weighing ≥40 kg) with laboratory-confirmed SARS-CoV-2 infection and at high risk for progressing to severe COVID-19 and/or hospitalization. These mAb therapies must be administered by IV infusion and/or subcutaneous injection and patients must be monitored through at least 1 hour following infusion as hypersensitivity (eg, anaphylaxis, infusion-related reactions) has been reported for patients receiving anti-SARS-CoV-2 mAbs [16].

Some mAb therapies may become less effective as new SARS-CoV-2 variants emerge with mutations in the spike protein which may alter the antibody binding site [17]. A recent study evaluated the sensitivity of the Delta variant to the humoral immune response and found that some antibodies targeting the N-terminal and receptor binding domains of the spike protein had impaired binding and neutralization of the Delta variant [11].

2.3 Description of Product

MOV, an oral direct-acting antiviral agent, will address the critical unmet need for therapeutic agents to treat mild to moderate COVID-19 during the ongoing pandemic. MOV is an investigational medicinal product; as of 05-NOV-2021, it has not been approved by the FDA for the treatment of COVID-19 or any other indication. The Medicines and Healthcare products Regulatory Agency granted a Conditional Marketing Authorisation in Great Britain on 04-NOV-2021 for treatment of mild to moderate COVID-19 in adults with a positive SARS-CoV-2 diagnostic test and who have at least 1 risk factor for developing severe illness.

NHC (which turns into NHC-TP, the active metabolite of MOV, in cells) is a potent anti-SARS-CoV-2 agent which introduces errors in the viral RNA, impairing replication and infection. In nonclinical models, NHC has a high barrier to the development of resistance and retains activity against SARS-CoV-2 with RdRp mutations associated with remdesivir resistance as well as variants associated with changes in the viral spike protein (eg, Delta variant).

The proposed dosing regimen is MOV 800 mg (administered as four 200 mg capsules) taken orally Q12H with or without food for 5 days. The oral administration of MOV enables initiation in an outpatient setting, which can help limit direct patient interactions with health care staff and decrease transmission risk.

2.4 Proposed Authorized Use Under EUA

Under the submitted EUA, the Sponsor is proposing the use of MOV for the treatment of mild to moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19 including hospitalization or death.

3 NONCLINICAL DEVELOPMENT PROGRAM

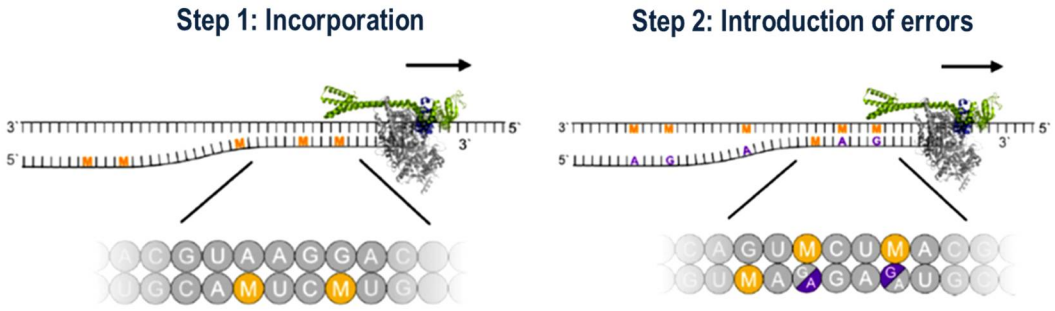
3.1 Nonclinical Pharmacology

3.1.1 Mechanism of Action

MOV is an orally administered prodrug that is rapidly metabolized to NHC in plasma. Then, NHC is distributed into cells where it is phosphorylated to form the pharmacologically active ribonucleoside triphosphate (NHC-TP). 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 [18] [19]. NHC introduces viral RNA errors through a two-step mechanism: first incorporating into the nascent RNA by substituting for either CTP or UTP, then when copied, base-pairing with either guanosine or adenosine resulting in errors in RNA products [Figure 1].

The MOA for NHC has been demonstrated for MERS-CoV, VEEV, MHV, and IAV viruses. When in the presence of NHC, these viruses have increased errors and multi-log decreases in the amount of infectious virus produced [20] [21] [22]. Clinical data presented in this document further support the MOA of MOV [Sec. 4.3.1.1] [Sec. 4.3.2.2.5]. Sequence analysis of pre- and post-treatment samples showed an increase in nucleotide errors across the entire viral genome which were not localized to genes in the viral RdRp complex.

Figure 1 A Two-Step Model of NHC-Induced Viral RNA Error

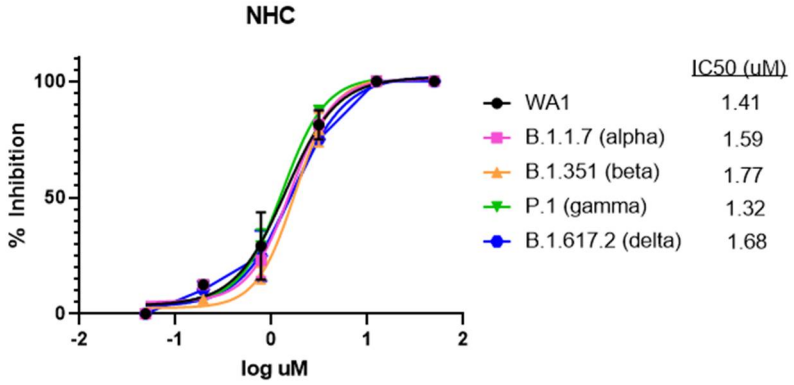


M=molnupiravir, representing NHC
Adapted from Kabinger, et al, 2021 [19]

3.1.2 In vitro and In vivo Antiviral Studies

Primary pharmacology studies demonstrating the antiviral activity of MOV and NHC against SARS-CoV-2 and other RNA viruses were conducted in vitro and in vivo (ie, mouse, guinea pig, hamster, and ferret) models of viral infection. In vitro, NHC has broad-spectrum activity against multiple viruses including coronaviruses SARS-CoV-2, SARS-CoV, and MERS-CoV. NHC was equally effective against SARS-CoV-2 variants of concern B.1.1.7 (Alpha), B.1351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta) compared with the original WA1 isolate in vitro [Figure 2]. NHC was also active against coronaviruses that have mutations which reduce susceptibility to remdesivir in cell culture assays [23] [24]. NHC was similarly active against replicons with remdesivir resistance-associated amino acid substitutions in NSP12 (polymerase).

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



IC_{50} = half-maximal effective concentration; NHC = N-hydroxycytidine or EIDD-1931; SARS-CoV-2= SARS-associated coronavirus-2

The antiviral activity of MOV has been demonstrated in animal infection models of SARS-CoV-2. MOV (500 mg/kg) significantly reduced infectious SARS-CoV-2 levels in lung tissue from LoM when administered 12 hours prior to, 24 hours post, or 48 hours post direct infection of human lung tissue, followed by twice daily dosing thereafter [25]. In a ferret

model, treatment with MOV reduced SARS-CoV-2 infectious viral titers in nasal secretions from infected ferrets and suppressed all viral transmission to the untreated direct contacts, despite prolonged direct proximity between source and contact animals [26]. In a Syrian hamster model of SARS-CoV-2 infection and disease, MOV prophylactic or therapeutic treatment showed decreased viral RNA titers and infectious virus from lungs several days post-infection [27]. Additionally, these antiviral effects were associated with an increase in transition errors in the viral genome. In a second study, Syrian hamsters infected with the SARS-CoV-2 variants B.1-G (Wuhan strain), B.1.1.7 (Alpha), or B.1.351 (Beta) and treated with 200 mg/kg BID MOV showed statistically significant reductions in viral RNA copies and in infectious virus titers in lung tissue regardless of SARS-CoV-2 variant [28].

There was no impact on the in vitro antiviral activity of NHC against SARS-CoV-2 in two-drug combination studies with 3TC, abacavir, FTC, hydroxychloroquine, nelfinavir, remdesivir, ribavirin, sofosbuvir, or tenofovir.

3.1.3 In vitro Cytotoxicity & Secondary Pharmacology Studies

In vitro cytotoxicity studies (evaluated in 10 cell lines) were conducted in parallel with the antiviral assays to demonstrate that the observed antiviral activity of MOV and NHC are due to effects on the virus, not due to effects on the cells. MOV showed no cytotoxicity at concentrations up to 100 μM (CC_{50} >100 μM), and NHC had CC_{50} values ≥88 μM. Prolonged in vitro exposure (14 days) of CEM and HepG2 cells with MOV did not result in mitochondrial toxicity or dysfunction. Neither MOV nor NHC exhibited off-target activities of clinical concern. In vitro, NHC-TP did not inhibit DNA polymerases alpha, beta or gamma (IC_{50} > 1000 μM) [29].

The potential effects of MOV on erythroid and myeloid progenitor proliferation were evaluated in a semi-solid methylcellulose-based culture system supporting the proliferation of human erythroid and myeloid progenitors. The inhibition of erythroid and myeloid progenitor proliferation was observed following 14-day continuous MOV exposure (IC_{50} concentrations: 7.7 μM [myeloid] and 24.9 μM [erythroid]). MOV was shown to be efficiently metabolized to NHC (and eventually NHC-TP) in vitro. These sustained MOV and NHC concentrations cannot be extrapolated to in vivo clinical MOV or NHC exposures.

3.2 Pharmacokinetics and Product Metabolism in Animals

An extensive nonclinical evaluation of the pharmacokinetics (PK) and metabolism of MOV and NHC, as well as the distribution and exposure of NHC-TP in tissues, was completed to support administration of MOV in clinical studies. Based on the totality of nonclinical data, the disposition of MOV in rats and dogs following oral administration can be characterized as rapid hydrolysis of the prodrug during absorption/hepatic first pass resulting in near complete drug absorption (>90%) and high NHC bioavailability (>50%). Circulating NHC is then rapidly taken up from systemic circulation into cells via nucleoside transporters, where it is phosphorylated by host kinases to the pharmacologically active triphosphate, NHC-TP. NHC and NHC-TP were observed in all tissues analyzed from each species tested (mice, rats, dogs, monkeys, and ferrets), with the highest levels of NHC-TP typically observed in the spleen and lung. Additionally, MOV and/or NHC are taken up by all tissue culture cells

tested and converted to the pharmacologically active NHC-TP, and the intracellular NHC-TP levels are generally concentration-dependent.

Studies of the PK and metabolism of MOV/NHC support a low likelihood of interactions with other drugs. The predominant elimination pathway of NHC appears to be metabolism to uridine and cytidine which mix with the endogenous nucleotide pool, while renal excretion of NHC is minor. Both cytidine deaminase and the mitochondrial amidoxime reducing components (mARC1 and mARC2) have demonstrated the capability to convert NHC to endogenous pyrimidines in vitro. Given that the rapid hydrolysis of MOV to NHC involves at least two widely distributed high-capacity carboxylesterases (CES1 and CES2), and the uptake of NHC and formation of NHC-TP are by host transporters and kinases important in the regulation of pyrimidine nucleosides, it is unlikely that other drugs will impact the exposure of NHC-TP in tissues. While the similarity of NHC to cytidine (1 hydroxyl different) allows recognition by the nucleoside transporters and kinases which confer its intracellular uptake and activity, it is also consistent with the observed lack of either inhibitory or inductive activity of MOV/NHC towards any of the metabolic enzymes and transporters tested in vitro, further suggesting a low potential for drug-drug interactions (DDIs) between MOV/NHC and co-medications.

3.3 Nonclinical Safety

3.3.1 Overview of the Nonclinical Safety Program

MOV was evaluated in a comprehensive nonclinical safety program including:

- A standard battery of in vitro and in vivo safety pharmacology studies
- A standard battery of in vitro and in vivo genotoxicity assays (Ames assays, in vitro and in vivo micronucleus assays)
- Additional 28-day in vivo mutagenicity assays (an in vivo Pig-a mutation assay, and an in vivo mutation assay in Big Blue® transgenic rats)
- An exploratory nonstandard in vitro mammalian cell gene mutation assay (HPRT gene mutation assay) conducted by an independent academic laboratory
- Tolerability studies in mice, rats, dogs, nonhuman primates, and rabbits
- Repeat-dose toxicity studies of up to 3 months in rats and 1 month in mice and dogs
- Developmental and reproductive toxicity studies (including fertility studies in male and female rats, embryo-fetal developmental toxicity [EFD] studies in rats and rabbits, and a pre- and postnatal developmental [PPND] study in rats).

Nonclinical exposure margins of NHC to humans presented below were based on population PK (popPK) analysis in adults with COVID-19 from the Phase 2 part of the two Phase 2/3 (P001 and P002) clinical studies, where an 800 mg Q12H MOV dose resulted in systemic mean exposures AUC0-24hr of 75.6 μM*hr and Cmax of 10.8 μM. MOV AUC0-24hr exposure multiples were not calculated given that MOV is rapidly hydrolyzed to NHC and is generally undetectable in human plasma (LOQ of 0.0152 μM). Of note, MOV and NHC Cmax achieved in the nonclinical studies were much higher than the clinical Cmax of

0.026 μM and 10.8 μM, respectively, in COVID-19 patients at the MOV clinical dose of 800 mg Q12H.

3.3.2 Repeat-dose Toxicity

Repeat-dose toxicity studies of up to 3 months were performed in rats and up to 1 month in mice and dogs. Target organs of toxicity identified in the pivotal repeat-dose toxicity studies included bone marrow in dogs and growth plate of long bones in rats. These findings were not seen in other species. In addition, gastrointestinal toxicity and liver enzyme elevations were noted in the rat and dog 7-day tolerability studies at doses that exceeded the maximum tolerated doses. The details of these findings are outlined below.

Bone marrow/hematopoietic findings

In the 1-month repeat-dose toxicity study in dogs (doses of 6, 17, and 50 mg/kg/day), mild dose-related hematologic findings affecting all cell lines were observed following 7 days of dosing. More severe hematologic changes were apparent after 14 to 21 days of continuous dosing leading to pancytopenia, including severe thrombocytopenia and associated hemorrhage at 17 mg/kg/day (0.4-fold the clinical NHC AUC0-24hr exposure) and 50 mg/kg/day (2-fold the clinical NHC AUC0-24hr exposure). This resulted in early termination of treatment at 50 mg/kg/day after 2 weeks and at 17 mg/kg/day after 3 weeks. These hematologic changes were secondary to decreased cellularity of the bone marrow hematopoietic precursors (bone marrow depletion) observed at postmortem examinations. The hematopoietic changes were fully reversible at 17 mg/kg/day with essentially normal bone marrow and hematologic parameters following a 1-month recovery period. Animals in the 50 mg/kg/day group were euthanized approximately 10 days after treatment termination; hematopoietic changes were partially reversible during the shortened recovery period. Only minor, reversible, nonadverse hematopoietic changes were seen in animals administered 6 mg/kg/day for 28 days. The NOAEL in dogs was therefore 6 mg/kg/day (0.1-fold the NHC AUC0-24hr exposure at the 800 mg Q12H human dose).

These hematopoietic findings are of low risk for the proposed patient population. Hematologic changes observed after 7 days of dosing in dogs in the 28-day study were relatively mild compared with later time points and the bone marrow and hematologic changes demonstrated reversibility upon discontinuation of treatment. The proposed duration of treatment for COVID-19 is 5 days, and the clinical safety database shows no hematologic effects indicating bone marrow toxicity [Sec. 4.4].

There were no hematopoietic findings in rats dosed for 3 months up to 1000 mg/kg/day (9-fold [female] and 15-fold [male] the clinical NHC AUC0-24hr exposure), or in mice dosed for 1 month up to 2000 mg/kg/day (19-fold the clinical NHC AUC0-24hr exposure). Additionally, there were no hematologic changes observed in non-pivotal exploratory studies in female rabbits dosed for 2 weeks up to 1000 mg/kg/day (29-fold the clinical NHC AUC0-24hr exposure), or in rhesus monkeys dosed for 7 days up to 500 mg/kg/day (4-fold the clinical NHC AUC0-24hr exposure). Decreased hematology values, notably RETs (89%), white blood cells, and absolute lymphocyte counts (52%), were considered secondary to stress/decreases in food consumption/body weight at a non-tolerated dose of 2000 mg/kg/day

in a 7-day rat tolerability study (61-fold [female] or 91-fold [male] the clinical NHC AUC0-24hr exposure).

Bone/cartilage findings: Increased thickness of growth plate

Changes in the growth plate of bones were observed in the 3-month oral toxicity study in rats only, in males at ≥500 mg/kg/day (5-fold the clinical NHC AUC0-24hr at the 800 mg Q12H dose) and in females at 1000 mg/kg/day (9-fold the clinical NHC AUC0-24hr exposure). The findings consisted of an increase in the thickness of the growth plate (physis), associated with decreased bone formation at the end of long bones in males at 1000 mg/kg/day and thickening of the subarticular cartilage in males and females at 1000 mg/kg/day. Minimal thickening of subarticular cartilage was also observed in males at 500 mg/kg/day. There were no changes observed in remaining tissues in the femorotibial joint, including articular surfaces, ligaments, synovial tissue, other soft tissue, and the cortical bone. The NOAEL was 150 mg/kg/day in males (0.7-fold the clinical NHC AUC0-24hr exposure) and 500 mg/kg/day in females (3-fold the clinical NHC AUC0-24hr exposure).

There were no growth plate findings in rapidly growing rats dosed for 1-month up to 500 mg/kg/day (4-fold [female] and 8-fold [male] the clinical NHC AUC0-24hr exposure), in rapidly growing mice dosed for 1 month up to 2000 mg/kg/day (19-fold the clinical NHC AUC0-24hr exposure), or in dogs dosed for up to 14 days at 50 mg/kg/day (2-fold the clinical NHC AUC0-24hr exposure).

These growth plate findings are not relevant to adult humans, because growth plates are no longer present in the mature skeleton of adult humans.

The growth plate findings (seen after 3 months of continuous treatment, but not after 1 month of dosing) are of unclear significance in the context of short duration treatment in children. The changes were noted in rapidly growing rats (5 to 6 weeks of age at study start) that approximately doubled their body weights over the study duration. This very rapid bone growth cannot be directly translated to humans due to species-specific differences in skeletal development and bone turnover [30]. Further evaluation is being conducted in juvenile rats before initiation of pediatric clinical studies and results will be available to support the pediatric development program.

Gastrointestinal Findings and Liver Enzyme Elevations

Gastrointestinal findings (eg, stomach distention, emesis, diarrhea) and liver enzyme elevations were noted in the non-pivotal rat and dog 7-day tolerability studies at high doses that exceeded the maximum tolerated doses (2000 mg/kg/day in rats [61-fold (female) and 91-fold (male) the clinical NHC AUC0-24hr exposure] and ≥300 mg/kg/day in dogs [19-fold the clinical NHC AUC0-24hr exposure]).

Liver enzyme elevations consisted of ≤2-fold increases in ALT and/or AST in rats at 2000 mg/kg/day as well as ~2-fold increases in AST at 300 mg/kg/day, up to 5-fold increases in ALP and ALT, and 30-fold increases in AST at 1000 mg/kg/day in dogs (66-fold the clinical NHC exposure).

3.3.3 Genotoxicity

The mutagenic and genotoxic potential of MOV was comprehensively assessed in standard and follow-up regulatory in vitro and in vivo assays designed to detect potential effects on genes (ie, mutations); the overall conclusion was that MOV was not mutagenic or genotoxic in vivo.

MOV and NHC induced mutations in the bacterial reverse mutation assay (Ames assay) with or without an exogenous metabolic activation system. MOV did not induce chromosome damage in an in vitro micronucleus assay in the human TK6 cell line using short incubation (4-hour; with and without an exogenous metabolic activation system) and long incubations (27-hour; without an exogenous metabolic activation system) tested up to 1 mM, or in an in vivo micronucleus assay in rats administered MOV up to the limit dose of 2000 mg/kg/day for 2 days.

Merck also noted and took into consideration literature describing a positive in vitro mutagenicity result from an exploratory nonstandard in vitro mammalian cell gene mutation assay (HPRT gene mutation assay), conducted by an independent academic laboratory at the University of North Carolina [31]. It is important to note the assay was conducted in extreme conditions as the duration of exposure (32 days) was significantly longer than the maximum 6 to 24 hours recommended in the OECD regulatory test guideline (OECD Test Guideline Test No. 476). Additionally, the absence of appropriate cytotoxicity assessments, the resulting lack of calculation of mutant frequency per surviving cell, the high variability in background mutation rate between cultures and likelihood of nucleoside pool imbalance due to accumulation of cytidine and uridine over the 32-day continuous exposure [32] make interpretation of the results and comparison with existing published HPRT assay data problematic.

Consistent with current regulatory guidances (ICH S2[R1], ICH M7[R1], WHO/IPCS) which recommend follow-up in vivo testing to address the biological/in vivo relevance of in vitro positive results; two robust in vivo mutagenicity studies were performed in rats to understand the in vivo relevance of in vitro positive mutagenicity assays. Both Pig-a mutagenicity and Big Blue® (cII Locus) transgenic rodent assays were conducted per recommended guidelines by international groups [33] [34] [35] and OECD TG 488 [36], respectively. These assays included evaluation of standard tissues/cell populations including bone marrow (rapid proliferating tissue) and liver (slow proliferating tissue; high metabolizing capacity) for the Big Blue® (cII Locus) transgenic rodent assay, and reticulocytes and red blood cells for the Pig-a mutagenicity assay. The animals were administered MOV at doses up to the maximum tolerated dose, 500 mg/kg/day, and for longer durations (28 days) than the proposed 5-day clinical administration of MOV in humans. The negative results of these in vivo mutagenicity assays provide strong evidence that the in vitro mutagenicity is not relevant to in vivo mammalian systems. Potential reasons for lack of translation of in vitro findings to in vivo mammalian systems include differences in metabolism, pharmacokinetics, exposure, replication, and DNA repair processes within a whole animal model compared with in vitro test conditions.

In the in vivo Pig-a assay, MOV treatment resulted in a frequency of mutations in red blood cells and reticulocytes similar to spontaneous background levels in untreated historical control animals. At the highest dose (500 mg/kg), the mutation frequencies (number mutations per million cells) for red blood cell (2.6) and reticulocyte (10.98) were each well within the historical control range for untreated control animals (red blood cells: 0.4 to 7.78; reticulocytes: 0.57 to 16.08).The results were considered equivocal based on slight statistically significant ($p \leq 0.05$) increases in mutant red blood cells or reticulocytes in several MOV dose groups, when compared to the concurrent negative control group. These increases relative to the concurrent control did not demonstrate a statistically significant dose-related trend. The observed frequencies were within the 95% confidence limit, and thus, were considered not biologically meaningful. The positive control (N-ethyl-N-nitrosourea [ENU]) treatment produced a statistically significant increase in mutant frequencies for red blood cells and reticulocytes (red blood cells: 156.63; reticulocytes: 259.05) comparable with those generated in the historical positive control

According to regulatory guideline recommendations (ICH S2R1, OECD Genetic toxicology overview and the WHO/IPCS Harmonized Scheme on mutagenicity testing for chemical risk assessment), a repeat study is recommended as follow up to an equivocal result, eg. “chosen on a case-by-case basis (ordinarily on a different end point or in a different tissue, depending on toxicokinetics, metabolism and mode of action) "(WHO/IPCS Harmonized Scheme on mutagenicity testing). The follow up in vivo assay chosen in this case was the Big Blue® Transgenic F344 Rat assay (cII locus). In this study, MOV treatment at doses up to 500 mg/kg/day for 28 consecutive days was negative for the induction of cII mutants in the liver (slow proliferating tissue) and bone marrow (rapid proliferating tissue) of male transgenic Fischer 344 Big Blue® rats. Treatment with MOV did not cause any increases mutant frequency (number mutations per million cells) at the cII gene in the liver (34.1 at 500 mg/kg/day) or bone marrow (39.1 at 500 mg/kg/day), compared to controls (liver: 34.0; bone marrow: 33.0). The mutant frequencies for both bone marrow and liver were also within the 95% confidence limits of the laboratory historical control range for each tissue. The ENU positive control treatment produced a statistically significant increase in mutant frequencies for both tissues tested (liver: 221.7; bone marrow: 434.2), demonstrating the utility of the test system to detect and quantify induced mutants, following exposure to a known direct acting mutagen.

In conclusion, in two distinct rodent mutagenicity models, the effect of MOV treatment on mutation frequency was not differentiable from background. Overall, the comprehensive genotoxicity assessment in robust and well-characterized standard regulatory assays indicates MOV has low risk for genotoxicity.

3.3.4 Reproductive and Developmental Toxicity

MOV potential for reproductive and developmental toxicity was evaluated in a comprehensive nonclinical program including fertility studies in male and female rats, EFD studies in rats and rabbits, and a PPND study in rats. These studies are designed to evaluate the potential for developmental and reproductive effects through the whole reproductive life cycle.

A high dose of 1000 mg/kg/day was selected for a preliminary EFD study in rats. This dose produced severe maternal toxicity, resulting in the euthanasia of individual animals, and exceeded the maximum maternal tolerated dose. A high dose of 500 mg/kg/day was therefore selected for subsequent reproductive and developmental toxicity studies in pregnant rats. A high dose of 500 mg/kg/day was selected for the fertility study in male rats, based on the excessive body weight gain decrease observed in males at 1000 mg/kg/day in the 3-month toxicity study in rats.

A high dose of 1000 mg/kg/day was selected for the preliminary EFD study in rabbits. This dose resulted in decreased food consumption and decreased mean body weight gain with individual body weight losses. A high dose of 750 mg/kg/day was therefore selected for the definitive EFD rabbit study.

3.3.4.1 Fertility

The objective of the fertility study in female rats was to assess potential effects on fertility resulting from once daily oral administration of MOV to female rats (doses: 0, 100, 250, and 500 mg/kg/day), beginning approximately 2 weeks before cohabitation, and through mating and implantation. Assessment of reproductive performance was based on estrous cyclicity (pre-dose and during the premating dosing phase), mating, fertility, and ovarian and uterine examinations on gestation day (GD) 13. There were no MOV-related effects on estrous cyclicity, mating, fertility, pregnancy indices, or early embryonic development up to the highest dose tested, 500 mg/kg/day (2-fold the clinical NHC exposure).

The objective of the fertility study in male rats was to test for potential effects on fertility following once daily oral administration of MOV to male rats (doses: 0, 100, 250, and 500 mg/kg/day) beginning approximately two weeks before cohabitation, through mating, and until the day prior to sacrifice (approximately 6 weeks total). Assessment of reproductive performance was based on mating, fertility, and ovarian and uterine examinations of the untreated female rats mated with treated males. There were no MOV-related effects on mating, fertility, pregnancy indices, or early embryonic development indices up to the highest dose tested, 500 mg/kg/day (6-fold the clinical NHC exposure).

3.3.4.2 Embryo-fetal Developmental Toxicity

The objective of the EFD studies in rats and rabbits was to evaluate potential effects on embryo-fetal development resulting from once daily oral administration of MOV to pregnant rats and rabbits during the organogenesis period (GDs 6 through 17 in rats; GDs 7 through 19 in rabbits). Evaluation of developmental toxicity was based on embryonic/fetal viability (as assessed by numbers of corpora lutea, implantations, and live fetuses per pregnant female), fetal weights and sex ratios, and fetal external, coronal, visceral, and skeletal morphology.

In pregnant rats administered MOV during the organogenesis period (doses of 0, 100, 200, 500, and 1000 mg/kg/day in a preliminary EFD study, and 0, 100, 250, and 500 mg/kg/day in the definitive EFD study), developmental toxicity was observed at the highest doses of 1000 and 500 mg/kg/day. Developmental toxicity findings consisted of embryo-fetal lethality (post-implantation losses), teratogenicity (abnormal and/or small eye/eye socket, absent

kidney and axial skeleton abnormalities) and variations (cervical ribs and trace supernumerary ribs) at 1000 mg/kg/day (8-fold the clinical NHC exposure at 800 mg Q12H) and reduced fetal growth (reduced mean fetal body weight and delayed ossification) at ≥500 mg/kg/day (≥3-fold the clinical NHC exposure at 800 mg Q12H). There was no developmental toxicity at doses up to 250 mg/kg/day (0.8-fold the clinical NHC exposure at 800 mg Q12H). Maternal toxicity included decreased food consumption and body weight loss, resulting in the early euthanasia of individual animals at 1000 mg/kg/day and decreased body weight gain at ≥500 mg/kg/day.

In pregnant rabbits administered MOV during the organogenesis period (doses of 0, 60, 200, 500, and 1000 mg/kg/day in a preliminary EFD study, and 0, 125, 400, and 750 mg/kg/day in the definitive EFD study), developmental toxicity was limited to reduced mean fetal body weights at 750 mg/kg/day (18-fold the clinical NHC exposure at 800 mg Q12H). There was no developmental toxicity at up to 400 mg/kg/day (7-fold the clinical NHC exposure at 800 mg Q12H). Maternal toxicity included decreased food consumption and body weight gain at ≥400 mg/kg/day.

3.3.4.3 Pre- and Postnatal Developmental Toxicity

The objective of the PPND study was to evaluate potential effects on the development of the offspring resulting from once daily oral administration of MOV to female rats (doses of 0, 100, 250, and 500 mg/kg/day) from implantation through lactation and weaning. Female rats were administered MOV from GD 6 through lactation day 20. Assessment of preweaning F1 development was based on viability, clinical signs, body weight, and developmental landmarks. Assessment of postweaning F1 development was based on viability, clinical signs, body weights, food consumption, sexual maturation, changes in behavior (as evaluated by motor activity, acoustic startle habituation, and Morris water maze), reproductive performance, fertility, and macroscopic necropsy observations.

There were no MOV-related effects on development, growth, behavior, reproductive performance, and fertility of the F1 generation when F0 female rats were administered MOV from gestation day 6 to lactation day 20 up to 500 mg/kg/day (2-fold the clinical NHC exposure at 800 mg Q12H). Maternal effects were limited to non-adverse decreased body weight gain at ≥250 mg/kg/day during pregnancy (0.8-fold the clinical NHC exposure). NHC was detected in plasma of pups from lactating rats administered MOV.

3.3.5 Nonclinical Safety Conclusions

Overall, the nonclinical safety profile supports short-term clinical use of MOV in the intended adult population.

The comprehensive genotoxicity assessment in robust and well-characterized standard regulatory assays, detailed in Sec. 3.3.3, indicates MOV has low risk for genotoxicity.

Target organs identified in the pivotal repeat-dose studies were the bone marrow (in dogs only) and the growth plate (in rats only). Reversible hematopoietic findings affecting all cell lines was observed in dogs only. Hematologic changes were mild after 7 days of MOV administration and were more severe after 14 days of dosing. Similar findings were not

observed in other species. Notably, no hematologic effects indicating hematopoietic toxicity were seen in the clinical studies. The dose and time-dependent growth plate findings observed in only 1 species (rapidly growing rats) are not relevant to adult humans, given that growth plates are no longer present in the mature skeleton of adult humans.

Based on embryo-fetal lethality and teratogenicity noted in pregnant rats administered MOV during the organogenesis period (NHC AUC 8-fold the clinical NHC AUC exposure at 800 mg Q12H), the use of MOV is not recommended during pregnancy. Individuals of child-bearing potential should use effective contraception for the duration of NHC systemic exposure.

4 CLINICAL DEVELOPMENT PROGRAM

The clinical evaluation of MOV supporting the intended use under EUA consists of 6 studies conducted in humans to date (including a Phase 1 study in healthy participants, 3 smaller Phase 2a studies, and 2 large Phase 2/3 studies) across the various COVID-19 patient populations [Table 1].

Table 1 Summary of the Molnupiravir Clinical Development Program

Study ID Status	Countries	Study Description	Study Design	Dosing Regimens	Study Population	Number of Participants who received ≥1 dose
Phase 1 Study in Healthy Participants						
MK-4482-004 (P004; EIDD-2801-1001) Complete	UK, US[a]	First-in-Human study to evaluate safety and PK of MOV in healthy adults (Phase 1)	Part 1 double-blind, single dose Part 2 open-label, food effect study Part 3 double-blind, multiple dose	Part 1 MOV 50, 100, 200, 400, 600, 800, 1200, 1600 mg or placebo single dose Part 2 MOV 200 mg single dose Part 3 MOV 50, 100, 200, 300, 400, 600, 800 mg or placebo Q12H × 5.5 days	Males/Females (nonchildbearing potential), 18 to 60 years of age, healthy participants	Part 1: 64 (6 per dose levels and 16 in the placebo group) Part 2: 10 Part 3: 56 (6 per dose level and 14 in the placebo group)
Phase 1/2a Studies in Participants with COVID-19						
MK-4482-005 (P005; AGILE CST-2) Ongoing	UK	Dose-ranging study to evaluate safety and efficacy of MOV (Phase 1/2)	Phase 1 open-label (standard-of-care-controlled) Phase 2 double-blind, placebo-controlled	Phase 1 2:1 MOV 300, 600, 800 mg or control BID × 10 doses Phase 2 1:1 MOV 800 mg or placebo BID × 10 doses	Males/Females, ≥60 years of age (or ≥50 years of age with ≥1 comorbidity), non-hospitalized, with lab-confirmed SARS-CoV-2	Planned enrollment: 198 As of 31-OCT-21, Phase 1: 18 (6 per dose level) Phase 2: 132
MK-4482-006 (P006, EIDD-2801-2003) Complete	US	Dose-ranging study to evaluate safety and efficacy of MOV in non-hospitalized adults (Phase 2a)	double-blind, placebo-controlled	Part 1 1:1 MOV 200 mg or placebo BID x 5 days Parts 2 to 9 3:1 MOV up to 800 mg or placebo BID x 5 days	Males/Females, ≥18 years of age, non-hospitalized with lab-confirmed SARS-CoV-2	Part 1 MOV 200 mg: 23 Placebo: 23 Parts 2 to 9 MOV 400 mg: 62 MOV 800 mg: 55 Placebo: 39
MK-4482-007 (P007, EIDD-2801-2004) Ongoing	US	Dose-ranging study to evaluate safety and efficacy of MOV in hospitalized adults (Phase 2a)	double-blind, placebo-controlled	Part 1 1:1:1 MOV 200, 400 mg or placebo BID x 5 days Parts 2 to 4 2:1 MOV (Part 2=400 mg; Part 3=800mg; Part 4=up to 800 mg) or placebo BID x 5 days	Males/Females, ≥18 years of age, hospitalized with lab-confirmed SARS-CoV-2	Planned enrollment: 84 As of 01-OCT-2021: 65

Study ID Status	Countries	Study Description	Study Design	Dosing Regimens	Study Population	Number of Participants who received ≥1 dose
Phase 2/3 Studies in Participants with COVID-19						
MK-4482-001 (P001; MOVe-IN) Enrollment Complete	16 countries[b]	Study to evaluate efficacy, safety, PK of MOV in hospitalized adults (Phase 2/3)	double-blind, placebo-controlled	Phase 2 1:1:1:1 MOV 200, 400, 800 mg or placebo Q12H × 5 days Phase 3 1:1 MOV (selected dose) or placebo Q12H x 5 days	Males/Females, ≥18 years of age, hospitalized with lab-confirmed SARS-CoV-2	Phase 2 MOV 200 mg: 73 MOV 400 mg: 73 MOV 800 mg: 72 Placebo: 75 Phase 3 will not be conducted
MK-4482-002 (P002; MOVe-OUT) Enrollment Complete	23 countries[c]	Study to evaluate efficacy, safety, PK of MOV in non-hospitalized adults (Phase 2/3)	double-blind, placebo-controlled	Phase 2 1:1:1:1 MOV 200, 400, 800 mg or placebo Q12H × 5 days Phase 3 1:1 MOV (selected dose) or placebo Q12H x 5 days	Males/Females, ≥18 years of age, non-hospitalized with lab-confirmed SARS-CoV-2	Phase 2 MOV 200 mg: 74 MOV 400 mg: 77 MOV 800 mg: 74 Placebo: 74 Phase 3 IA[d] MOV 800 mg: 386 Placebo: 379 Phase 3 Total[d]: 1433

BID=twice daily; COVID-19=coronavirus disease 2019; EIDD =Emory Institute for Drug Development; FE=food effect; IA=interim analysis; ID=identification; MAD=multiple-ascending dose; MOV=molnupiravir (MK-4482, EIDD-2801); PCR=polymerase chain reaction; PK=pharmacokinetics; po = oral(ly); Q12H = every 12 hours RNA=ribonucleic acid; SAD=single-ascending dose; SARS-CoV-2=SARS-associated coronavirus-2; UK=United Kingdom; US=United States

[a] One site in the UK enrolled all study participants. No sites in the US enrolled participants.

[b] P001 countries include Brazil, Canada, Chile, Colombia, France, Israel, Mexico, Philippines, Poland, Russia, South Africa, South Korea, Spain, Ukraine, UK, US

[c] P002 countries include those with sites that achieved site ready: Argentina, Brazil, Canada, Chile, Colombia, Egypt, France, Germany, Guatemala, Israel, Italy, Japan, Mexico, Philippines, Poland, Russia, South Africa, Spain, Sweden, Taiwan, Ukraine, UK, US.
A total of 20 countries had randomized at least 1 participant in Phase 3 and 173 sites had achieved site ready at the time enrollment in P002 was closed.

[d] The Phase 3 IA occurred per protocol after 775 participants (50% of the planned Phase 3 enrollment) were randomized (765 received at least 1 dose) and followed through Day 29 in P002. Upon review of the Phase 3 IA results, as the primary efficacy endpoint was met, enrollment was closed at the recommendation of the eDMC and in consultation with the US FDA.

4.1 Overview of the Clinical Development Plan

The results from 6 clinical studies supporting the use of MOV for the treatment of mild to moderate COVID-19 in adults are summarized in this document [Table 2].

Table 2 Clinical Study Results Summarized in this Document

Study	Phase (Population)	Results Summarized in this Document
Clinical Pharmacology		
MK-4482-004 (P004)	Phase 1 (healthy participants)	Final results for safety and PK
Dose Ranging		
MK-4482-001 (P001)	Phase 2 (hospitalized)	IA[a] results (all Phase 2 participants who completed Day 29) for safety, efficacy (including virology), and PK
MK-4482-002 (P002)	Phase 2 (non-hospitalized)	IA[a] results (all Phase 2 participants who completed Day 29) for safety, efficacy, (including virology), and PK
MK-4482-006 (P006)	Phase 2a (non-hospitalized)	Final results for safety, virology, and PK
Pivotal Clinical Study		
MK-4482-002 (P002)	Phase 3 (non-hospitalized)	IA[b] results (50% of Phase 3 planned participants complete through Day 29) for safety, efficacy, and available virology results
Supplemental (blinded safety only)		
MK-4482-005 (P005)	Phase 1/2 (non-hospitalized)	Preliminary (blinded) summary of safety
MK-4482-007 (P007)	Phase 2a (hospitalized)	Preliminary (blinded) summary of safety

IA=interim analysis, PK=Pharmacokinetics

[a] The efficacy and safety results presented for the Phase 2 part of P001 and P002 are primarily comprised of results from the Phase 2 IA (planned when all Phase 2 participants completed through Day 29). At the time of the database lock for the Phase 2 IAs, testing for evaluation of virologic response was ongoing; hence virology data is from the Phase 2 IAs or a later database lock.

[b] The Phase 3 IA for P002 was planned in order to assess futility/early efficacy when 50% of the planned Phase 3 enrollment had completed the Day 29 follow-up visit. At the time of the database lock for the Phase 3 IA, testing for evaluation of virologic response was ongoing; hence, virology data for the P002 Phase 3 IA is based on results available at the time of database lock, and baseline viral clade data that became available through 01-NOV-2021.

4.1.1 P004 (Phase 1 Study in Healthy Participants)

P004 is a completed Phase 1 study that assessed the safety and PK of single ascending and multiple ascending doses of MOV in healthy adult participants (Part 1: single dose of MOV 50 to 1600 mg, Part 2: single dose of MOV 200 mg with a high fat meal, and Part 3: MOV 50 to 800 mg as multiple doses Q12H for 5.5 days). A total of 130 participants were enrolled (n=100 MOV; n=30 placebo). MOV was well tolerated at all doses. The results indicate that NHC PK is linear and dose-proportional, with single-dose PK exposure predictive of multi-dose exposure. No accumulation was observed following multiple doses. NHC had a short effective plasma half-life (~3.3 hours), which resulted in minimal accumulation after

multiple dosing, with a longer terminal phase characterized by a half-life of up to ~19 hours. No significant food effect was observed with a single MOV 200 mg dose, indicating that MOV can be dosed without regard to food.

4.1.2 P001 (Phase 2/3 Study in Hospitalized Adults with COVID)

P001 was designed as a Phase 2/3, 2-part study to evaluate the efficacy, safety, and PK of MOV in hospitalized adults with laboratory-confirmed SARS-CoV-2 infection and symptom onset within 10 days prior to randomization. The primary efficacy endpoint was to evaluate the rate of sustained recovery from randomization through Day 29 for participants receiving MOV compared with placebo. Exploratory endpoints supporting dose selection included change from baseline in SARS-CoV-2 RNA, percentage of participants with undetectable SARS-CoV-2 RNA at various timepoints, viral RNA errors as assessed by comparison of baseline and post-baseline virus sequencing, and PK parameters.

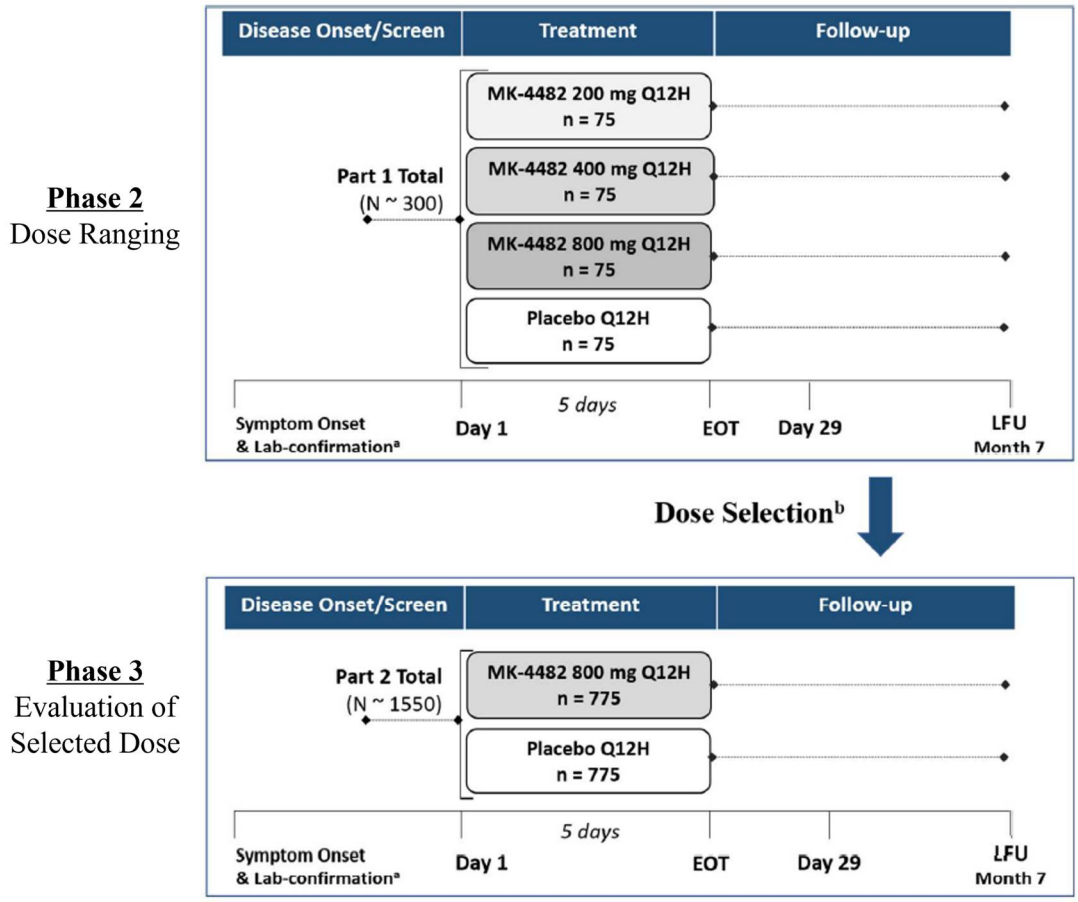
In the completed Phase 2 part of P001, a dose range evaluation was performed to support the dose selection of MOV for further evaluation in Phase 3. Participants were randomized 1:1:1:1 to receive MOV 200, 400, or 800 mg or placebo Q12H for 5 days. A protocol-specified IA was performed when all Phase 2 participants were enrolled (N=304) and completed the Day 29 visit. Results from Phase 2 showed no clear effect of MOV treatment on sustained recovery for hospitalized participants in P001. MOV doses were well tolerated with no dose-limiting toxicity observed at the highest dose.

The Phase 2 results from P001 and P002 indicated that treatment with MOV is likely to have a greater benefit if initiated earlier in the disease course during peak viral replication (≤5 days of symptom onset) compared with initiation during the later stages of disease when the host inflammatory response predominates. As patients who are hospitalized due to COVID-19 are likely to be later in the course of disease and early initiation of MOV treatment may be difficult in this population, the Phase 3 part of P001 was not conducted.

4.1.3 P002 (Phase 2/3 Study in Non-Hospitalized Adults with COVID)

P002 is an ongoing Phase 2/3, 2-part study evaluating the efficacy, safety, and PK of MOV in non-hospitalized adults with laboratory-confirmed SARS-CoV-2 infection [Figure 3]. The primary efficacy objective was to evaluate the percentage of participants who are hospitalized and/or die through Day 29 for participants receiving MOV compared with placebo. SARS-CoV-2 vaccines were prohibited any time prior to randomization and through Day 29.

Figure 3 Protocol 002 (Phase 2/3) Study Design



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 had laboratory-confirmed SARS-CoV-2 infection with signs/symptoms attributable to COVID-19 for ≤7 days (Phase 2) or ≤5 days (Phase 3) prior to randomization.
[b] The dose was selected based on virologic, clinical, and PK results from the Phase 1 and Phase 2 studies [Sec. 4.3.1].

P002 Phase 2

The completed Phase 2 part of P002 enrolled participants with symptom onset within 7 days prior to randomization. Participants with mild COVID-19, and at least 75% of participants overall, were to have at least 1 characteristic (eg, age >60 years) or underlying medical condition (eg, obesity, diabetes mellitus) associated with being at increased risk for severe illness from COVID-19.

In Phase 2, a dose range evaluation was performed to support the dose selection of MOV for further evaluation in Phase 3. Participants were randomized 1:1:1:1 to receive MOV 200, 400, or 800 mg or placebo Q12H for 5 days. Exploratory endpoints supporting dose selection included change from baseline in SARS-CoV-2 RNA, percentage of participants with undetectable SARS-CoV-2 RNA at various timepoints, viral RNA error rate as assessed by comparison of baseline and post-baseline virus sequencing, and PK parameters. A protocol-

specified IA was performed when all Phase 2 participants were enrolled (N=302) and completed the Day 29 visit.

While the Phase 2 results showed that the percentage of participants who were hospitalized or died through Day 29 was comparable across intervention groups, subgroup analyses (post-hoc) showed clinical benefit of MOV for participants with time to symptom onset within 5 days of randomization and with risk factors for developing severe COVID-19. The Phase 2 results also showed that all MOV doses were well tolerated with no dose-limiting toxicity observed at the highest dose (800 mg). These results supported proceeding to Phase 3 in non-hospitalized participants. The MOV 800 mg Q12H dose was selected based on virologic, clinical, PK, and safety results from the Phase 1 and Phase 2 studies [Sec. 4.3.1].

Based on the Phase 2 results from P001 and P002, the study criteria for the Phase 3 part of P002 were revised (by a protocol amendment) to randomize participants within 5 days of symptom onset. In addition, all participants in Phase 3 were to have mild or moderate COVID-19 and at least 1 characteristic (eg, age >60 years) or underlying medical condition (eg, obesity. diabetes mellitus) associated with being at increased risk for severe illness from COVID-19.

P002 Phase 3

Phase 3 of P002 is ongoing. Participants were randomized 1:1 to receive either MOV 800 mg or placebo Q12H for 5 days. A total of 775 participants (50% of the planned Phase 3 enrollment) were randomized, followed for the primary efficacy evaluation through Day 29, and included in the protocol-specified Phase 3 IA presented in this document.

Results from the Phase 3 IA demonstrated the clinical efficacy of MOV 800 mg for the proposed indication. Upon review of the Phase 3 IA results, as the primary efficacy endpoint was met, enrollment was closed at the recommendation of the external data monitoring committee (eDMC) and in consultation with the US FDA. At the time enrollment was closed in P002, a total of 1433 participants had been randomized into Phase 3.

Additionally, the safety results from the Phase 3 IA demonstrated that MOV is well tolerated in patients with COVID-19 and support the favorable safety profile of MOV.

4.1.4 P006 (Phase 2a Study in Non-Hospitalized Adults with COVID)

P006 is a completed Phase 2a study that assessed the safety and efficacy of 200, 400, and 800 mg of MOV compared with placebo in non-hospitalized adult participants with laboratory-confirmed SARS-CoV-2 infection and symptom onset ≤7 days prior to study entry. The primary efficacy objective for the study was to evaluate if MOV reduces the time to viral RNA negativity as assessed by RT-PCR of nasal swabs.

The results from P006 contributed to dose selection of MOV 800 mg. The median time to clearance of SARS-CoV-2 RNA was shorter, and the decrease from baseline in SARS-CoV-2 RNA viral load was greater for the MOV 800 mg group compared with placebo. Additionally, the percentage of participants with infectious, culture-positive, SARS-CoV-2

(assessed by an infectivity assay) decreased faster for participants treated with MOV 800 mg compared with placebo. MOV was well tolerated at all doses.

4.1.5 P005 and P007 (Blinded Studies in Adults with COVID)

P005 (a Phase 1/2 ongoing blinded study) is evaluating MOV in non-hospitalized adults with COVID-19 and symptom onset ≤5 days prior to randomization. P007 (a Phase 2a ongoing blinded study) is evaluating MOV in hospitalized adults with COVID-19 and symptom onset ≤7 days prior to randomization.

4.2 Overview of Clinical Pharmacology

The clinical pharmacology evaluation of MOV includes the Phase 1 study in healthy participants (P004) and a PopPK analysis including data from P004 and the Phase 2 part of P001 and P002. Exposure-response modeling was performed using efficacy data from the 3 Phase 2 studies in participants with COVID-19 (P001, P002, P006) to support dose selection [Sec. 4.3.1].

As renal and hepatic elimination do not significantly contribute to elimination of MOV or NHC, no meaningful effect of renal or hepatic impairment on MOV or NHC PK is expected, and no dedicated renal or hepatic impairment studies were conducted. No DDIs are expected because of the routes of MOV and NHC uptake and elimination. Also, in vitro data indicate neither MOV nor NHC are inhibitors or inducers of major metabolic enzymes or transporters. Therefore, no DDI studies were conducted.

4.2.1 Pharmacokinetics in Healthy Participants and Participants with COVID

The PopPK analysis included 2834 NHC concentrations above the lower limit of quantification from 497 participants, including 99 healthy participants from P004 and 398 participants with COVID-19 across the Phase 2 parts of P001 and P002.

The following key results were observed:

- Following oral administration, MOV is converted to NHC during or after absorption, likely involving the high capacity and widely distributed CES1 and CES2 carboxylesterases. MOV was quantifiable in only a minority of participants and only at early timepoints with peak concentrations of MOV being <0.5% of NHC.
- The median time to maximum plasma concentration (Tmax) of NHC is approximately 1.5 hours. Plasma concentrations of NHC decline with an effective t1/2 of 3.3 hrs. There is minimal accumulation with Q12H dosing.
- The PK of NHC following administration of MOV is similar in participants with COVID-19 and healthy participants.
- The mean Cmax (relevant PK parameter for safety) and AUC0-12hr (relevant PK parameter for efficacy) for NHC is 10.8 μM and 37.8 hr*μM, respectively, following 5 days of dosing with MOV 800 mg Q12H (Phase 2 of P001 and P002).
- AUC and Cmax for NHC increase approximately dose proportionally.

4.2.2 Effect of Intrinsic and Extrinsic Factors

Intrinsic Factors

The impact of age, sex, BMI, weight, race, ethnicity, and geographic region on the PK of NHC was evaluated using PopPK modeling and was associated with <2-fold alterations in exposures.

Renal impairment is not anticipated to meaningfully impact on the PK of NHC. Minimal renal involvement in the elimination of NHC was observed in P004, with 3% of an 800 mg dose of MOV taken every 12 hours excreted as NHC in urine over 12 hours. In P001 and P002, the PK of NHC in participants with moderate or mild renal impairment (eGFR ≥30 to <90 mL/min/1.73 m^2, MDRD calculation) was comparable with results in participants with normal renal function. Based on these results and the route of elimination for MOV and NHC, severe renal impairment and ESRD are not expected to have a significant effect on NHC elimination. Therefore, no dedicated study of renal impairment was conducted and no dose adjustment in patients with any degree of renal impairment is required.

Hepatic elimination is not expected to be a major route of elimination for NHC based on nonclinical data. Drug absorption is not expected to be altered in hepatic impairment due to high solubility in buffers with and without bile acids. Therefore, no dedicated hepatic impairment study was conducted, and no dose adjustment is proposed in patients with any degree of hepatic impairment.

Extrinsic Factors

In P004, a standard high fat meal did not significantly impact the extent of MOV and NHC absorption; the geometric mean ratio (90% CI) for NHC AUC0-inf and AUC0-last were 0.955 (0.881, 1.03) and 0.959 (0.881, 1.04), respectively. Food slowed the absorption rate as evidenced by a 2-hour delay in NHC Tmax and a 35.6% reduction in Cmax.

MOV is unlikely to be a victim or perpetrator of CYP-related DDIs based on its anticipated metabolic pathways and lack of CYP inhibition/induction in vitro. Given that the hydrolysis of MOV to NHC is likely by high-capacity esterases, and the uptake of NHC and formation of NHC-TP are by host transporters and kinases important in the regulation of pyrimidine nucleotides, it is unlikely that other drugs will impact the exposure of NHC-TP in tissues. In the PopPK analysis, remdesivir had no effect on NHC PK when used as a concomitant medication in P001 and P002. In addition, MOV and NHC did not inhibit or induce the activity of any of the xenobiotic metabolic enzymes and transporters tested in vitro. These results suggest that the potential for DDIs between MOV/NHC and co-medications is low. Therefore, no clinical drug-drug interaction studies were conducted.

MOV and NHC have properties of high solubility and high intestinal permeability/absorption. MOV does not show significant pH-dependent solubility over gastrointestinal pH values. Based on these data, gastric acid reducers are not expected to have a meaningful effect on the absorption of MOV.

Key conclusions of the effect of intrinsic and extrinsic factors are:

- The 800-mg dose of MOV can be used in patients with COVID-19 with no dose adjustment due to age, sex, body weight, race, ethnicity, geographic region, or renal or hepatic impairment.
- MOV may be administered without regard to food. Co-administration of MOV with food does not have a clinically meaningful effect on the plasma exposures of NHC.
- MOV is not a substrate, inhibitor or inducer of major metabolic enzymes or transporters, and is not expected to meaningfully interact with other drugs.
- Gastric acid modifying agents are not expected to have a meaningful effect on MOV or NHC PK.

4.2.3 Dose Selection

The MOV 800 mg Q12H dose was selected for evaluation in Phase 3 for P002 based on virologic, clinical, and PK results from the Phase 1 and Phase 2 studies [Sec. 4.3.1].

4.3 Overview of Clinical Efficacy

The clinical efficacy of MOV was demonstrated based on the IA results from the Phase 3 portion of P002. Efficacy results from the Phase 2 dose-ranging studies (P001, P002, P006) are presented as evidence for the dose selection of MOV 800 mg.

4.3.1 Phase 2 Clinical Studies – Dose Selection

The selection of the MOV clinical dose of 800 mg Q12H for evaluation in P002 Phase 3 was based on the totality of the evidence provided by:

- Virologic response (viral load, infectivity, viral error analysis) results from Phase 2 (P001, P002, P006)
- Clinical efficacy trends (P002 Phase 2)
- PK analyses, including PopPK [Sec. 4.2.1] and exposure-response modeling, from Phase 2 (P001, P002)
- Clinical safety data from P004, P001, P002, and P006 available at the time of dose selection [Sec. 4.4.4].

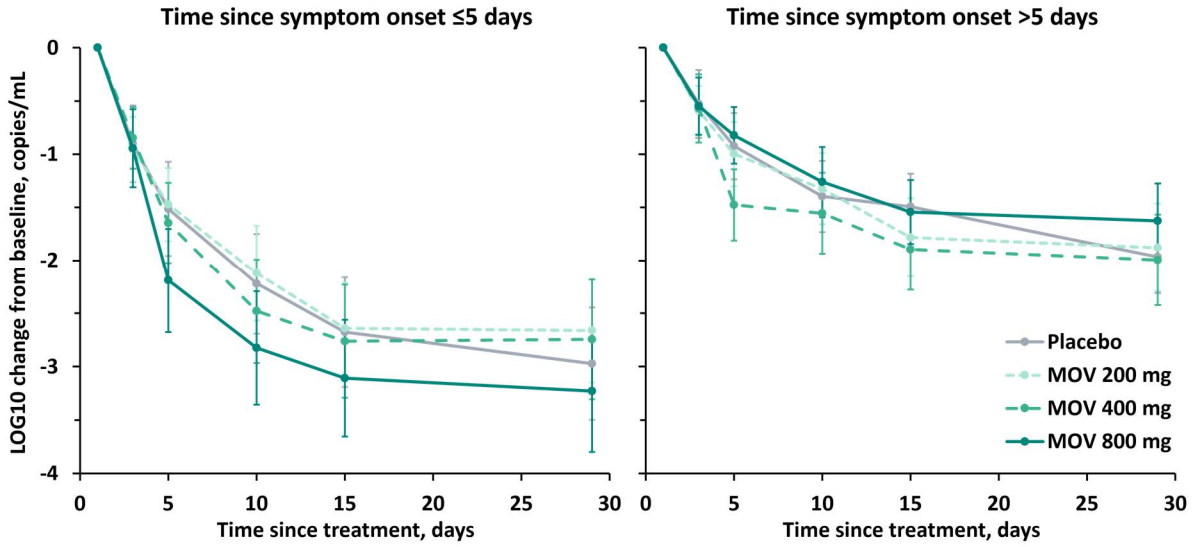
4.3.1.1 Virologic Response

The SARS-CoV-2 genotypes present at baseline in Phase 2 of P001 and P002 were representative of clades circulating globally at the time of enrollment (OCT-2020 to JAN-2021). The most frequent (≥5% in either group) genotype clades (P001; P002) were: 20A (20.4%; 23.9%), 20B (51.3%; 38.1%), 20C (9.7%; 12.9%), 20E (6.2%; 5.2%), and 20G (5.3%; 15.5%).

SARS-CoV-2 RNA

In Phase 2 of P001 and P002, decreases in SARS-CoV-2 RNA from baseline (>10^6 copies/mL) were larger among participants treated ≤5 days from symptom onset, with the MOV 800 mg group having the largest mean decrease in SARS-CoV-2 RNA at all timepoints [Figure 4]. For participants treated >5 days after symptom onset, the mean decreases in SARS-CoV-2 RNA were comparable across intervention groups at all timepoints.

Figure 4 Mean Change from Baseline in SARS-CoV-2 RNA by Time of Symptom Onset MITT Population (P001 Phase 2 and P002 Phase 2)

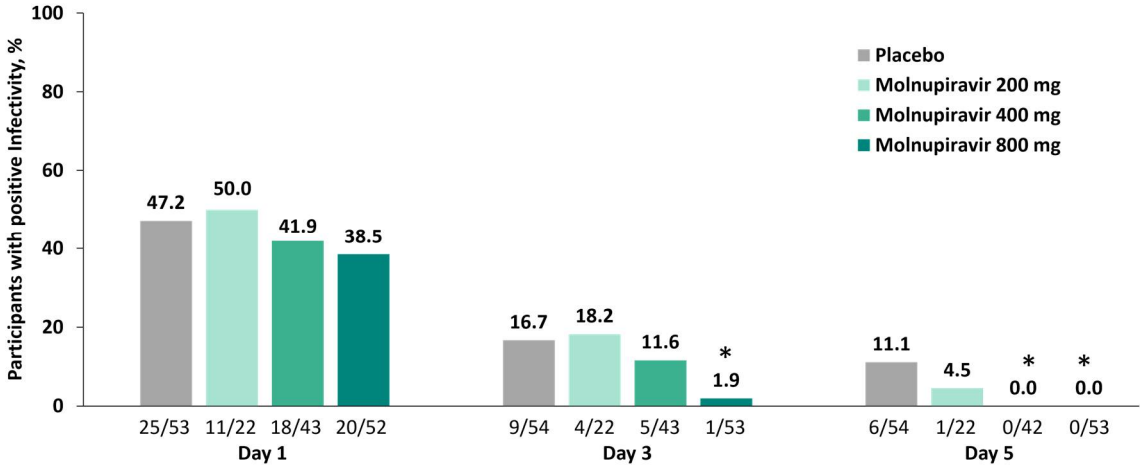


In P006, the median time to undetectable SARS-CoV-2 RNA was shorter for the MOV 800 mg group (14 days [95% CI: 13, 14]) compared with placebo (15 days [95% CI: 15, 27]). The percentage of participants who achieved undetectable SARS-CoV-2 RNA at Days 3, 5, 7, 14, and 28 was higher in the MOV 800 mg group compared with placebo with the greatest differences observed at Day 5 (30.2% vs. 13.1%) and Day 28 (95.8% vs. 82.1%). Beginning at Day 3, larger decreases from baseline in mean SARS-CoV-2 viral load were observed for the MOV 800 mg group compared with placebo and the MOV 200 and 400 mg groups.

Viral Infectivity

Treatment with MOV led to a rapid decline in infectious, culture-positive, virus (as evaluated in nasopharyngeal [NP] samples with viral RNA titers ≥100,000 copies/mL using a plaque assay in Vero cells) in Phase 2 of P001 and P002, and P006. As demonstrated in P006, all participants who received MOV 400 or 800 mg cleared infectious virus by Day 5. In contrast, 11.1% of participants in the placebo group had infectious virus detected on Day 5 [Figure 5]. Similar results were observed in Phase 2 of P001 and P002.

Figure 5 SARS-CoV-2 Infectivity Results MITT Population (P006)



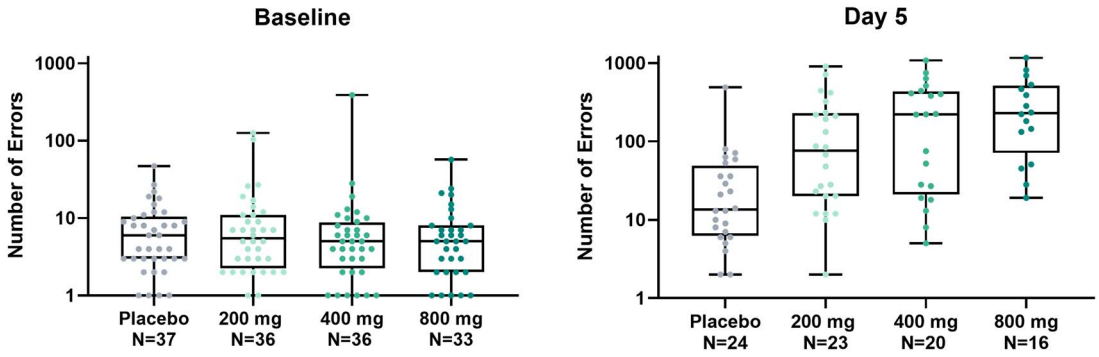
* p<0.05

Viral RNA Error Rate

Next generation sequencing (NGS) was performed on virus from nasal swabs at baseline and during treatment in Phase 2 of P001 and P002, and P006 to analyze the frequencies of viral RNA errors. Consistent with the MOA of MOV, an increased SARS-CoV-2 RNA error rate across the viral genome was observed in postbaseline samples from participants who received MOV compared with placebo.

As observed in P002 Phase 2, the highest mean SARS-CoV-2 RNA error rate (number of mutations/10,000 bases, [SD]; allele frequency ≥2%) occurred in the MOV 800 mg group at Day 5 (7.6 [7.69]); in contrast, the viral RNA error rate in the placebo group was 2.7 [3.70]). Results from an analysis of low allele frequency 0.4% to 10% (minor error analysis) also showed a linear trend in dose-response relationship between MOV dose level and the median number of nucleotide substitutions across the SARS-CoV-2 genome; the highest number of errors was observed at the MOV 800 mg dose [Figure 6].

Figure 6 Number of Errors Detected in SARS-CoV-2 Genome Nasopharyngeal Samples Intent-to-Treat Population (P002 Phase 2)



Each point represents the number of minor variants in one participant. Boxes are drawn between the 25th and 75th percentile of the data. The central horizontal lines correspond to the median.
Source: [Ref. 5.3.5.3: 07W3MS]

Errors occurring in the viral genome were further characterized in Phase 2 of P001 and P002 by determining the frequency of nucleotide transition and transversion errors in sequences at Day 5 compared with baseline. Consistent with the MOA of MOV, higher mean numbers of transition errors were observed across the genome in NP samples from participants in the MOV 800 mg group compared with placebo [Table 3].

Table 3 Mean Number of Transition Errors at Day 5 (EOT) Nasopharyngeal Samples MITT Population (P001 Phase 2 and P002 Phase 2)

Transition	P001 Phase 2		P002 Phase 2	
	MOV 800 mg (n=13)	Placebo (n=10)	MOV 800 mg (n=14)	Placebo (n=20)
C to U	5.9	3.1	9.0	2.6
U to C	2.0	0.2	2.5	0.2
G to A	1.5	0.1	5.7	0.2
A to G	0.9	0.6	2.6	0.3

n = number of participants with both baseline and post-baseline SARS-CoV-2 gene sequencing data at Day 5
EOT = end-of-treatment (Day 5 of the study)

Mean numbers of nucleotide transversions were low in all groups in both studies. These results are consistent with results from nonclinical animal model studies that showed a higher number of nucleotide transitions, compared with transversions, in viral RNA recovered from MOV-treated animals infected with SARS-CoV-2 [37].

Treatment-Emergent Amino Acid Variant Analysis

An analysis of NGS data was performed among the participants with paired baseline and post-baseline samples (nasopharyngeal [NP] and oropharyngeal [OP]). This analysis was performed to determine if treatment with MOV selected for specific amino acid substitutions

in the viral replicase complex (with the potential to confer resistance to MOV) and in the Spike protein (with the potential to impact the efficacy of monoclonal antibody therapies that target Spike). A variant frequency cutoff of ≥5% was used to distinguish between errors associated with the MOA of MOV (which would be expected to occur at a much lower frequency) and those possibly associated with reduced MOV susceptibility. The analysis focused on treatment-emergent variants that occurred at a frequency of ≥5% in ≥2 participants in the combined MOV groups.

In P001, no treatment-emergent amino acid substitutions were detected in ≥2 participants in the combined MOV groups (n=89) for any of the replicase complex genes (nsp7-14), including the viral RNA dependent RNA polymerase (RdRp; nsp12).

Treatment emergent changes in the Spike protein coding sequence were observed in both MOV and placebo participants in P001. Deletions ΔL141-Y144 and ΔY145 and substitution P681H were observed in 2 MOV treated participants each; the ΔY145 was also observed in a placebo participant. One of these MOV participants had multiple spike changes (ΔY145, N501Y and P681H) with a high number changes emergent at other genome locations. This participant was subsequently found to have switched genotypes between baseline (Clade 20E) and Day 3 (Clade 20B), suggesting either possible co-infection or sample processing error. All of the emergent changes in spike in MOV participants were deletions or transversion errors; these types of changes are not associated with the MOA of MOV which results in transition errors (eg, C to U, G to A).

Similar to P001, in P002, no treatment emergent substitutions were detected in RdRp (nsp12) in ≥2 participants in the combined MOV groups (n=113). In the viral helicase protein (nsp13), a A446T substitution was detected in samples from 2 participants, 1 each in the 200 and 800 mg groups. In the viral exonuclease (nsp14), 2 participants had a substitution at position A220S or A220V and 2 participants had a V466I substitution detected. Neither the nsp14 A220S or A22V substitutions affected phenotypic susceptibility of SARS-CoV-2 replicons to MOV in cell culture. The impact of nsp13-A446T and nsp14-V466I on susceptibility to MOV is being evaluated. None of the MOV participants with treatment-emergent substitutions in replicase complex genes (nsp7-14) met the primary endpoint of hospitalization or death.

Treatment-emergent amino acid substitutions in the spike protein coding sequence were observed in both MOV and placebo participants in P002. Substitutions G261I/V, T385I, E484K, P681H, A1022T were observed in samples in 2 MOV treated participants each. In single MOV participants, substitutions, or deletions/insertions in the hypervariable N-terminal region between amino acids 139-145 (P139S, ΔP139-Y145, ΔL141-144, ΔL141-144/Fins, ΔL145) were observed. The G261I/V (N-terminal domain), T385I (RBD) and A1022T (S2) substitutions have not been associated with loss of antibody binding. The spike substitution E484K (receptor binding domain, RBD), P681H and N-terminal region 139-145 changes, have been observed in some SARS-CoV-2 variants of concern; however, the P681H substitution and 139-145 region deletions were not transition errors and therefore, unlikely attributable to treatment with MOV.

Several substitutions in Spike were also identified in both a single MOV and a single placebo participant (S297L, S884F) or in placebo participants only (eg, M153T, G446V).

In MOV participants with two or more evaluable post baseline samples, emergent mutations were only observed in a single sample on Day 3 but not at Day 5 or decreased in frequency from Day 3 to Day 5, arguing against selection.

Importantly in both P001 and P002 trials, no MOV-treated participant with substitutions, in either replicase or spike genes, had infectious virus that could be recovered in post baseline samples. In contrast, 2 participants in the placebo arm with amino acid changes in spike had infectious virus recovered at Day 5. Together the totality of data from P001 and P002 is consistent with the preclinical findings indicating that MOV has a high barrier to resistance and does not select for infectious SARS-CoV-2 variants with substitutions in the replicase complex or spike genes.

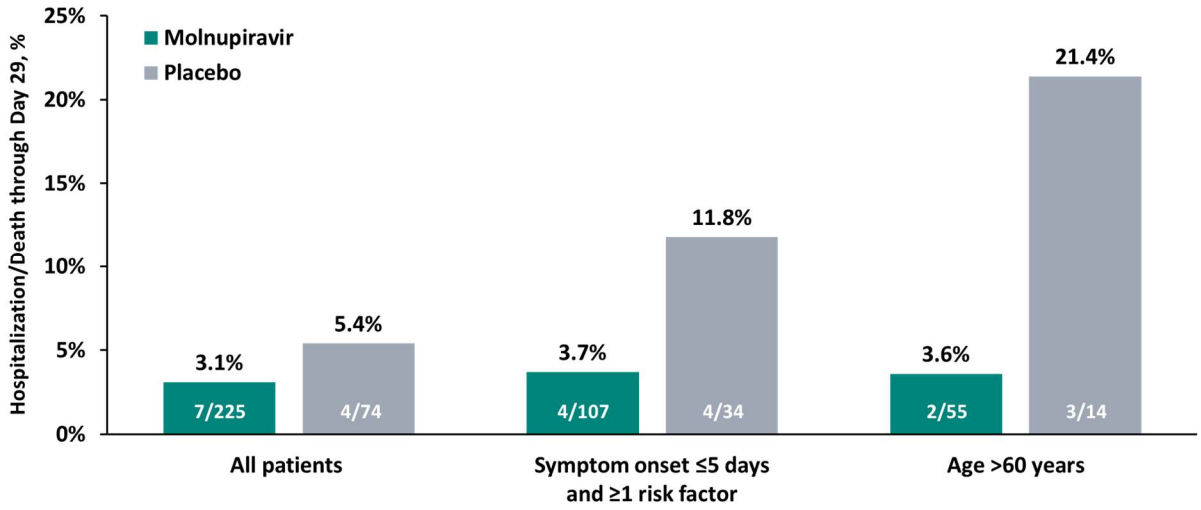
4.3.1.2 Clinical Efficacy

The primary endpoint in P002, a composite endpoint of hospitalization/death, was evaluated in the Phase 2 part of the study to support MOV dose selection; no hypothesis testing was planned or conducted for Phase 2. The efficacy analyses were based on the MITT population (defined as all participants who received at least 1 dose of study intervention), which included 225 participants in the MOV group (n=74 MOV 800 mg; n=74 placebo). At baseline, participants in P002 (Phase 2) were non-hospitalized with COVID-19 with symptom onset within 7 days prior to randomization and approximately 75% of participants were at increased risk for severe illness from COVID-19.

The number of hospitalization events contributing to the primary endpoint in the MITT population was low in all groups through Day 29 [Figure 7]. No deaths were reported for any participants through Day 29 (1 death was reported in the placebo group beyond Day 29, [Sec. 4.4.4]). All 11 hospitalized participants had at least 1 risk factor for severe illness from COVID-19 (eg, obesity, >60 years of age, diabetes). Results from post-hoc subgroup analyses evaluating the primary endpoint in participants with increased risk of severe illness from COVID-19 and/or with ≤5 days from symptom onset to randomization showed a lower percentage of hospitalizations in the combined MOV groups (3.7% [4/107]) compared with placebo (11.8% [4/34]) [Figure 7]. For participants >60 years of age, a larger difference in percentage of hospitalizations was observed between the combined MOV groups (3.6% [2/55]) and placebo (21.4% [3/14]).

Combined with the clinical efficacy results from P001 Phase 2, which showed no clear effect of MOV treatment on sustained recovery for hospitalized participants [Sec. 4.1.2], the results from P002 Phase 2 suggested that treatment with MOV would be more likely to be beneficial if started early (ie, ≤5 days after symptom onset) in the COVID-19 disease course.

Figure 7 Incidence of Death or Hospitalization Through Day 29 Overall and in Key Subgroups MITT Population (P002 Phase 2)



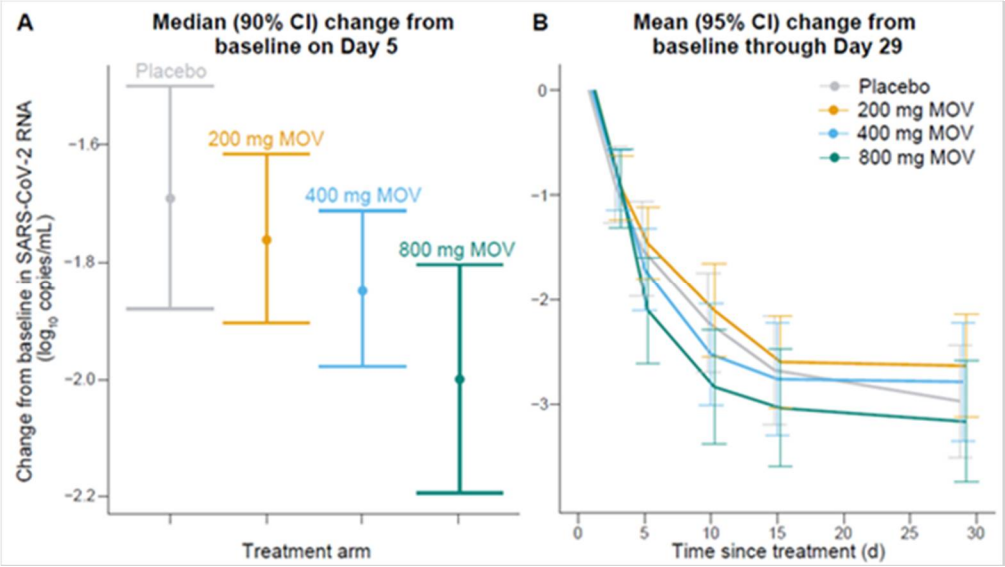
4.3.1.3 Exposure Response Analyses

Exposure-response analyses of efficacy were conducted using SARS-CoV-2 RNA virologic endpoints (P001 [Phase 2], P002 [Phase 2], P006) and clinical efficacy results (P002 [Phase 2]). As limited drug effect was observed for the clinical efficacy endpoints in P001 (Phase 2), exposure-response analyses were not conducted for P001. Investigations of exposure-response were not conducted for safety endpoints because there was no clinically relevant safety pattern identified with respect to dose.

Virology

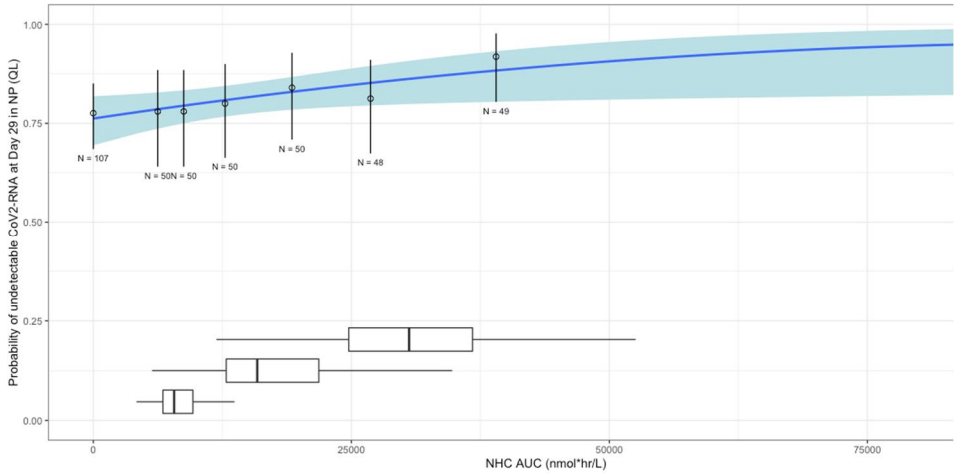
The SARS-CoV-2 viral load change from baseline in P002, and the model-estimated viral load reduction among participants with symptom onset within 5 days of randomization in P001 and P002 suggest that the MOV 800 mg dose provides a larger viral load decline [Figure 8], a steeper slope of viral RNA decline, and a higher percentage of participants achieving undetectable viral RNA by Day 29 [Figure 9] compared with placebo, MOV 200 mg, or MOV 400 mg.

Figure 8 Model Estimated Relationship between Dose and Viral Load Change from Baseline on Day 5 Simulated from Exposure-Response Model (A) and Observed Viral Load Reduction over Time Based on TSSO ≤ 5 days Subset in P001/P002 (Log10 Baseline Viral Load Fixed to Typical Value of 6) (B)



CI=confidence interval; MOV=molnupiravir; NHC=metabolized form of MOV prodrug; TSSO=Time to Symptom Onset

Figure 9 Exposure-Response Analysis for Probability of Undetectable Viral Load on Day 29 P001 Phase 2 and P002 Phase 2

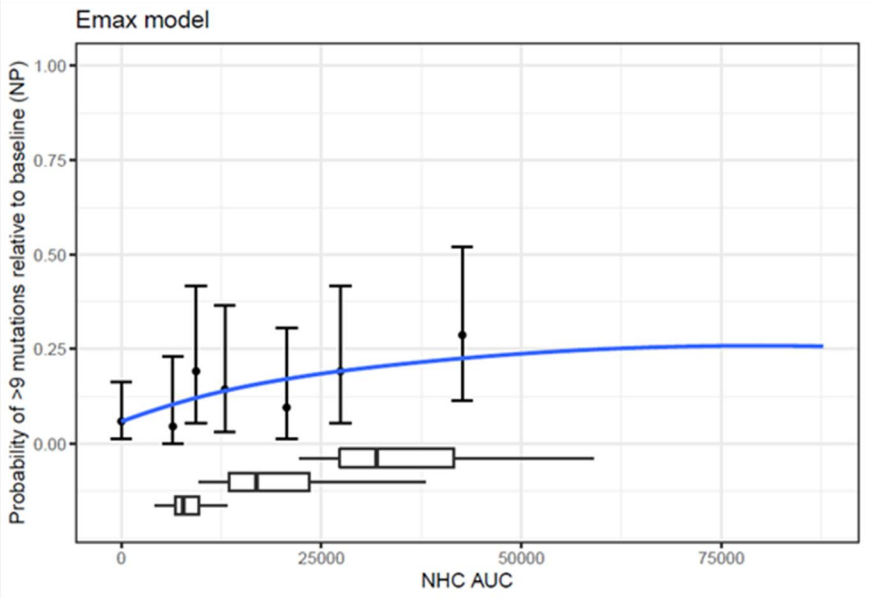


CI=confidence interval; NHC= metabolized form of molnupiravir prodrug; AUC= area under the concentration-time curve
Note: Predicted probability (95% CI): lowest of the predicted probability and 95% CI (to smooth out influence of exposure)
Observations: Open symbols representing the observed percentage of participants with undetectable RNA for each sextile of exposure, plotted at the median of the sextile. Vertical bars representing the 95% exact CIs corresponding to the observed percentage of participants with undetectable RNA.
Boxplots: distribution of exposures at 200, 400, or 800 mg

In P006, treatment with MOV 800 mg resulted in a greater virologic response, as assessed by SARS-CoV-2 RNA titers, compared with any of the other groups [Sec. 4.3.1.1]. The impact of MOV on viral infectivity in P006, as assessed by the percentage of participants with a positive viral culture on-treatment and post-treatment, also supports a drug effect and a trend for a dose effect [Sec. 4.3.1.1].

Analysis of the SARS-CoV-2 error rate in P001 and P002 identified a trend in exposure-response relationship at >3 and >6 thresholds, and a significant exposure-response relationship at the >9 threshold. The highest percentage of participants with >9 viral RNA errors per 10,0000 bases was observed in the MOV 800 mg group. The error rate exposure-response relationship was best described by Emax logistic regression models, which indicate that the drug effect may be saturating at exposures in the range of the 800 mg dose based on the estimated plateau [Figure 10].

Figure 10 Binned Data and Logistic Regression Model-Estimated Exposure-Response Relationship for Probability of Mutation Rate > 9 per 10,000 Bases Relative to Baseline
P001 Phase 2 and P002 Phase 2



CI=confidence interval; NHC=metabolized form of molnupiravir prodrug; AUC= area under the concentration-time curve
Vertical bars represent the 95% confidence intervals corresponding to the observed mutation rate relative to baseline.

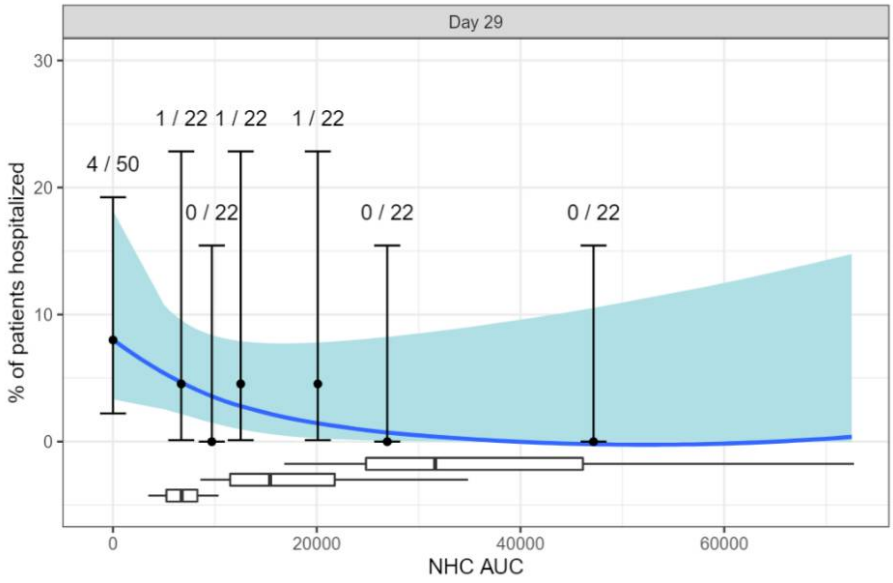
Virologic data from P001, P002, and P006 provide evidence of MOV drug effect and support a conclusion that the magnitude of this drug effect is larger at the 800 mg dose than at lower doses. The magnitude of the effect observed with the 800 mg dose is in the range of virologic effects seen with therapeutic mAbs authorized for emergency use.

Efficacy

For participants who had symptom onset within 5 days prior to randomization, trends were observed in the dose- and exposure-response relationships for the endpoint of hospitalization [Sec. 4.3.1.2], suggesting that the MOV 800 mg Q12H dose provides an increased clinical effect over lower MOV doses [Figure 11]. The exposure-response analyses included only participants with available PK data. Three participants in the 800 mg group were hospitalized after receiving only 1 to 3 doses and therefore had no PK samples collected.

The results suggest a potential drug and dose effect and the importance of early treatment on the clinical outcome of hospitalization but should be interpreted with caution given the small sample size and number of events.

Figure 11 Logistic Regression Exposure-Response Model Prediction of the Probability of Hospitalization Rate in P002 Participants with TSSO ≤ 5 days (p-value: 0.098)



CI=confidence interval; NHC=metabolized form of molnupiravir prodrug; AUC= area under the concentration-time curve
Note: A 2-tailed hypothesis test was conducted to test the effect of exposure (NHC AUC) on hospitalization rates, resulting in the corresponding p-value.
Blue line (shaded area): Predicted probability (95% confidence interval)
Observations: symbols representing the observed proportion of subjects hospitalized for each sextile of exposure, plotted at the median of the sextile. Vertical bars representing the 95% confidence intervals corresponding to the observed proportion of subjects hospitalized
Boxplots: distribution of exposures at 200, 400, or 800 mg

Key results of the exposure-response analyses include:

- Across all studies, the largest overall magnitude of antiviral effect was observed for the 800 mg dose of MOV compared with the 200 and 400 mg doses, with differences even more pronounced in participants treatment ≤5 days following symptom onset.
- Available virologic data show that the MOV dose of 800 mg Q12H provides a substantial effect and suggest that the effect is near the plateau of the dose response curve.
- For participants who had symptom onset within 5 days of randomization, trends were observed in the exposure-response relationship for the endpoint of hospitalization, suggesting that the MOV 800 mg Q12H dose provides an increased clinical effect over lower MOV doses.

4.3.2 Phase 3 Clinical Study – P002 Phase 3 IA

4.3.2.1 Statistical Methods for Efficacy Analyses

Evaluation of efficacy in P002 was based on all-cause hospitalization or death (primary), other aspects of clinical progression of COVID-19 disease (secondary), and SARS-CoV-2 virologic endpoints (exploratory) [Table 4]. Efficacy analyses were based on the MITT population, which included all randomized participants who received at least 1 dose of study intervention and were not hospitalized prior to administration of the first dose of study intervention (participants were included in the intervention group to which they were randomized).

In Phase 3, formal evaluation (via hypothesis testing) of the efficacy of MOV relative to placebo was planned at 2 study milestones: (1) 50% of the Phase 3 participants completed through Day 29 (Phase 3 IA), and (2) all Phase 3 participants completed through Day 29 (primary analysis). Hypothesis testing was based on the difference in the percentages of participants who met the primary endpoint (using the stratified Miettinen and Nurminen method [38] [by time from symptom onset: ≤3 days, >3 (4 to 5) days]) and only included participants enrolled in Phase 3 per the statistical analysis plan. Strong control of the type I error rate at an overall 1-sided 0.025 level was built into the statistical analysis plan via efficacy boundaries determined using the Gamma family spending function with γ = -1 (corresponding to a p-value boundary for efficacy of 0.0092 at the Phase 3 IA based on the number of participants in the MITT population). Phase 3 was designed and powered to demonstrate efficacy, independent from Phase 2.

Table 4 Efficacy Endpoints in the Phase 3 Clinical Study (P002)

Phase 3 Efficacy Endpoint	Definition
Primary	
Percentage of participants who were hospitalized or died through Day 29	Hospitalization (all-cause) was defined as ≥24 hours of acute care in a hospital or similar acute care facility, including emergency rooms or facilities created to address hospitalization needs during the COVID-19 pandemic.
Secondary	
Time to sustained improvement or resolution, and time to progression of each targeted self-reported COVID-19 sign/symptom through Day 29	Time to sustained improvement or resolution was defined as the number of days from randomization to the first of 3 consecutive days when resolution or improvement was demonstrated for the targeted self-reported sign/symptom. Time to progression was defined as the number of days from randomization to the first of 2 consecutive days when the targeted self-reported sign/symptom worsened.
Odds of a more favorable response on the WHO 11-point ordinal outcome scale through Day 29	Analyzed using the cumulative logits function and the proportional odds model [39] to provide an estimate of the common odds ratio for assessing differences between treatment groups.
Exploratory	
Change from baseline in mean SARS-CoV-2 RNA titer and percentage of participants with undetectable SARS-CoV-2 RNA at various timepoints	Change from baseline calculated as log10 (post) minus log10 (baseline), as measured by quantitative RT-PCR of samples from NP swabs. Undetectable viral RNA defined as below limit of detection as measured by qualitative RT-PCR of samples from NP swabs.
Percentage of participants with undetectable infectious SARS-CoV-2 in NP swabs through Day 29	Analysis of infectious virus in NP samples (with SARS-CoV-2 RNA titers ≥100,000 copies/mL) via plaque assay in Vero cells
Viral RNA mutation rate and detection of treatment-emergent sequence variants by comparing baseline and post-baseline virus sequencing	NGS analysis of SARS-CoV-2 RNA in participants with paired sequence data from baseline and post-baseline samples

4.3.2.2 Efficacy Results

The efficacy results for P002 Phase 3 presented in this document are comprised of results from the IA conducted during the Phase 3 portion of the study.

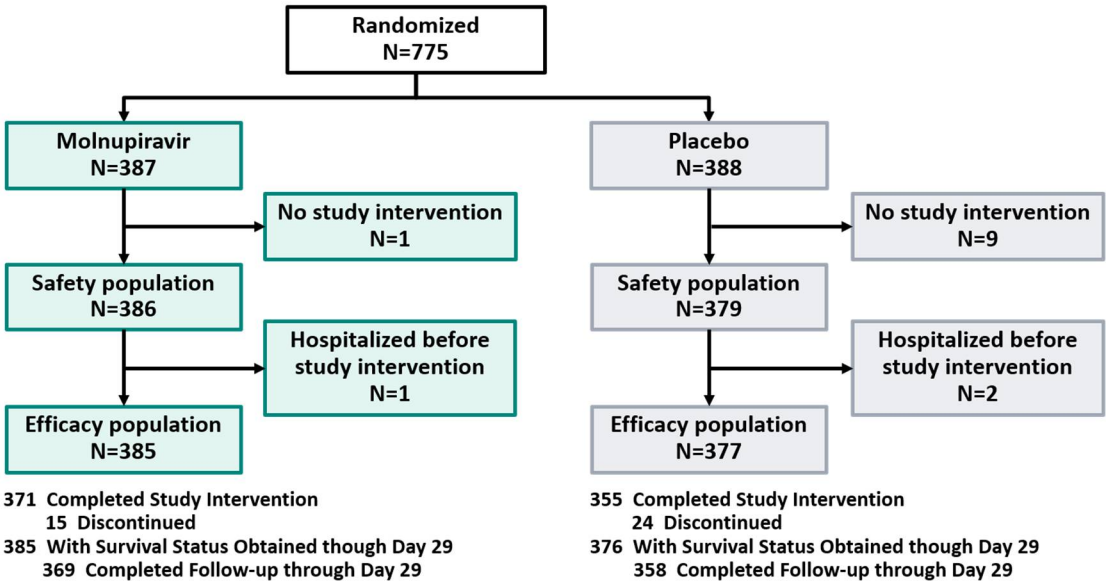
4.3.2.2.1 Analysis Population

The interim analysis cohort includes the first 775 participants randomized into the Phase 3 portion of P002. Nearly all (98.3%; 762/775) randomized participants were included in the MITT population (defined as all participants who received at least 1 dose of study intervention and were not hospitalized prior to their first dose) [Figure 12]. Overall, 94% participants received 9 or 10 doses of study intervention Q12H and completed through Day 29 of the study.

Thirteen randomized participants were excluded from the MITT population:

- 10 participants (n=1 MOV; n=9 placebo) did not receive study intervention and were also excluded from the safety population.
- 3 participants (n=1 MOV; n=2 placebo) were hospitalized prior to their first dose and were included in the safety population.

Figure 12 Consort Diagram for Participant Disposition and Analysis Population (P002 Phase 3 IA)



4.3.2.2.2 Key Features of the Participant Population

P002 (Phase 3) enrolled a diverse global participant population representative of patients likely to receive treatment with MOV for COVID-19. This resulted in diverse SARS-CoV-2 genotypes in the participant population that was representative of variant clades circulating globally at the time of enrollment (JUN-2021 to AUG-2021 for participants included in the Phase 3 IA). Of participants with SARS-CoV-2 viral sequence data available as of 01-NOV-2021 (527/775; 68%), the 3 most common SARS-CoV-2 genotype clades at baseline were 21A/I/J (Delta; 42.1%), 21H (Mu; 28.5%), and 20J (Gamma; 15.7%).

The participants in the Phase 3 IA had the following key baseline and disease characteristics; all were comparable for the MOV and placebo groups [Table 5]:

- All randomized participants reported symptom onset within 5 days prior to randomization with approximately half of the participants having symptom onset ≤3 days prior to randomization.

- Most randomized participants (>99%) had at least 1 risk factor for progressing to severe illness from COVID-19. The most common risk factors were obesity (BMI ≥30, 76.5%), age >60 years (13.7%), and diabetes mellitus (13.5%).
- Severity of COVID-19 at baseline was moderate for 43.4% of participants and mild for 56.0% of participants (as determined based on standard protocol-defined definitions using clinical data [eg, heart rate, respiratory rate, O2 saturation] entered in the clinical database).
- Most participants (85.5%) had detectable SARS-CoV-2 RNA (NP sample) and 18.2% of participants had positive SARS-CoV-2 antibody results (via Roche Elecsys® Anti-SARS-CoV-2 total nucleocapsid antibody assay).
- The most common (self-reported by >60% of participants) signs and symptoms of COVID-19 present at baseline in the Phase 3 IA were cough, fatigue, muscle or body aches, headache, and nasal congestion.

Table 5 Participant Baseline Characteristics
All Randomized Participants (P002 Phase 3 IA)

	Molnupiravir		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 to74	24	(6.2)	24	(6.2)	48	(6.2)
≥75	7	(1.8)	13	(3.4)	20	(2.6)
Race						
American Indian or Alaska Native	20	(5.2)	9	(2.3)	29	(3.7)
Asian	7	(1.8)	11	(2.8)	18	(2.3)
Black or African American	27	(7.0)	20	(5.2)	47	(6.1)
White	194	(50.1)	209	(53.9)	403	(52.0)
Multiple	139	(35.9)	139	(35.8)	278	(35.9)
Ethnicity						
Hispanic Or Latino	224	(57.9)	228	(58.8)	452	(58.3)
Not Hispanic Or Latino	163	(42.1)	159	(41.0)	322	(41.5)
Not Reported	0	(0.0)	1	(0.3)	1	(0.1)
Region						
North America	15	(3.9)	22	(5.7)	37	(4.8)
Latin America	216	(55.8)	214	(55.2)	430	(55.5)
Europe	89	(23.0)	90	(23.2)	179	(23.1)
Asia Pacific	5	(1.3)	6	(1.5)	11	(1.4)
Africa	62	(16.0)	56	(14.4)	118	(15.2)
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)

	Molnupiravir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
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)
Unknown[a]	1	(0.3)	2	(0.5)	3	(0.4)
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 Viral Clade at Baseline						
19B	1	(0.3)	1	(0.3)	2	(0.3)
20A	3	(0.8)	2	(0.5)	5	(0.6)
20B	4	(1.0)	4	(1.0)	8	(1.0)
20C	0	(0)	1	(0.3)	1	(0.1)
20D	2	(0.5)	1	(0.3)	3	(0.4)
20H (Beta)	5	(1.3)	6	(1.5)	11	(1.4)
20I (Alpha)	12	(3.1)	8	(2.1)	20	(2.6)
20J (Gamma)	35	(9)	48	(12.4)	83	(10.7)
21A (Delta)	96	(24.8)	90	(23.2)	186	(24.0)
21G (Lambda)	12	(3.1)	7	(1.8)	19	(2.5)
21H (Mu)	70	(18.1)	80	(20.6)	150	(19.4)
21I (Delta)	6	(1.6)	3	(0.8)	9	(1.2)
21J (Delta)	12	(3.1)	15	(3.9)	27	(3.5)
Unknown (could not be classified)	2	(0.5)	1	(0.3)	3	(0.4)
Sequence data not available	127	(32.8)	121	(31.2)	248	(32.0)
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.

4.3.2.2.3 Hospitalization or Death Through Day 29

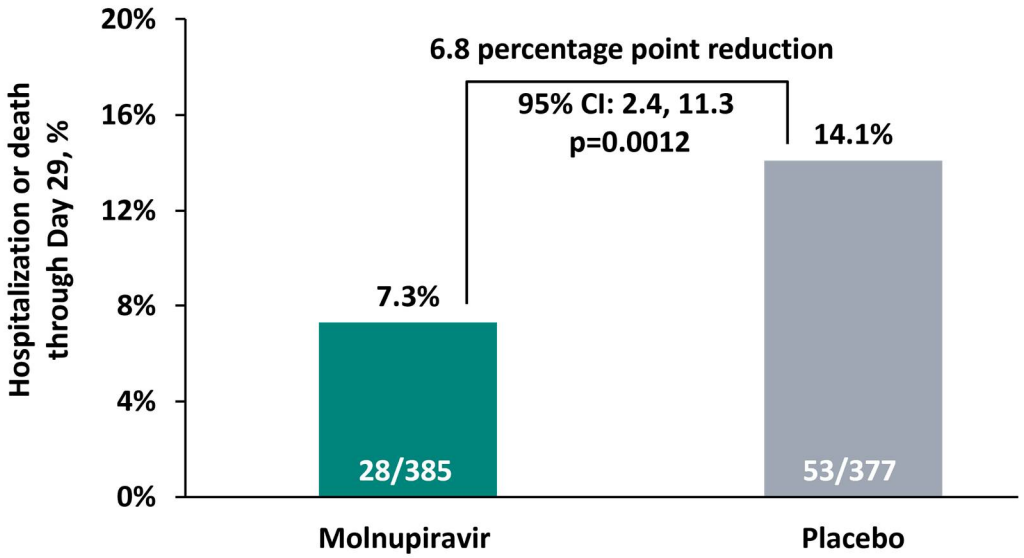
The percentage of participants who were hospitalized or died through Day 29 in the MOV group (7.3%) was statistically significantly lower than in the placebo group (14.1%) [Figure 13]. Treatment with MOV resulted in a 6.8 percentage point reduction [95% CI: -11.3, -2.4; p=0.0012] in the risk of hospitalization or death through Day 29 compared with placebo (approximately 50% relative risk reduction). MOV met the protocol-defined criterion (1-sided p-value boundary <0.0092 for the Phase 3 IA) for demonstration of superiority to placebo for the primary efficacy endpoint.

Key results for the primary endpoint include:

- All 8 participants who died through Day 29 were in the placebo group and were hospitalized prior to their death [Table 6]. No participants in the MOV group died. One participant in the placebo group with unknown Day 29 survival status was, per prespecified rules for addressing missing endpoint data, counted as having an outcome of hospitalization or death in the analysis of the primary endpoint.

- Based on the adjusted difference in rates between MOV and placebo in the primary endpoint analysis, for every ~15 patients treated with MOV, 1 hospitalization/death would be prevented (1/0.068). For every ~50 patients, 1 death would be prevented (1/0.021) [Table 6].
- Results of an analysis of time to hospitalization or death [Figure 14] and of an analysis of COVID-related hospitalizations or deaths (as assessed by the investigator) [Figure 15] were consistent with the results of the primary analysis.

Figure 13 Incidence of Hospitalization or Death Through Day 29 MITT Population (P002 Phase 3 IA)



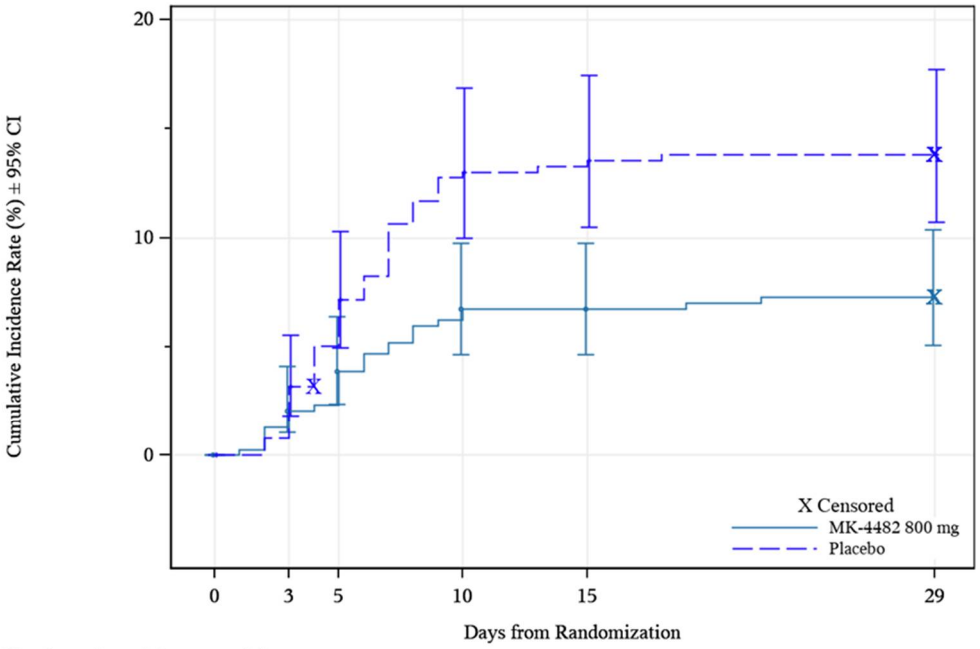
Adjusted differences, the corresponding confidence intervals and the 1-sided p-value is based on Miettinen & Nurminen method stratified by randomization strata.
Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.
The p-value boundary for early efficacy is 0.0092 using the Gamma family spending function with γ = -1 based on the final evaluable sample size at the Phase 3 IA timepoint (n = 762 in the MITT population out of a total of 1550 planned; information fraction = 49%).

Table 6 Summary of Hospitalization or Death Through Day 29 MITT Population (P002 Phase 3 IA)

	Molnupiravir		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. All 8 participants who died were hospitalized prior to death; such participants are counted once each in the hospitalization and death rows.
[a] Unknown survival status at Day 29 was counted as an outcome of hospitalization or death in the primary efficacy analysis.

Figure 14 Kaplan-Meier Plot for Hospitalization or Death Through Day 29 MITT Population (P002 Phase 3 IA)



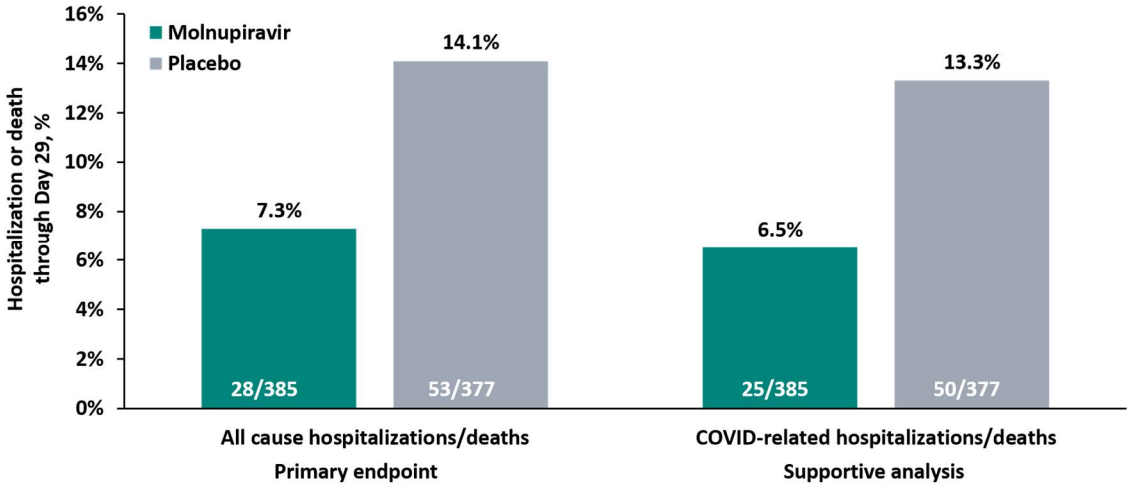
Number of participants at risk

MK-4482 800 mg	385	380	376	361	359	357
Placebo	377	374	357	328	326	324

Number of events inside period

MK-4482 800 mg	5	4	15	2	2	0
Placebo	3	16	29	2	2	0

Figure 15 Incidence of Hospitalization or Death (All-Cause and COVID-Related) Through Day 29 MITT Population (P002 Phase 3 IA)



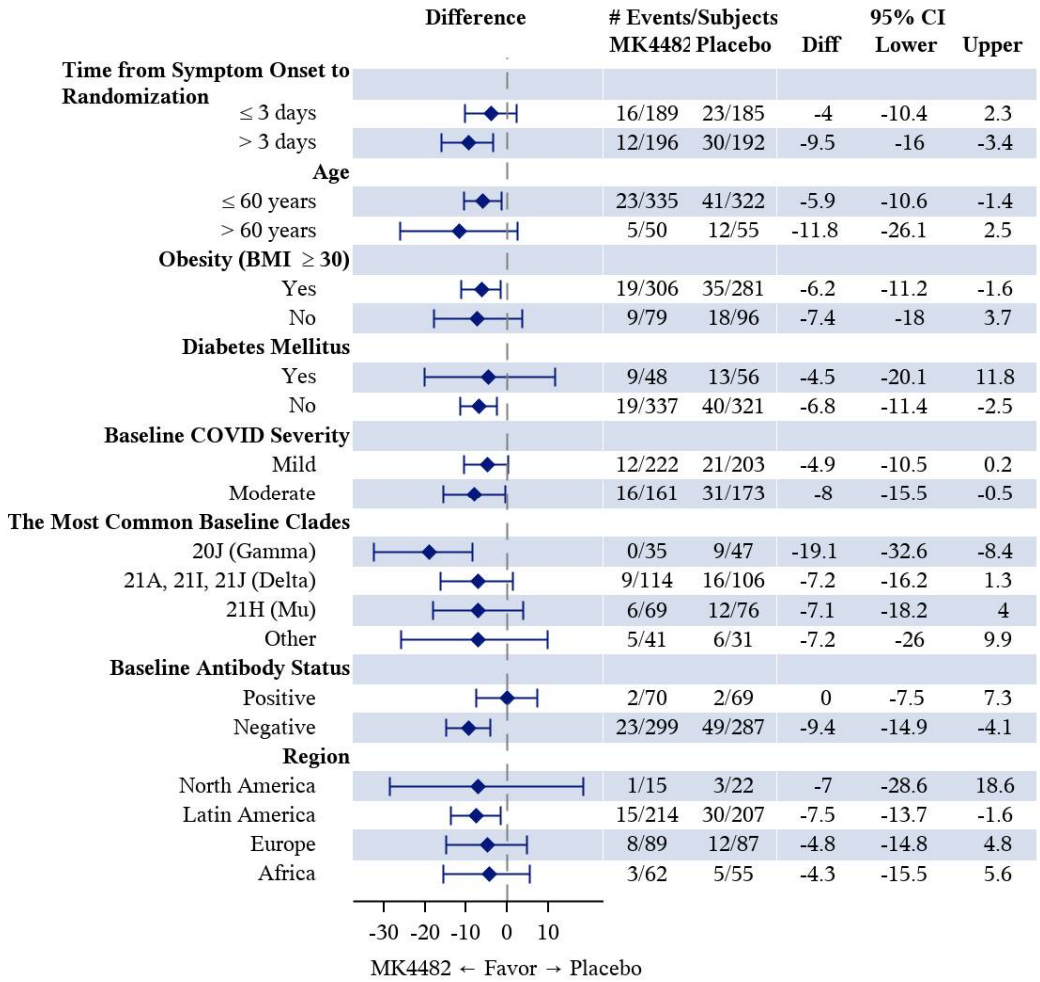
COVID-related as assessed by the investigator
Numerator=number of participants died or hospitalized through Day 29; Denominator=number of participants in the MITT population.
Unknown survival status at Day 29 was not counted as having an outcome of COVID-related hospitalization or death.

Results of subgroup analyses of the primary endpoint based on baseline characteristics were consistent with the results of the primary analysis, except for the subgroup of participants who were positive for SARS-CoV-2 antibodies (described below) [Figure 16].

Subgroups with results consistent with the primary analysis were: time from symptom onset to randomization (≤3 days; >3 [4 to 5] days), age group (≤60 years; >60 years), obesity (BMI ≥30; yes, no), diabetes mellitus (yes, no), the most common viral clades (20J [Gamma], 21A/I/J [Delta], 21H [Mu]), COVID-19 severity (mild, moderate), region (North America, Latin America, Europe, and Africa), and participants negative for SARS-CoV-2 antibodies (as measured by the Roche Elecsys® Anti-SARS-CoV-2 assay).

In the subgroup of participants positive for SARS-CoV-2 antibodies at baseline (~18% in each group; suggesting recent or prior SARS-CoV-2 infection), there was no observed difference between intervention groups in the percentage of participants who were hospitalized or died (2.9% in both groups) [Figure 16].

Figure 16 Incidence of Hospitalization or Death Through Day 29 by Subgroup MITT Population (P002 Phase 3 IA)



The corresponding confidence interval is based on Miettinen & Nurminen method.
Time from symptom onset to randomization is based on the value of the stratification factor collected at randomization.

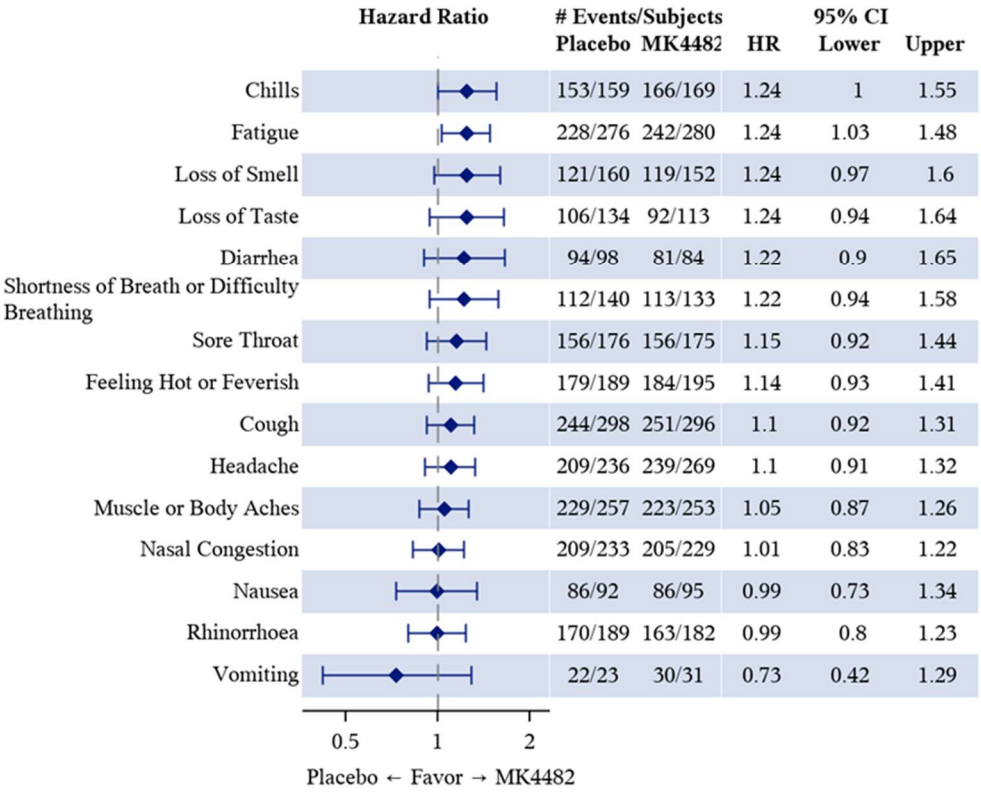
4.3.2.2.4 Signs/Symptoms and WHO Ordinal Scale Score

Participant Self-Reported COVID-19 Signs/Symptoms

Self-reported signs and symptoms attributable to COVID-19 were collected on a 15-item paper symptom diary completed daily by the participant. The analysis of these data was based on pre-specified definitions for time to sustained improvement or resolution and time to progression [Table 4].

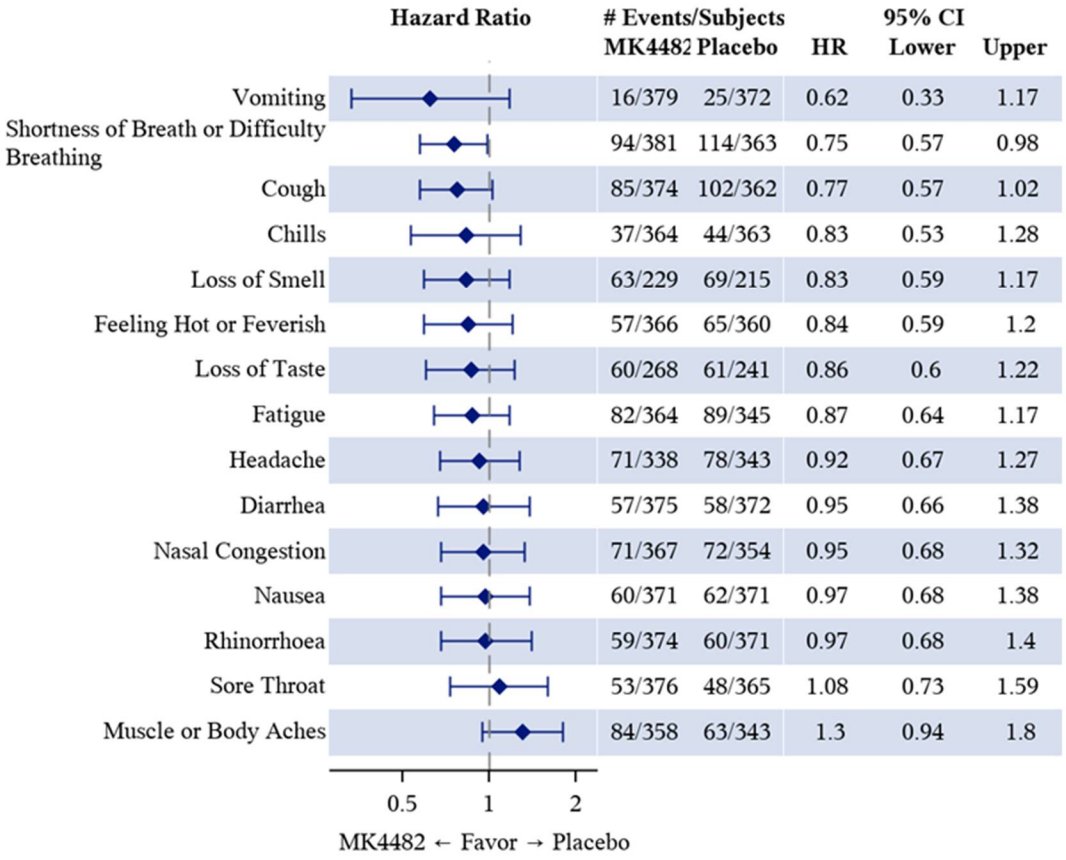
A higher percentage of participants reported sustained improvement or resolution in the MOV group compared with the placebo group for most of the self-reported COVID-19 signs and symptoms [Figure 17]. A lower percentage of participants reported progression in the MOV group compared with the placebo group for most of the self-reported COVID-19 signs and symptoms [Figure 18]. These results are supportive of a clinical benefit of treatment with MOV.

Figure 17 Hazard Ratio of Time to Sustained Improvement or Resolution of Signs/Symptoms Through Day 29 MITT Population (P002 Phase 3 IA)



Based on Cox regression model with Efron's method of tie handling with treatment and randomization stratification factor as covariates. Hazard ratio > 1 favors the molnupiravir group.

Figure 18 Hazard Ratio of Time to Progression of Signs/Symptoms Through Day 29 MITT Population (P002 Phase 3 IA)



Based on Cox regression model with Efron's method of tie handling with treatment and randomization stratification factor as covariates. Hazard ratio < 1 favors the molnupiravir group.

WHO 11-Point Ordinal Scale Score

The WHO 11-point ordinal scale was used to assess clinical progression of COVID-19 illness where a score of 0 is uninfected (no viral RNA detected), 1 is asymptomatic disease, 2 is symptomatic ambulatory disease without assistance, 3 is ambulatory disease requiring assistance, and 4 and higher require increasing hospital intervention with 10 assigned at death [40].

Most (>98%) participants in both intervention groups had a baseline score of 2. By Day 5, a higher percentage of participants who received MOV showed improved outcomes on the WHO 11-point ordinal scale compared with those who received placebo; the largest observed differences occurred at Days 10 and 15 [Figure 19] [Table 7]. The majority (66.3%) of participants in both intervention groups improved to a score of 0 or 1 by Day 29. These results are supportive of a clinical benefit of treatment with MOV.

Figure 19 Summary of WHO-11 Scale by Visit MITT Population (P002 Phase 3 IA)

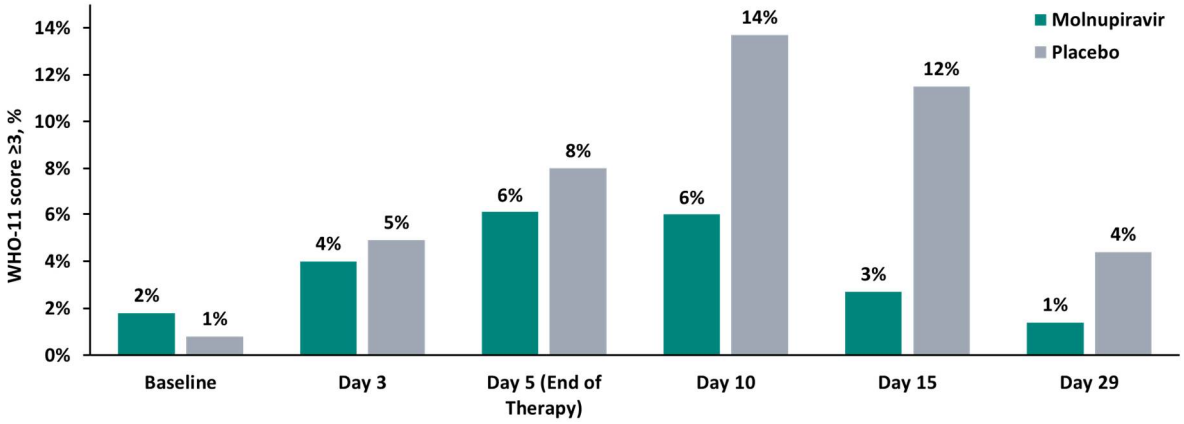


Table 7 Analysis of WHO-11 Scale by Visit MITT Population (P002 Phase 3 IA)

Visit	Score Category	Molnupiravir	Placebo	Total
		N=385	N=377	N=762
		n/m (%)	n/m (%)	n/m (%)
Baseline	0 (Uninfected)	0/382 (0.0)	0/374 (0.0)	0/756 (0.0)
	1-3 (Ambulatory Mild disease)	382/382 (100.0)	374/374 (100.0)	756/756 (100.0)
	4-5 (Hospitalized: Moderate disease)	0/382 (0.0)	0/374 (0.0)	0/756 (0.0)
	6-9 (Hospitalized: Severe disease)	0/382 (0.0)	0/374 (0.0)	0/756 (0.0)
	10 (Death)	0/382 (0.0)	0/374 (0.0)	0/756 (0.0)
	Missing	3	3	6
Day 3	0 (Uninfected)	1/375 (0.3)	2/369 (0.5)	3/744 (0.4)
	1-3 (Ambulatory Mild disease)	366/375 (97.6)	354/369 (95.9)	720/744 (96.8)
	4-5 (Hospitalized: Moderate disease)	7/375 (1.9)	13/369 (3.5)	20/744 (2.7)
	6-9 (Hospitalized: Severe disease)	1/375 (0.3)	0/369 (0.0)	1/744 (0.1)
	10 (Death)	0/375 (0.0)	0/369 (0.0)	0/744 (0.0)
	Missing	10	8	18
	Comparison	Odds Ratio (95% CI)[a]		p-Value[b]
	Molnupiravir vs. Placebo	1.43 (0.63, 3.26)		0.3951
EOT (Day 5)	0 (Uninfected)	9/377 (2.4)	8/366 (2.2)	17/743 (2.3)
	1-3 (Ambulatory Mild disease)	354/377 (93.9)	332/366 (90.7)	686/743 (92.3)
	4-5 (Hospitalized: Moderate disease)	11/377 (2.9)	23/366 (6.3)	34/743 (4.6)
	6-9 (Hospitalized: Severe disease)	3/377 (0.8)	3/366 (0.8)	6/743 (0.8)
	10 (Death)	0/377 (0.0)	0/366 (0.0)	0/743 (0.0)
	Missing	8	11	19
	Comparison	Odds Ratio (95% CI)[a]		p-Value[b]
	Molnupiravir vs. Placebo	1.65 (0.95, 2.86)		0.0776

Visit	Score Category	Molnupiravir	Placebo	Total
		N=385	N=377	N=762
		n/m (%)	n/m (%)	n/m (%)
Day 10	0 (Uninfected)	17/366 (4.6)	13/366 (3.6)	30/732 (4.1)
	1-3 (Ambulatory Mild disease)	330/366 (90.2)	307/366 (83.9)	637/732 (87.0)
	4-5 (Hospitalized: Moderate disease)	15/366 (4.1)	33/366 (9.0)	48/732 (6.6)
	6-9 (Hospitalized: Severe disease)	4/366 (1.1)	13/366 (3.6)	17/732 (2.3)
	10 (Death)	0/366 (0.0)	0/366 (0.0)	0/732 (0.0)
	Missing	19	11	30
	Comparison	Odds Ratio (95% CI)[a]		p-Value[b]
	Molnupiravir vs. Placebo	2.10 (1.33, 3.29)		0.0013
Day 15	0 (Uninfected)	44/366 (12.0)	34/355 (9.6)	78/721 (10.8)
	1-3 (Ambulatory Mild disease)	313/366 (85.5)	284/355 (80.0)	597/721 (82.8)
	4-5 (Hospitalized: Moderate disease)	7/366 (1.9)	24/355 (6.8)	31/721 (4.3)
	6-9 (Hospitalized: Severe disease)	2/366 (0.5)	9/355 (2.5)	11/721 (1.5)
	10 (Death)	0/366 (0.0)	4/355 (1.1)	4/721 (0.6)
	Missing	19	22	41
	Comparison	Odds Ratio (95% CI)[a]		p-Value[b]
	Molnupiravir vs. Placebo	1.97 (1.32, 2.94)		0.0009
Day 29	0 (Uninfected)	146/354 (41.2)	146/344 (42.4)	292/698 (41.8)
	1-3 (Ambulatory Mild disease)	204/354 (57.6)	184/344 (53.5)	388/698 (55.6)
	4-5 (Hospitalized: Moderate disease)	3/354 (0.8)	6/344 (1.7)	9/698 (1.3)
	6-9 (Hospitalized: Severe disease)	1/354 (0.3)	0/344 (0.0)	1/698 (0.1)
	10 (Death)	0/354 (0.0)	8/344 (2.3)	8/698 (1.1)
	Missing	31	33	64
	Comparison	Odds Ratio (95% CI)[a]		p-Value[b]
	Molnupiravir vs. Placebo	1.02 (0.76, 1.37)		0.8821

For the proportional odds model, the score categories were collapsed into 5 levels as follows: 0 (uninfected), 1-3 (Ambulatory Mild Disease), 4-5 (Hospitalized; Moderate Disease), 6-9 (Hospitalized; Severe Disease) and 10 (dead).

[a] Analyses are based on the proportional odds model with WHO-11 score categories as the response variable. Due to sparse data, the final model includes only treatment as covariate. CIs are based on Wald Chi-Squire Test. Odds ratio > 1 favors molnupiravir.

[b] P-values are based on Wald Chi-Squire Test.

N=Number of participants in each treatment group; n=number of participants in each subcategory; m= number of participants with non-missing ordinal scale at the time point assessed; CI=Confidence Interval

Day 3 includes post-baseline records up to day 4 relative to randomization. EOT (Day 5) includes post-baseline records from day 5 (relative to randomization) up to day 7. End of treatment visits occurring earlier than day 5 (relative to randomization) are included in the Day 3 visit.

4.3.2.2.5 Virologic Response

At the time of the database lock for the Phase 3 IA, testing for evaluation of virologic response was ongoing. Postbaseline SARS-CoV-2 viral sequence data are limited; available results from 92 participants (n=42 MOV; n=50 placebo) with both baseline and postbaseline data are presented. Data for SARS-CoV-2 viral infectivity are very limited, precluding presentation of meaningful results for participants in P002 Phase 3 at this time.

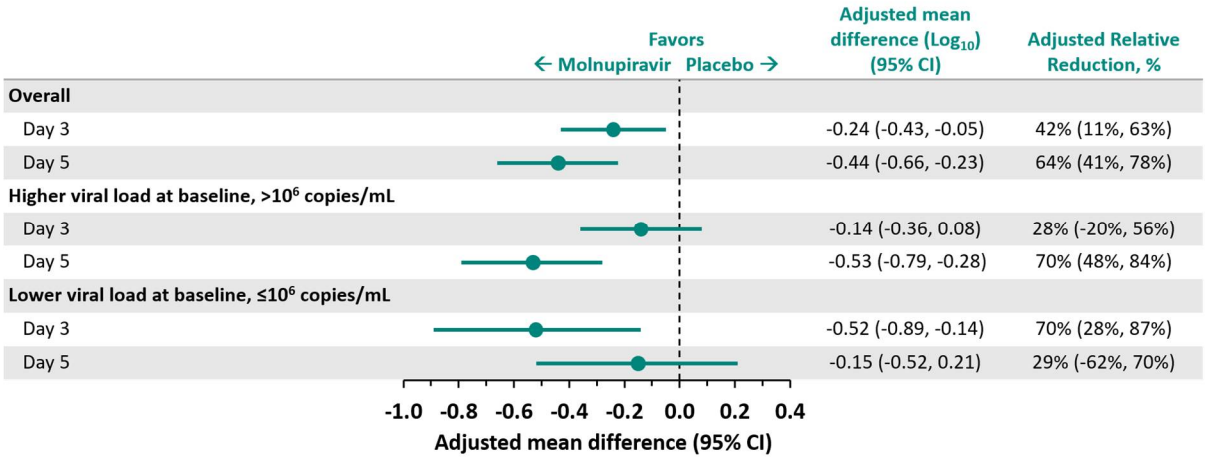
SARS-CoV-2 RNA

Treatment with MOV was associated with a greater decrease in mean SARS-CoV-2 RNA from baseline compared with placebo at Days 3 and 5. After adjusting for baseline RNA titer, the mean difference in SARS-CoV-2 RNA (in $\log_{10}$ scale; MOV minus placebo) 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 titer for the MOV group compared with the placebo group.

The largest mean difference between MOV and placebo groups was observed in participants with a high viral load at baseline (>10^6 copies/mL); after adjusting for baseline RNA titer, a difference of -0.53 was observed at Day 5, representing a 70% relative reduction in the geometric mean SARS-CoV-2 RNA in the MOV group compared with placebo [Figure 20]. Among participants with a lower viral load at baseline (≤10^6 copies/mL), the largest mean difference was -0.52 at Day 3 (after adjusting for baseline RNA titer), when treatment with MOV was associated with a 70% relative reduction in the geometric mean SARS-CoV-2 RNA compared with placebo.

Figure 20 Difference in Mean Change in SARS-CoV-2 RNA (MOV minus placebo) Overall and by Viral Load at Baseline MITT Population (P002 Phase 3 IA)



The percentage of participants who achieved undetectable SARS-CoV-2 RNA in NP samples by qualitative PCR was comparable for both intervention groups at various timepoints through Day 29, overall and regardless of baseline SARS-CoV-2 RNA titer (>10^6 and ≤10^6 copies/mL).

Viral RNA Error Rate

Consistent with the MOA for MOV, treatment with MOV was associated with a higher viral RNA error rate across the viral genome compared with placebo (with allele frequency ≥2%). A higher mean error rate (number of mutations/10,000 bases, [SD]) was observed in the MOV group (7.4 [10.1]) compared with placebo (3.4 [6.4]) among participants with paired baseline and Day 5 SARS-CoV-2 viral sequences. A higher percentage of participants in the MOV group had >3, >6, or >9 mutations per 10,000 bases at Day 5 compared with placebo.

Errors occurring in the viral genome were further characterized by determining the frequency of specific nucleotide transitions and transversions in sequences at Day 5 compared with baseline. Higher mean numbers of C to U, G to A, and A to G transition errors were observed

across the genome in NP samples from participants in the MOV group (6.6, 3.6, 2.2) compared with placebo (4.1, 0.4, 0.5). Mean numbers of transversion mutations were low in both groups. These results are consistent with results from nonclinical animal model studies that showed a higher number of nucleotide transitions, compared with transversions, in viral RNA recovered from MOV-treated animals infected with SARS-CoV-2 [37].

4.3.3 Summary of Key Efficacy Results

Clinical Outcomes

- In P002 (Phase 3 IA), the percentage of participants who were hospitalized or died through Day 29 in the MOV group (7.3%) was statistically significantly lower compared with the placebo group (14.1%). Treatment with MOV 800 mg Q12H resulted in a 6.8 percentage point reduction [95% CI: -11.3, -2.4; p=0.0012] in the risk of hospitalization or death through Day 29 (corresponding to approximately 50% relative risk reduction). All 8 participants who died through Day 29 were in the placebo group, and all were hospitalized before their death; no participants in the MOV group died.
- Treatment with MOV 800 mg Q12H was associated with improved clinical outcomes compared with placebo based on assessments of self-reported COVID-19 signs/symptoms and categories on the WHO 11-point ordinal scale in P002 (Phase 3 IA).

Virologic Response

- Treatment with MOV 800 mg Q12H was associated with a greater decrease in mean SARS-CoV-2 RNA from baseline to Days 3 and 5 (end of treatment) compared with placebo (P002 [Phase 3]). Results from the Phase 2 studies (P002, P001, P006) also provided evidence that treatment with MOV 800 mg Q12H reduced the percentage of participants with infectious virus compared with placebo.
- Treatment with MOV 800 mg Q12H was associated with a higher viral error rate compared with placebo, consistent with the proposed MOA of MOV (viral error induction) (P002 [Phase 2 and Phase 3 IA], P001 [Phase 2], P006).

4.3.4 Efficacy Conclusion

In adults with mild to moderate COVID-19, treatment with MOV 800 mg Q12H for 5 days is superior to placebo in reducing hospitalization or death within 29 days of initiating treatment.

4.4 Overview of Clinical Safety

4.4.1 Safety Evaluation Plan

The clinical safety assessment of MOV was primarily based on the results from the protocol-specified IA conducted during Phase 3 of P002 [Table 2]. Supportive safety results from Phase 2 in participants with COVID-19 [non-hospitalized (P002 and P006) and hospitalized (P001)] and in healthy participants (P004) are also presented. Available blinded safety results are also briefly summarized from 2 ongoing studies (P005, P007).

Safety analyses in each study were based on the APaT population, which included all randomized participants who received at least 1 dose of study intervention. Participants were included in the group per the intervention they received. Safety data were collected from the time of randomization through 14 days after completing study intervention. Results from all studies are presented separately due to differences in study populations.

4.4.2 Overall Extent of Exposure

Unblinded safety data are available for a total of 1069 adults who received at least 1 dose of MOV in P002 (Phase 2 and Phase 3 IA), P006, P001, and P004. Of these, 593 participants received at least 1 dose of MOV 800 mg in a dosing regimen of Q12H for 5 days [Table 8].

Table 8 Participants in the Unblinded Analyses who Received Molnupiravir (P002, P006, P001, P004)

Phase	Study	Number of Unblinded Participants (n)	
		Any Dose of Molnupiravir	Molnupiravir 800 mg Q12H[a]
Phase 3	P002	386	386
Phase 2	P002	225	74
	P006	140	55
	P001	218	72
Phase 1	P004	100	6
Total		1069	593

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

4.4.3 Primary Safety Results - P002 Phase 3 IA

The safety results for P002 Phase 3 that are presented in this document are comprised of results from the protocol-specified Phase 3 IA.

4.4.3.1 Participant Disposition and Exposure

A total of 765 non-hospitalized participants with COVID-19 received at least 1 dose of study intervention and were included in the APaT population (n=386 MOV; n=379 placebo) for the Phase 3 IA [Figure 12]. The disposition of participants and duration of exposure to study intervention were comparable between the 2 intervention groups. Overall, 94% of the participants received 9 or 10 doses of study intervention (mean duration of 4.4 days in each group) and completed through Day 29 of the study.

4.4.3.2 Adverse Events

The percentage of participants with at least 1 AE was comparable between the MOV (35.0%) and placebo (39.6%) groups [Table 9]. The percentages of participants with SAEs and with SAEs leading to discontinuation of study intervention were lower in the MOV group compared with placebo. AEs leading to death were only reported in the placebo group. The safety endpoints of SAEs and deaths overlap the primary efficacy endpoints, and for these

endpoints, the safety results were consistent with the results from the primary efficacy analysis.

Table 9 Adverse Event Summary
APaT Population (P002 Phase 3 IA)

	Molnupiravir		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)

n=number of participants with the corresponding event.
[a] Based on Miettinen & Nurminen method.
[b] Determined by the investigator to be related to the drug.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

The most frequently reported AEs (≥2% of participants in either group) were COVID-19 (worsening), COVID-19 pneumonia, diarrhea, nausea, pneumonia bacterial, and respiratory failure [Table 10].

Most reported AEs had a maximum toxicity of Grade 1 or Grade 2. Few Grade 3 and Grade 4 AEs were reported in the MOV (6.7% and 1.0%) and placebo (7.4% and 5.3%) groups.

Table 10 Participants with Adverse Events
(Incidence ≥ 2% in One or More Treatment Groups)
APaT Population (P002 Phase 3 IA)

	Molnupiravir		Placebo	
	n	(%)	n	(%)
Participants in population	386		379	
COVID-19[a]	31	(8.0)	56	(14.8)
COVID-19 pneumonia	19	(4.9)	34	(9.0)
Diarrhea	15	(3.9)	17	(4.5)
Nausea	11	(2.8)	5	(1.3)
Pneumonia bacterial	8	(2.1)	3	(0.8)
Respiratory failure	4	(1.0)	8	(2.1)

n=number of participants with the corresponding event.
[a] Worsening of COVID-19.

4.4.3.2.1 Drug-Related Adverse Events

The percentages of participants with drug-related AEs (as assessed by the investigator) were comparable in the MOV (12.4%) and placebo (11.1%) groups [Table 9]. The most frequently reported drug-related AEs (≥1% of participants in the MOV group) were diarrhea, nausea, dizziness, and headache in the MOV group [Table 11]. Most drug-related AEs had a maximum toxicity of Grade 1. Grade 3 drug-related AEs were reported for 0.3% of participants in each group.

Table 11 Participants with Drug-Related Adverse Events (Incidence ≥ 1% Participants in the MOV Group) APaT Population (P002 Phase 3 IA)

	Molnupiravir		Placebo	
	n	(%)	n	(%)
Participants in population	386		379	
Diarrhea	12	(3.1)	12	(3.2)
Nausea	9	(2.3)	4	(1.1)
Dizziness	5	(1.3)	1	(0.3)
Headache	4	(1.0)	0	(0.0)

n=number of participants with the corresponding event.
Based on all AEs assessed as drug-related by the investigator.

4.4.3.2.2 Serious Adverse Events

The percentage of participants with SAEs was lower in the MOV group (7.3%) compared with the placebo group (14.0%) [Table 9]. The percentages of participants with SAEs leading to discontinuation of study intervention were also lower in the MOV group (0.3%) compared with the placebo group (2.4%) [Table 9].

No SAEs were considered drug-related by the investigator. The most frequently reported SAEs (≥5% of participants in either group) were COVID-19 (worsening) in both groups and COVID-19 pneumonia in the placebo group [Table 12].

One SAE of pulmonary embolism (MOV group) occurred during the AE reporting period but was reported after database lock for the Phase 3 IA; therefore, it is not included in the safety summary tables. The SAE was considered not related to study intervention by the investigator. The participant was hospitalized for the SAE (the event of hospitalization was included in the efficacy analysis).

Table 12 Participants with Serious Adverse Events (Incidence ≥ 2 Participants in One or More Treatment Groups) APaT Population (P002 Phase 3 IA)

	Molnupiravir		Placebo	
	n	(%)	n	(%)
Participants in population	386		379	
Participants with ≥1 SAE	28	(7.3)	53	(14.0)
COVID-19[a]	22	(5.7)	45	(11.9)
COVID-19 pneumonia	15	(3.9)	28	(7.4)
Respiratory failure	4	(1.0)	8	(2.1)
Pneumonia bacterial	2	(0.5)	2	(0.5)
Pneumonia	1	(0.3)	2	(0.5)
Acute respiratory failure	0	(0.0)	2	(0.5)

n=number of participants with the corresponding event.
[a] Worsening COVID-19.

4.4.3.2.3 Adverse Events Leading to Discontinuation of Study Intervention

AEs leading to discontinuation of study intervention were reported for 1.3% of participants in the MOV group and 3.4% of participants in the placebo group [Table 9]. In the MOV group (n=5), these AEs include: nausea (n=2), vomiting (n=2), headache (n=1), peritonsillitis/tonsillitis (n=1), dizziness (n=1), fatigue (n=1), vision blurred (n=1). Drug-related AEs (as assessed by the investigator) leading to discontinuation of study intervention were reported for 0.8% of participants in each group [Table 9]. In the MOV group, these drug-related AEs include: nausea (n=1), vomiting (n=1), headache (n=1), dizziness (n=1), fatigue (n=1), vision blurred (n=1).

4.4.3.2.4 Adverse Events Leading to Death

AEs leading to death were reported for 0 (0.0%) participants in the MOV group and 10 (2.6%) participants in the placebo group [Table 9]. Of these, the 2 most frequently reported were COVID-19 and COVID-19 pneumonia, all in the placebo group.

Of the 10 deaths reported in the placebo group, 8 were included in the primary efficacy analysis (death occurred on or before Day 29) [Sec. 4.3.2.2.3]. The additional 2 deaths were associated with AE onset dates within the time period for AE reporting (refractory septic shock considered COVID-19 related by the investigator and worsening lung metastasis), but with death occurring after Day 29.

4.4.3.3 Laboratory Evaluations

Laboratory findings for hematologic parameters, liver enzymes, and lipase were comparable for the MOV and placebo groups [Table 13]. Laboratory findings that met predefined Grade criteria and were worse in Grade than at baseline were mostly Grade 1 or Grade 2 in both groups. The percentages of participants with Grade 3 or Grade 4 laboratory values were low in the MOV group and generally comparable for both groups [Table 13].

No participants in the MOV group met predetermined laboratory criteria of special interest (ie, laboratory values associated with potential drug-induced liver injury or platelet count of <50,000 cells/μL). One participant in the placebo group had a platelet count of <50,000 cells/μL.

No evidence of hematologic toxicity was observed in participants who received MOV. Additionally, no participants in the MOV group had a ≥50% decrease from baseline in platelet count compared with 0.9% of the participants in the placebo group.

Table 13 Participants with Laboratory Findings that Met Predetermined Criteria (Grade 1 to 4) APaT Population (P002 Phase 3 IA)

Criterion [a]	Molnupiravir		Placebo	
	n/m	%	n/m	%
Alanine Aminotransferase (IU/L)				
Grade 1: 1.25 - <2.5 x ULN	56/316	(17.7)	58/323	(18.0)
Grade 2: 2.5 - <5.0 x ULN	9/316	(2.8)	31/323	(9.6)
Grade 3: 5.0 - <10.0 x ULN	4/316	(1.3)	8/323	(2.5)
Grade 4: ≥10.0 x ULN	1/316	(0.3)	0/323	(0.0)
Aspartate Aminotransferase (IU/L)				
Grade 1: 1.25 - <2.5 x ULN	33/359	(9.2)	55/350	(15.7)
Grade 2: 2.5 - <5.0 x ULN	6/359	(1.7)	17/350	(4.9)
Grade 3: 5.0 - <10.0 x ULN	4/359	(1.1)	2/350	(0.6)
Grade 4: ≥10.0 x ULN	0/359	(0.0)	0/350	(0.0)
Bilirubin (mg/dL)				
Grade 1: 1.1-<1.6 x ULN	10/359	(2.8)	9/354	(2.5)
Grade 2: 1.6 - <2.6 x ULN	2/359	(0.6)	0/354	(0.0)
Grade 3: 2.6 - <5.0 x ULN	0/359	(0.0)	0/354	(0.0)
Grade 4: ≥5.0 x ULN	0/359	(0.0)	0/354	(0.0)
Lipase (IU/L)				
Grade 1: 1.1 - <1.5 x ULN	19/357	(5.3)	12/353	(3.4)
Grade 2: 1.5 - <3.0 x ULN	6/357	(1.7)	19/353	(5.4)
Grade 3: 3.0 - <5.0 x ULN	0/357	(0.0)	3/353	(0.8)
Grade 4: ≥5.0 x ULN	0/357	(0.0)	3/353	(0.8)
Hemoglobin (g/dL)				
Grade 1: Male: 10.0 - 10.9 Female: 9.5 - 10.4	8/323	(2.5)	1/326	(0.3)
Grade 2: Male: 9.0 - <10.0 Female: 8.5 - <9.5	4/323	(1.2)	2/326	(0.6)
Grade 3: Male: 7.0 - <9.0 Female: 6.5 - <8.5	1/323	(0.3)	3/326	(0.9)
Grade 4: Male: <7.0 Female: <6.5	0/323	(0.0)	0/326	(0.0)
Absolute Neutrophil Count (10^9/L)				
Grade 1: 0.800 - 1.000	3/248	(1.2)	8/250	(3.2)
Grade 2: 0.600 - 0.799	3/248	(1.2)	1/250	(0.4)
Grade 3: 0.400 - 0.599	0/248	(0.0)	0/250	(0.0)
Grade 4: <0.400	0/248	(0.0)	0/250	(0.0)
Platelets (10^9/L)				
Grade 1: 100 - <125	6/317	(1.9)	11/321	(3.4)
Grade 2: 50 - <100	2/317	(0.6)	3/321	(0.9)
Grade 3: 25 - <50	0/317	(0.0)	0/321	(0.0)
Grade 4: <25	0/317	(0.0)	1/321	(0.3)
Leukocytes (10^9/L)				
Grade 1: 2.000 - 2.499	9/323	(2.8)	7/326	(2.1)
Grade 2: 1.500 - 1.999	0/323	(0.0)	1/326	(0.3)
Grade 3: 1.000 - 1.499	0/323	(0.0)	1/326	(0.3)
Grade 4: <1.000	0/323	(0.0)	0/326	(0.0)

[a]For graded criteria: participants are counted once per test in the highest grade reported.
For inclusion in this analysis, both a baseline and at least one post-baseline laboratory value had to be present. Only subjects with a worsened grade from baseline were included.
Grades are based on the NIH DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 or predefined limit of change (PDLC).
n = Number of participants with on-treatment postbaseline test results that met the predetermined criterion and are worse in grade than at baseline.
m = Number of participants with a baseline and at least one postbaseline test result.
ULN = Upper limit of normal range.

4.4.3.4 Subgroup Analyses

The percentages of participants with at least 1 AE were comparable in the age subgroups of ≥65 years and <65 years for both MOV and placebo groups. The results of subgroup analyses were consistent with results from the overall AE analyses. Participants aged ≥65 years had higher rates of SAEs compared with participants aged <65 years in both intervention groups. This reflects the epidemiology of COVID-19 where it has been observed that older patients are at higher risk for severe disease and adverse outcomes.

4.4.4 Supportive Safety Results

P002 (Phase 2)

A total of 299 non-hospitalized participants with COVID-19 received at least 1 dose of MOV (n=74 MOV 800 mg) or placebo (n=74) in the completed Phase 2 part of P002. Participant disposition and duration of exposure were comparable across all intervention groups. The majority of participants (94.7% MOV combined; 94.6% placebo) received 9 to 10 doses with a mean duration of treatment of ~4.4 days.

The safety profiles for MOV (all doses) and placebo were comparable. No trends in AEs or changes in clinical laboratory values were observed as a function of dose or study intervention. The following key safety results were observed:

- The most frequently reported AEs (≥5%) were COVID-19 pneumonia (5.4%) in the MOV 800 mg group, and diarrhea (5.4%) and COVID-19 (6.8%) in the placebo group.
- The percentage of participants with drug-related AEs (as assessed by the investigator) was comparable across all intervention groups.
- SAEs were reported for 3.6% participants in the MOV combined group, and 5.4% participants in the placebo group. None were considered drug-related by the investigator.
- AEs leading to study intervention discontinuation were reported for 1.3% participants in the MOV groups combined (none were drug-related per the investigator) and for 1.4% in the placebo group (drug-related per the investigator).
- One death was reported (in the placebo group on Day 36).
- No participants met predetermined laboratory criteria of special interest (ie, laboratory values associated with potential drug-induced liver injury, platelet count of <50,000 cells/μL, or lipase values >3x the upper limit of normal).
- No evidence of hematologic or hepatic toxicity was observed for MOV.

P006

A total of 202 non-hospitalized participants with COVID-19 received at least 1 dose of MOV (n=55 MOV 800 mg) or placebo (n=62) in the completed Phase 2a outpatient study (P006). Participant disposition was comparable across all groups. Most (>90%) participants in each group received 10 doses with a mean duration of treatment being approximately 5 days.

No treatment- or dose-related trends in AEs or changes in clinical laboratory values (including hematology and clinical chemistry) were observed. The most frequently reported AE (≥5% participants) in any group was insomnia (2.9% combined MOV group; 6.5% placebo group). SAEs were reported for 4 participants (n=3/140 [2.1%] combined MOV group; n= 1/62 [1.6%] placebo group); none were considered drug-related by the investigator. No participants died while enrolled in the study. One participant in the placebo group died 31 days after discontinuation from the study. AEs leading to discontinuation of study intervention were reported for 2/140 (1.4%) participants in the combined MOV groups, and 1/62 (1.6%) in the placebo group.

P001

A total of 293 hospitalized participants with COVID-19 received at least 1 dose of MOV (n=72 MOV 800 mg) or placebo (n=75) in the completed Phase 2 part of P001. The majority of participants (93.6% MOV combined; 96.0% placebo) received 9 to 10 doses with a mean duration of treatment of approximately 4.4 days.

The safety profiles for MOV (all doses) and placebo were comparable. No trends in AEs or changes in clinical laboratory values were observed as a function of dose or study intervention. The following key safety results were observed:

- The most frequently reported AEs (≥5%) in any MOV group (200 mg, 400 mg, 800 mg) were COVID-19 (9.6%, 8.2%, 6.9%), AST/ALT elevations (4.1%/5.5%, 6.8%/6.8%, 6.9%/9.7%), constipation (6.8%, 2.7%, 0.0%), bacterial pneumonia (1.4%, 0.0%, 5.6%), hyperglycemia (5.5%, 6.8%, 0.0%), and respiratory failure (4.1%, 5.5%, 4.2%), and in the placebo group were constipation (6.7%), COVID-19 (9.3%), COVID-19 pneumonia (6.7%), ALT increased (10.7%), and respiratory failure (5.3%).
- SAEs were reported for 15.1% participants in the MOV groups combined and 16.0% in the placebo group. One drug-related SAE (Grade 3 urticaria; per investigator assessment) was reported for 1 participant in the MOV 200 mg group.
- AEs leading to study intervention discontinuation were reported for 1 participant in the MOV 400 mg group (not drug-related per the investigator).
- AEs leading to death were reported for 16 participants (6.4% in the MOV groups combined and 2.7% in the placebo group). Most deaths occurred in participants who had severe COVID-19 at baseline (12/16 [75%]), were >60 years of age (13/16 [81%]), had underlying comorbidities (14/16 [87%]), and/or had duration of COVID-19 symptoms >5 days before randomization (12/16 [75%]). The deaths were associated with COVID-19

complications, respiratory failure, sepsis, or thrombosis. None of the deaths were considered drug-related per investigator assessment.

- No evidence of hematologic or hepatic toxicity was observed for MOV.
- Two participants met predetermined laboratory criteria of special interest. One participant (placebo group) had a confirmed platelet value <50,000 cells/µL on Day 10. One participant (MOV 800 mg) met the criteria for potential drug induced liver injury on Day 14 and did not meet the criteria by Day 15. The laboratory parameters were considered to be secondary to fatal septic shock and cholestasis and not associated with drug induced liver injury. No participant met predetermined laboratory criteria of special interest of a confirmed amylase or lipase value >3X ULN.

P004

A total of 64 healthy participants in Part 1 (single ascending dose assessment), 10 participants in Part 2 (food effect assessment), and 56 participants in Part 3 (multiple ascending dose assessment) were randomized, dosed, and completed the Phase 1 study (P004).

MOV single doses up to 1600 mg (including the food effect panel evaluated at 200 mg MOV) and multiple doses up to 800 mg MOV Q12H for 5.5 days were generally well tolerated in these healthy participants. No SAEs were reported. No clinically meaningful trends were observed for changes in clinical laboratory values (including hematology values), vital signs, or ECGs as a function of dose or treatment. One participant discontinued study intervention after receiving 3 days of 800 mg MOV Q12H due to a rash.

P005

This study in non-hospitalized participants with COVID-19 is ongoing and remains blinded. No safety concerns were identified in the most recent Data Monitoring and Ethics Committee report (n=60). The committee recommended continuation of the study uninterrupted. As of 31-OCT-2021, a total of 150 participants have been enrolled and received MOV or placebo. Five SAEs were reported; 1 of these SAEs was assessed as drug-related by the investigator and led to discontinuation of study intervention. No deaths or Grade 4 AEs were reported.

P007

This study in hospitalized participants with COVID-19 is ongoing and remains blinded. No safety concerns were observed based on the second interim analysis (n=52). The safety review committee for the study recommended continuation of the study uninterrupted. As of 31-OCT-2021, a total of 65 participants have been enrolled and received MOV or placebo. Three SAEs were reported; none of the SAEs were considered drug-related by the investigator and 1 led to discontinuation of study intervention. A nonserious AE leading to discontinuation of study intervention was reported for 1 participant and assessed by the investigator as drug-related. No participant had a platelet count <50,000 cells/µL.

4.4.5 Summary of Key Safety Results

In adult participants with COVID-19:

- MOV (800 mg Q12H for 5 days) was generally well-tolerated with no major safety concerns identified.
- There was no evidence of hematologic toxicity for MOV (doses ranging between 200 mg and 800 mg Q12H for 5 days) based on laboratory evaluations.

4.4.6 Safety Conclusion

The totality of the safety data from Phase 1, Phase 2, and Phase 3 studies demonstrates MOV has an acceptable safety and tolerability profile and supports the proposed use under EUA.

5 BENEFIT-RISK ASSESSMENT

The benefit/risk profile for MOV is strongly favorable, supporting use of MOV for the proposed use under EUA. MOV has been shown to be efficacious in significantly reducing hospitalization and death in adult patients with mild to moderate COVID-19, at risk for progressing to severe illness, when administered within 5 days of symptom onset.

MOV represents a major clinical benefit for both the individual patient and for public health. Based on the totality of data, the treatment benefits of MOV in patients with mild to moderate COVID-19 include:

- A 50% reduction in the risk of hospitalization or death [Sec. 4.3.2.2.3]
- Consistent benefit across subgroups (including age, underlying medical conditions, and across viral clades, including variants of concern such as Delta variant) [Sec. 4.3.2.2.3]
- Potential improvement in patient-reported signs/symptoms of COVID-19 [Sec. 4.3.2.2.4]
- Oral administration with or without food, a low potential for DDIs, and no dose adjustments for individuals with renal or hepatic impairment [Sec. 4.2]
- Reduction in SARS-CoV-2 RNA and infectious virus [Sec. 4.3.1.1] [Sec. 4.3.2.2.5]
- Low risk for development of viral resistance [Sec. 4.3.1.1].

Safety analyses demonstrate that MOV is well tolerated in patients with COVID-19 with no organ toxicities observed in clinical studies. Nonclinical safety findings have been comprehensively assessed and support the proposed short-term use of MOV for the treatment of mild to moderate COVID-19 in adults, specifically:

- The comprehensive genotoxicity assessments in robust and well-characterized regulatory studies indicate MOV has low risk for genotoxicity [Sec. 3.3.3].
- Hematopoietic findings, observed in dogs only, were not seen in clinical studies [Sec. 3.3.2] [Sec. 4.4.3.3].
- Growth plate findings in rapidly growing rats administered MOV for 3 months are not relevant for adults [Sec. 3.3.2].
- Embryo-fetal lethality and teratogenicity were observed in pregnant rats at exposures 8-fold the clinical NHC exposure, and not observed in rabbits at 18-fold the NHC clinical exposure [Sec. 3.3.4]. There were no MOV-related effects on growth, sexual maturation, neurobehavioral, or reproductive function in the offspring observed in preliminary PPND study results (in pregnant rats at ~2-fold the clinical NHC exposure).

Based on the findings in rats, use of MOV during pregnancy is not recommended, and use of contraception in individuals of child-bearing potential is advised for the duration of NHC systemic exposure (during treatment and for the 4 days following completion).

There is an urgent unmet need for safe and effective oral agents for the treatment COVID-19 in non-hospitalized patients, especially in the context of an ongoing pandemic with emergence of SARS-CoV-2 variants of concern. The risk-benefit assessment of MOV to date supports an EUA for MOV under Section 564 of the Federal Food, Drug, and Cosmetic Act.

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