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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

This list serves as the first appearance in text.

The following terms may be used interchangeably within the document:

- Participant and subject
- Study and trial
- Intervention and medication

Abbreviation	Definition
A	Adenine
AE	Adverse event
ALT	Alanine aminotransferase
APaT	All participants as treated
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{0-12}	Are under the concentration-time curve from time 0 up to 12 hours
AUC_{0-inf}	Area under the concentration-time curve from time 0 extrapolated to infinity
BCS	Biopharmaceutics classification system
BMI	Body mass index
C	Cytosine
CI	Confidence interval
C_{max}	Maximum concentration
COVID	Coronavirus
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
CSR	Clinical study report
CYP	Cytochrome P450
DDI	Drug-drug interaction
DFC	Dry-filled capsule
DILI	Drug-induce liver injury
ECG	Electrocardiogram
ECI	Events of clinical interest
eDMC	External data monitoring committee
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOT	End-of-treatment

Abbreviation	Definition
E-R	Exposure-response
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FMI	Final market image
FSA	Financial sharing area
G	Guanine
GMR	Geometric mean ratio
IA	Interim analysis
IAV	Influenza A virus
ISS	Integrated Summary of Safety
JNDA	Japanese New Drug Application
MAA	Marketing Authorization Application
mAb	Monoclonal antibody
MAH	Marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
MHRA	Medicines and Healthcare Products Regulatory Agency
MHV	Mouse hepatitis virus
MITT	Modified intent-to-treat
MOA	Mechanism of action
MOV	Molnupiravir, MK-4482, EIDD-2801
NEWS	National Early Warning System
NGS	Next-generation sequencing
NHC	N-hydroxycytidine
NHC-TP	N-hydroxycytidine triphosphate
NP	Nasopharyngeal
OP	Oropharyngeal
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PDLC	Predefined limit of change
PIB	Powder-in-bottle
PK	Pharmacokinetics
PMDA	Pharmaceutical and Medical Device Agency

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Abbreviation	Definition
PopPK	Population pharmacokinetics
Q12H	Every 12 hours
QTc	QT interval corrected for heart rate
RdRp	RNA-Dependent RNA polymerase
RNA	Ribonucleic acid
RT-PCR	Reverse-transcriptase polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SMQ	Standardized MedDRA query
SOC	System organ class
SpO2	Oxygen saturation
sSAP	Supplemental statistical analysis plan
$t_{1/2}$	Terminal half-life
t_{max}	Time to reach C_{max}
U	Uracil
UK	United Kingdom
ULN	Upper limit of normal
US	United States
VEEV	Venezuelan equine encephalitis virus
WHO	World Health Organization
WOCBP	Women of childbearing potential

1 PRODUCT DEVELOPMENT RATIONALE

1.1 Introduction

Molnupiravir (also known as MK-4482 and EIDD-2801; hereafter referred to as MOV) is a novel ribonucleoside analog prodrug with broad-spectrum antiviral activity against a range of RNA viruses, including coronaviruses. This application provides results from 8 clinical studies supporting the use of MOV for treatment of COVID-19 in adults, including 3 studies providing efficacy data and 8 providing safety data (see [Table 2.5-covid19txallpop: 1]).

1.2 Pharmacological Class

MOV is the 5'-isobutyrate prodrug of the broadly active, antiviral ribonucleoside analog N-hydroxycytidine (NHC). MOV inhibits viral replication by inducing viral error catastrophe.

1.3 Mechanism of Action

MOV is a prodrug that is metabolized to NHC, which distributes into cells where it is phosphorylated to form the pharmacologically active ribonucleoside triphosphate (NHC-TP). NHC-TP acts by a mechanism known as viral error catastrophe. NHC-TP incorporation into viral RNA by the viral polymerase results in an accumulation of errors in the viral genome leading to inhibition of replication [Ref. 5.4: 06G338, 06G33J, 07ZS9M].

The viral error catastrophe mechanism of action for MOV/NHC has been demonstrated in vitro for SARS-CoV-2 and other viruses, including MERS-CoV, VEEV, MHV, and IAV. In the presence of NHC, these viruses were observed to have increased errors and concomitant multi-log decreases in the amount of infectious virus produced [Ref. 5.4: 05K8L0, 05JF05, 05JF0D] [Ref. 5.4: 05JF0F]. Clinical virology data presented in this application support the mechanism of action of MOV. Sequence analysis of samples collected pre- and post-treatment with MOV showed an increase in mutations across the entire viral genome, which were not localized to genes in the viral RdRp complex.

1.4 Scientific Background

1.4.1 Epidemiology of COVID-19

COVID-19, a disease resulting from SARS-CoV-2 infection, was declared a global pandemic by the WHO on 11-MAR-2020 [Ref. 5.4: 05LDCR]. As of March 2022, more than 450 million confirmed cases of SARS-CoV-2 infection and over 6.0 million COVID-19-related deaths have been reported globally [Ref. 5.4: 07ZNZ8, 07ZNMF]. SARS-CoV-2 variants of concern (ie, B.1.1.7, B.1.351, P1 B.1.617.2, or B.1.1.529) have been associated with gradual increases in the frequency of global COVID-19 cases and hospitalizations observed since late 2020 in Western Europe, South Africa, India, and the UK and since early 2021 in the US [Ref. 5.4: 05QSGT, 05QSGV, 06DRQH] [Ref. 5.4: 07ZHSX, 07ZGNF, 07ZGNC] [Ref. 5.4: 07ZGBW, 07ZGBD].

Patients with SARS-CoV-2 infection may experience a range of clinical manifestations, from no symptoms to critical illness [Ref. 5.4: 05QYK2]. Illness in adults infected with SARS-CoV-2 has typically been categorized as asymptomatic/presymptomatic, mild, moderate, severe, or critical [Ref. 5.4: 05QYK2, 05JSVW]. There is a markedly increased risk of more severe COVID-19 disease in adults, especially in the population 60 years of age or older [Ref. 5.4: 05JSVW, 05Q36T, 05Q5B2] [Ref. 5.4: 06CXMG]. Available data suggest that 5% to 20% of patients with COVID-19 progress to severe disease, characterized primarily by acute respiratory failure [Ref. 5.4: 05J92M, 05M3T6, 05JSVW] [Ref. 5.4: 05Q368, 05H4S0, 05JQSM]. The reported mortality rate for hospitalized patients with severe COVID-19 is approximately 28% (95% CI: 24% to 33%); mortality rates increase to >50% for patients who require admission to the intensive care unit [Ref. 5.4: 05M3T6, 05JSVW, 05H4S0] [Ref. 5.4: 05JQSM, 05Q339, 05Q59Q] [Ref. 5.4: 05Q59S]. The majority of COVID-19 fatalities have been observed in patients 60 years of age or older and/or those patients with 1 or more underlying comorbidities [Ref. 5.4: 05Q36T, 05Q5B2, 05Q28G] [Ref. 5.4: 06FNC6, 06FPGT, 07VXR4] [Ref. 5.4: 07VXR5]. It has been reported that a subset of individuals who have had COVID-19 experience prolonged symptoms months after their acute infection, including those with mild-to-moderate disease at baseline [Ref. 5.4: 05Q3BF].

1.4.2 Treatment Options for COVID-19

While several mAbs and antivirals have received various types of regulatory authorizations and/or approvals (depending on the specific country) for the treatment of COVID-19, there remains a signification unmet medical need for additional safe and effective therapeutic agents for COVID-19 in the post-vaccine rollout setting.

Emergency use and/or marketing authorization for the following mAbs has been granted for the treatment of mild-to-moderate COVID-19 in one or more jurisdictions:

- Casirivimab/imdevimab [Ref. 5.4: 05NDX9, 06CVLG]
- Bamlanivimab/etesevimab [Ref. 5.4: 05R0GM, 05N24Z, 06CKTQ] [Ref. 5.4: 06CVLD]
- Sotrovimab [Ref. 5.4: 06FJ2W, 07ZDFN, 07ZRZT]
- Regdanvimab [Ref. 5.4: 06CVLB]
- Bebtelovimab [Ref. 5.4: 0803XQ]

Monoclonal antibodies are intended for patients recently diagnosed as having COVID-19 who are not sick enough to be in the hospital, but who have risk factors for progressing to severe infection [Ref. 5.4: 06FZ2V]. Most mAb therapies are administered via intravenous infusion and patients must be monitored during the infusion and for at least 1 hour after infusion. Hypersensitivity reactions, including anaphylaxis and infusion-related reactions, have been reported in patients who received anti-SARS-CoV-2 mAbs [Ref. 5.4: 06FZ2W]. MOV is an oral antiviral easily administered in an outpatient setting.

As new SARS-CoV-2 variants emerge, mAbs may become less effective due to mutations in the spike protein that alter the antibody binding site [Ref. 5.4: 05QYJY, 06FXLB]. A recent study evaluated the sensitivity of the Delta variant to the humoral immune response and found that some antibodies targeting the N-terminal domain and receptor binding domain of the spike protein (S protein) showed impaired binding and neutralization of the Delta variant [Ref. 5.4: 06FXLB]. Loss of neutralizing activity of some mAbs due to mutations in the S protein has also been shown for the Omicron variant [Ref. 5.4: 07ZRN7, 07YNH8, 07ZP65] [Ref. 5.4: 07ZP62]. In vitro, NHC has a high genetic barrier to the development of resistance in preclinical models and retains activity against SARS-CoV-2 variants associated with changes in the viral spike protein [Ref. 5.4: 05JF0G, 07ZMDH].

In addition to MOV, the following antivirals received various types of regulatory authorizations and/or approvals (depending on the specific country) for the treatment of COVID-19:

- Nirmatrelvir/ritonavir [Ref. 5.4: 07Z89B, 07ZPQV]
- Remdesivir [Ref. 5.4: 05KD2T, 05QZ8C, 05NSZH] [Ref. 5.4: 05QSYW, 05LM0Q, 05LLZX] [Ref. 5.4: 06FJ2W]

For certain population segments, these agents may not be appropriate either due to DDIs or the presence of underlying medical conditions (eg, hepatic or renal impairment) [Ref. 5.4: 07Y69M]. These characteristics may preclude the use of some antiviral treatments for a proportion of the population. Assessment and/or mitigation of DDIs, including consultations with the prescriber and potentially specialty health care professionals may also be needed for certain patients which could potentially lead to delays in initiation of treatment. Antiviral treatments for COVID-19 are demonstrated to be more effective when initiated within 5 days of symptom onset. Thus, delay in antiviral treatment initiation to address DDIs may lead to suboptimal antiviral efficacy.

MOV is unlikely to be a victim or perpetrator of DDIs. MOV and NHC did not inhibit or induce the activity of any of the major CYP enzymes tested in vitro, nor did they inhibit any of the major drug transporters tested in vitro. These data suggest that the potential for DDIs between MOV/NHC and concomitant medications is low [Ref. 2.6.4: 7]. No PD interaction is expected between MOV and other commonly administered antivirals based on a lack of synergy or antagonism for antiviral activity in vitro against SARS-CoV-2 [Sec. 2.6.2: 5]. Additionally, a PopPK analysis on the impact of hepatic impairment and renal impairment on NHC exposures did not identify clinically meaningful differences in NHC exposures with either hepatic or renal dysfunction, and no dose adjustment is recommended in these patient populations [Sec. 2.7.2-covid19txallpop: 3.2.5, 3.2.6] [Ref. 5.3.5.3: 07ZRF9]. Therefore, MOV has the potential to provide a therapeutic option in patients with multiple medications or comorbidities.

1.5 Overview of Clinical Development Program

The results from 8 clinical studies supporting the use of MOV in adults ≥18 years of age for the treatment of COVID-19 are included in this application [Table 2.5-covid19txallpop: 1]. Additional details for these studies are provided in [Table 2.5-covid19txallpop: 2].

Table 2.5-covid19txallpop: 1
Summary of Molnupiravir Clinical Studies and Results Included in this Application

Study	Phase/Population	Study Results Included in Application
MK-4482-002 (P002)	Phase 2 (Part 1)/non-hospitalized Phase 3 (Part 2)/non-hospitalized	Phase 2 (Part 1): Results for safety, efficacy, and virology Phase 3 (Part 2): Results for safety, efficacy, and virology
MK-4482-006 (P006)	Phase 2a/non-hospitalized	Final results for safety, efficacy, and virology
MK-4482-001 (P001)	Phase 2/hospitalized	IA results for safety (through Day 29), efficacy (through Day 29; primary endpoint), virology, and PK
MK-4482-007 (P007)	Phase 2a/hospitalized	Preliminary (blinded) summary of safety
MK-4482-005 (P005)	Phase 1/2/hospitalized	Preliminary (blinded) summary of safety
MK-4482-004 (P004)	Phase 1/healthy participants	Final results for safety and PK
MK-4482-012 (P012)	Phase 1/healthy participants	Final results for safety and PK
MK-4482-008 (P008)	Phase 1/healthy participants	Final results for safety and PK
IA=interim analysis; PK=pharmacokinetic.		

1.5.1 Phase 2/3

1.5.1.1 P002

P002 is a Phase 2/3 study evaluating the efficacy, safety, and PK of MOV administered to non-hospitalized adults. Part 1 (Phase 2) was designed to enroll participants with laboratory-confirmed SARS-CoV-2 infection and symptom onset within 7 days before randomization. Participants with mild COVID-19 and at least 75% of overall participants were to have at least 1 characteristic (eg, age >60 years) or underlying medical condition (eg, obesity) associated with being at increased risk for severe illness from COVID-19. SARS-CoV-2 vaccines were prohibited any time before randomization and through Day 29. The primary efficacy objective was to evaluate the efficacy of MOV compared with placebo as assessed by the percentage of participants who are hospitalized and/or die through Day 29.

In Part 1, a dose-ranging evaluation was performed to select the dose of MOV for further evaluation in Part 2 (Phase 3) of the study. Participants in Part 1 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 mutation rate as assessed by comparison of baseline and post-baseline virus sequencing, and PK parameters. In Part 1, 302 participants were enrolled and all participants completed the Day 29 visit. The protocol-specified IA2 was then performed.

IA2 results showed that the percentage of participants who were hospitalized or died through Day 29 was comparable across intervention groups. Post-hoc subgroup analyses 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 IA2 results also showed that all MOV doses were generally well tolerated with no dose-limiting toxicity observed at the highest dose (800 mg). Based on the totality of safety and virologic data from the MOV clinical program, as well as trends in post-hoc subgroup analyses for clinical efficacy in P002, the 800 mg dose of MOV was selected for further evaluation in Part 2.

The IA2 results supported proceeding to Part 2. Study criteria were revised (by a protocol amendment) for Part 2 to randomize participants within 5 days of symptom onset. All participants in Part 2 were also to have mild or moderate COVID-19 and at least 1 characteristic (eg, age >60 years) or underlying medical condition (eg, obesity) associated with being at increased risk for severe illness from COVID-19. SARS-CoV-2 vaccines were prohibited any time before randomization and through Day 29 in order to avoid confounding the assessment of efficacy. The primary efficacy objective was to evaluate the efficacy of MOV compared with placebo as assessed by the percentage of participants who are hospitalized and/or die through Day 29.

In Part 2, participants were randomized 1:1 to receive either MOV 800 mg or placebo Q12H for 5 days and followed for primary efficacy evaluation through Day 29. P002 Part 2 was designed and powered to formally evaluate the efficacy of MOV at the 800 mg dose. A total of 1433 participants were randomized and followed through Day 29. MOV 800 mg Q12H demonstrated superiority to placebo in reducing the risk of hospitalization or death through Day 29. Results from P002 also showed that the safety profile of MOV 800 mg Q12H was comparable to placebo. In Part 2, all participants have completed through Day 29 (efficacy evaluation) and are continuing through the Late Follow-up Visit.

Safety results in this Clinical Overview present data from P002 Part 1 (MOV 800 mg and placebo) and Part 2 combined because these results include data from the participants who received MOV 800 mg Q12H for 5 days in P002. Select safety results from P002 Part 2 alone are also presented.

1.5.2 Phase 2

1.5.2.1 P006

The Phase 2a study P006 assessed the safety, virologic response, and clinical 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 before study entry.

The primary efficacy objective for the study was to determine if MOV reduces the time to viral RNA negativity as assessed by RT-PCR of NP swabs.

In Part 1 of the study, 46 participants were randomized 1:1 to receive 200 mg MOV or placebo Q12H for 5 days. In Parts 2 to 9 of the study, 156 participants were randomized 3:1 to receive 200, 400, or 800 mg MOV or placebo Q12H for 5 days.

Results showed that the median time to clearance of viral RNA was shorter and the decrease from baseline in SARS-CoV-2 RNA viral load was greater for the 800 mg Q12H MOV group compared with the placebo group. The proportion of participants with positive SARS-CoV-2 cultures also decreased faster for participants with 800 mg MOV compared with placebo. MOV was generally well tolerated at all doses. The results from this study contributed to the selection of the 800 mg dose for the evaluation in P002 Part 2.

1.5.2.2 P001 (Part 1)

P001 was designed as a Phase 2/3 study to evaluate the efficacy, safety, and PK of MOV administered to hospitalized adults with laboratory-confirmed SARS-CoV-2 infection and symptom onset within 10 days before randomization. The primary efficacy endpoint was to evaluate the efficacy of MOV compared with placebo as assessed by the rate of sustained recovery from randomization through Day 29.

Part 1 of P001 was designed as a dose-ranging study in which participants were randomized 1:1:1:1 to receive MOV 200, 400, or 800 mg or placebo Q12H for 5 days. Enrollment of 304 participants in Part 1 was completed in [redacted] 20[redacted], all participants completed the Day 29 visit in [redacted] 20[redacted], and the protocol-specified IA2 was performed in [redacted] 20[redacted] (during the same time period as P002).

Results from IA2 showed no clear effect of MOV treatment on sustained recovery for hospitalized participants. MOV doses were generally well tolerated with no dose-limiting toxicity observed at the highest dose (800 mg).

The IA2 results from P001 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, P001 Part 2 was not initiated.

Results from P001 Part 1 are included in this application as supportive evidence of the efficacy and safety of MOV.

1.5.3 Overview of the Phase 1 Program

The following Phase 1 clinical studies were conducted to assess the safety, tolerability, and PK of MOV:

- P004: randomized, double-blind placebo-controlled, first-in-human study evaluating single and multiple doses in healthy participants
- P012: randomized, double-blind, placebo-controlled study evaluating multiple doses of MOV in healthy participants
- P008: randomized, double-blind, placebo-controlled study evaluating single and multiple doses of MOV in healthy Japanese male participants

In the Phase 1 studies, 175 participants were enrolled and received single doses of MOV ranging from 50 to 1600 mg or multiple doses ranging from 50 to 800 mg. Results from the Phase 1 program showed that MOV administered as single doses up to 1600 mg and multiple doses up to 800 mg Q12H for up to 10.5 days were generally well tolerated in healthy participants.

1.5.4 Ongoing Blinded Studies

Part 2 of the P005 study (Phase 2) and the Phase 2a P007 study are ongoing and remain blinded.

P005 is implementing an adaptive design to evaluate the safety and efficacy of MOV for the treatment of COVID-19 in outpatient adults.

P007 is assessing MOV in adults who have tested positive for SARS-CoV-2 infection via PCR and are hospitalized with a diagnosis of COVID-19 with symptoms ≤7 days. Preliminary blinded safety summaries for these studies are included in this application.

An overview of the clinical development program is provided in [Table 2.5-covid19txallpop: 2].

Table 2.5-covid19txallpop: 2
Overview of the Molnupiravir Clinical Development Program

<table>
<tr><th>Study Number (Status) [CTD Location] Regions</th><th>Design</th><th>Number of Participants by Intervention Group</th><th>Study Population (N)</th><th>Primary Endpoint(s)</th></tr>
<tr><td colspan="5">Phase 2⁄3 Studies</td></tr>
<tr>
<td>MK-4482-002 (MOVe-OUT, P002) (Part 1 [Phase 2] completed; Part 2 [Phase 3] ongoing) [Ref. 5.3.5.1: P002V01MK4482] [Ref. 5.3.5.1: P002V03MK4482]
North America
Latin America
Europe
Asia Pacific
Africa</td>
<td>Randomized, placebo-controlled, double-blind study</td>
<td>Part 1 (Phase 2):
<table>
<tr><td>Group</td><td>R</td><td>T</td><td>C</td></tr>
<tr><td>MOV 200 mg</td><td>75</td><td>74</td><td>71</td></tr>
<tr><td>MOV 400 mg</td><td>77</td><td>77</td><td>75</td></tr>
<tr><td>MOV 800 mg</td><td>76</td><td>74</td><td>71</td></tr>
<tr><td>MOV combined</td><td>228</td><td>225</td><td>217</td></tr>
<tr><td>Placebo</td><td>74</td><td>74</td><td>72</td></tr>
</table>
Part 2 (Phase 3): all randomized participants
<table>
<tr><td>Group</td><td>R</td><td>T</td><td>C</td></tr>
<tr><td>MOV 800 mg</td><td>716</td><td>710</td><td>680</td></tr>
<tr><td>Placebo</td><td>717</td><td>701</td><td>672</td></tr>
</table>
</td>
<td>Males/females ≥18 years of age with confirmed SARS-CoV-2 infection, non-hospitalized, at high risk for disease progression
Part 1 (Phase 2):
with symptom onset ≤7 days
<table>
<tr><th>Group</th><th>Sex M/F</th><th>Median Age (range) years</th></tr>
<tr><td>MOV 200 mg</td><td>35 M/40 F</td><td>50.0 (18 76)</td></tr>
<tr><td>MOV 400 mg</td><td>45 M/32 F</td><td>51.0 (24 84)</td></tr>
<tr><td>MOV 800 mg</td><td>35 M/41 F</td><td>52.0 (19 83)</td></tr>
<tr><td>MOV Combined</td><td>115 M/113 F</td><td>50.5 (18 84)</td></tr>
<tr><td>Placebo</td><td>44 M/30 F</td><td>44.5 (21 82)</td></tr>
</table>
Part 2 (Phase 3): with symptom onset ≤5 days
<table>
<tr><th>Group</th><th>Sex M/F</th><th>Median Age (range) years</th></tr>
<tr><td>MOV 800 mg</td><td>332 M/384 F</td><td>42.0 (18 90)</td></tr>
<tr><td>Placebo</td><td>366 M/351 F</td><td>44.0 (18 88)</td></tr>
</table>
</td>
<td>• Hospitalization or death
• AEs, AEs leading to discontinuation from study intervention</td>
</tr>
</table>

<table>
<tr><th>Study Number
(Status)
[CTD Location]
Regions</th><th>Design</th><th>Number of Participants
by Intervention Group</th><th>Study Population (N)</th><th>Primary
Endpoint(s)</th></tr>
<tr><td colspan="5">Phase 2a Study</td></tr>
<tr><td>MK-4482-006
(EIDD-2801-2003, P006) (completed)
[Ref. 5.3.5.1: P006MK4482]
North America</td><td>Randomized, double-blind, placebo-controlled study</td><td>Parts 1 to 9 Pooled:<table><tr><th>Group</th><th>R</th><th>T</th><th>C</th></tr><tr><td>MOV 200 mg</td><td>23</td><td>23</td><td>23</td></tr><tr><td>MOV 400 mg</td><td>64</td><td>62</td><td>59</td></tr><tr><td>MOV 800 mg</td><td>55</td><td>55</td><td>52</td></tr><tr><td>MOV Combined</td><td>142</td><td>140</td><td>134</td></tr><tr><td>Placebo</td><td>62</td><td>62</td><td>61</td></tr></table></td><td>Males/females ≥18 years of age with laboratory-confirmed SARS-CoV-2 infection, initial symptom onset ≤7 days of randomization, non-hospitalized)
Parts 1 to 9 Pooled:<table><tr><th>Group</th><th>Sex
Male/Female</th><th>Median age
(range) years</th></tr><tr><td>MOV 200 mg</td><td>12 M/11 F</td><td>32.0 (19 65)</td></tr><tr><td>MOV 400 mg</td><td>30 M/32 F</td><td>42.5 (19 82)</td></tr><tr><td>MOV 800 mg</td><td>28 M/27 F</td><td>42 0 (18 68)</td></tr><tr><td>MOV Combined</td><td>70 M/70 F</td><td>41.0 (18 82)</td></tr><tr><td>Placebo</td><td>28 M/34 F</td><td>39.0 (19 71)</td></tr></table></td><td>• Qualitative RT-PCR
• All AEs leading to discontinuation of treatment, study drug-related discontinuation of treatment, new Grade 3 or higher AE, study drug-related new Grade 3 or higher AE</td></tr>
<tr><td>MK-4482-007
(P007) (ongoing)
United States</td><td>Randomized, placebo-controlled, double-blind study</td><td>Planned Enrollment: 84 participants
Part 1:
MOV 200 mg: 7 participants
MOV 400 mg: 7 participants
placebo: 7 participants
Part 2:
MOV 400 mg: 14 participants
placebo: 7 participants
Part 3:
MOV 800 mg: 14 participants
placebo: 7 participants
Part 4:
MOV TBD: 14 participants
placebo: 7 participants</td><td>Males/females ≥18 years of age with a new diagnosis of COVID-19 with a duration of symptoms ≤7 days</td><td>• Achievement of undetectable SARS-CoV-2 RNA by Day 5
• AEs, SAEs, physical examination (including vital signs) findings, safety laboratory assessments, and ECGs</td></tr>
</table>

<table>
<tr><th>Study Number
(Status)
[CTD Location]
Regions</th><th>Design</th><th>Number of Participants
by Intervention Group</th><th>Study Population (N)</th><th>Primary
Endpoint(s)</th></tr>
<tr><td colspan="5">Phase 2 Study</td></tr>
<tr><td>MK-4482-001
(MOVe-IN, P001)
(Part 1 [Phase 2] completed; Part 2 [Phase 3] not conducted)
[Ref. 5.3.5.1: P001V01MK4482]
North America
Latin America
Europe
the Middle East
Africa
Asia Pacific</td><td>Randomized, placebo-controlled, double-blind study</td><td>Part 1 (Phase 2):<table><tr><th>Group</th><th>R</th><th>T</th><th>C</th></tr><tr><td>MOV 200 mg</td><td>75</td><td>73</td><td>62</td></tr><tr><td>MOV 400 mg</td><td>75</td><td>73</td><td>60</td></tr><tr><td>MOV 800 mg</td><td>76</td><td>72</td><td>66</td></tr><tr><td>MOV Combined</td><td>226</td><td>218</td><td>188</td></tr><tr><td>Placebo</td><td>78</td><td>75</td><td>70</td></tr></table></td><td>Males/females ≥18 years of age with laboratory-confirmed SARS-CoV-2 infection (mild, moderate, or severe), initial symptom onset ≤10 days of randomization, hospitalized
Part 1:<table><tr><th>Group</th><th>Sex
Male/Female</th><th>Median age
(range) years</th></tr><tr><td>MOV 200 mg</td><td>43 M/32 F</td><td>59.0 (19 87)</td></tr><tr><td>MOV 400 mg</td><td>41 M/34 F</td><td>56.0 (28 91)</td></tr><tr><td>MOV 800 mg</td><td>44 M/32 F</td><td>56.5 (26 83)</td></tr><tr><td>MOV Combined</td><td>128 M/98 F</td><td>57.0 (19 91)</td></tr><tr><td>Placebo</td><td>44 M/34 F</td><td>58.5 (31 94)</td></tr></table></td><td>• Time to sustained recovery
• AEs, AEs leading to discontinuation from study intervention</td></tr>
<tr><td colspan="5">Phase 1/2 Study</td></tr>
<tr><td>MK-4482-005
(AGILE-CST 2; P005) (ongoing)
UK</td><td>Adaptive randomized, placebo-controlled, blinded study</td><td>Planned Enrollment: 180 participants
Phase 1: 6 cohorts randomized 2:1 to receive MOV or placebo
Phase 2: randomized 1:1 to receive MOV or placebo</td><td>Males/females ≥18 years of age with laboratory-confirmed COVID-19 who are within 5 days of symptom onset</td><td>• Dose-limiting toxicity using CTCAE over 7 days
• CTCAE grading related to platelets and/or lymphocytes
• Time to negative PCR</td></tr>
</table>

<table>
<tr><th>Study Number
(Status)
[CTD Location]
Regions</th><th>Design</th><th>Number of Participants
by Intervention Group</th><th>Study Population (N)</th><th>Primary
Endpoint(s)</th></tr>
<tr><td colspan="5">Phase 1 Studies</td></tr>
<tr>
<td>MK-4482-004
(P004) (completed)
[Ref. 5.3.3.1:
P004MK4482]
UK</td>
<td>Randomized,
double-blind,
placebo-controlled
first-in-human study</td>
<td>Part 1: single-ascending dose
<table>
<tr><th>Group</th><th>R</th><th>T</th><th>C</th></tr>
<tr><td>MOV 50 mg</td><td>6</td><td>6</td><td>6</td></tr>
<tr><td>MOV 100 mg</td><td>6</td><td>6</td><td>6</td></tr>
<tr><td>MOV 200 mg</td><td>6</td><td>6</td><td>6</td></tr>
<tr><td>MOV 400 mg</td><td>6</td><td>6</td><td>6</td></tr>
<tr><td>MOV 600 mg</td><td>6</td><td>6</td><td>6</td></tr>
<tr><td>MOV 800 mg</td><td>6</td><td>6</td><td>6</td></tr>
<tr><td>MOV 1200 mg</td><td>6</td><td>6</td><td>6</td></tr>
<tr><td>MOV 1600 mg</td><td>6</td><td>6</td><td>6</td></tr>
<tr><td>MOV Combined</td><td>48</td><td>48</td><td>48</td></tr>
<tr><td>Placebo</td><td>16</td><td>16</td><td>16</td></tr>
</table>
Part 2:
single-dose food effect;
MOV 200 mg fed/fasted: 10 randomized, treated, completed
Part 3: multiple oral doses Q12H × 5.5 days
<table>
<tr><th>Group</th><th>R</th><th>T</th><th>C</th></tr>
<tr><td>MOV 50 mg</td><td>6</td><td>6</td><td>6</td></tr>
<tr><td>MOV 100 mg</td><td>6</td><td>6</td><td>6</td></tr>
<tr><td>MOV 200 mg</td><td>6</td><td>6</td><td>6</td></tr>
</table>
</td>
<td>Healthy males/females ≥18 years of age
Part 1: single-ascending dose
<table>
<tr><th>Group</th><th>Sex M/F</th><th>Median age (range) years</th></tr>
<tr><td>MOV 50 mg</td><td>4/2</td><td>55.5 (34 57)</td></tr>
<tr><td>MOV 100 mg</td><td>4/2</td><td>39.5 (23 58)</td></tr>
<tr><td>MOV 200 mg</td><td>5/1</td><td>38.5 (26 60)</td></tr>
<tr><td>MOV 400 mg</td><td>4/2</td><td>42.5 (23 57)</td></tr>
<tr><td>MOV 600 mg</td><td>4/2</td><td>36.0 (21 57)</td></tr>
<tr><td>MOV 800 mg</td><td>6/</td><td>35.5 (23 56)</td></tr>
<tr><td>MOV 1200 mg</td><td>6/</td><td>31.5 (24 56)</td></tr>
<tr><td>MOV 1600 mg</td><td>6/</td><td>27.5 (25 46)</td></tr>
<tr><td>Placebo</td><td>14/2</td><td>38.5 (22 56)</td></tr>
</table>
Part 2:
Median age (range): 44.0 (30-60)
Sex M/F: 7/3
Part 3: multiple oral doses Q12H × 5.5 days
<table>
<tr><th>Group</th><th>Sex M/F</th><th>Median age (range) years</th></tr>
<tr><td>MOV 50 mg</td><td>5/1</td><td>31.0 (23 56)</td></tr>
<tr><td>MOV 100 mg</td><td>5/1</td><td>52.5 (20 58)</td></tr>
</table>
</td>
<td>Parts 1 and 3:
Safety evaluations, including safety laboratory assessments, physical examinations, ECGs, vital signs, and AEs
Part 2:
Plasma PK parameters, including C_{max}, t_{max}, $t_{1/2}$, CL/F, λz, V_z/F, and $AUC_{0\text{-inf}}$</td>
</tr>
</table>

<table>
<tr><th>Study Number (Status) [CTD Location] Regions</th><th>Design</th><th>Number of Participants by Intervention Group</th><th>Study Population (N)</th><th>Primary Endpoint(s)</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>MOV 300 mg</td><td>6</td><td>6</td><td>6</td></tr>
<tr><td>MOV 400 mg</td><td>6</td><td>6</td><td>6</td></tr>
<tr><td>MOV 600 mg</td><td>6</td><td>6</td><td>6</td></tr>
<tr><td>MOV 800 mg</td><td>6</td><td>6</td><td>6</td></tr>
<tr><td>MOV Combined</td><td>42</td><td>42</td><td>42</td></tr>
<tr><td>Placebo</td><td>14</td><td>14</td><td>14</td></tr>
</table>
</td><td>
<table>
<tr><td>MOV 200 mg</td><td>6/</td><td>32.5 (22 60)</td></tr>
<tr><td>MOV 300 mg</td><td>4/2</td><td>36.5 (20 58)</td></tr>
<tr><td>MOV 400 mg</td><td>5/1</td><td>38.5 (20 60)</td></tr>
<tr><td>MOV 600 mg</td><td>6/</td><td>23.5 (20 54)</td></tr>
<tr><td>MOV 800 mg</td><td>6/</td><td>27.5 (20 58)</td></tr>
<tr><td>Placebo</td><td>12/2</td><td>34.0 (19 59)</td></tr>
</table>
</td><td></td></tr>
<tr><td>MK-4482-012
(P012) (completed)
[Ref. 5.3.3.1: P012MK4482]
Belgium</td><td>Randomized, double-blind, placebo-controlled, multiple ascending dose study</td><td>MOV Q12H for 10.5 days
<table>
<tr><th>Group</th><th>R</th><th>T</th><th>C</th></tr>
<tr><td>MOV 400 mg</td><td>6</td><td>6</td><td>6</td></tr>
<tr><td>MOV 600 mg</td><td>6</td><td>6</td><td>6</td></tr>
<tr><td>MOV 800 mg</td><td>12</td><td>12</td><td>12</td></tr>
<tr><td>MOV Combined</td><td>24</td><td>24</td><td>24</td></tr>
<tr><td>Placebo</td><td>8</td><td>8</td><td>8</td></tr>
</table>
</td><td>Healthy males/females ≥18 years of age
<table>
<tr><th>Group</th><th>Sex M/F</th><th>Age Range</th></tr>
<tr><td>MOV 400 mg</td><td>2/4</td><td>33 52</td></tr>
<tr><td>MOV 600 mg</td><td>2/4</td><td>27 59</td></tr>
<tr><td>MOV 800 mg</td><td>6/6</td><td>27 59</td></tr>
<tr><td>MOV Combined</td><td>10/14</td><td>27 59</td></tr>
<tr><td>Placebo</td><td>6/2</td><td>30 59</td></tr>
</table>
</td><td>AEs, vital signs (temperature, heart rate, blood pressure, respiratory rate), ECG, laboratory safety tests (serum chemistry, hematology, and urinalysis)</td></tr>
<tr><td>MK-4482-008
(P008) (completed)
[Ref. 5.3.3.1: P008V01MK4482]
Japan</td><td>Randomized, placebo-controlled, double-blind study</td><td>Part 1: single oral dose with food effect
<table>
<tr><th>Group</th><th>R</th><th>T</th><th>C</th></tr>
<tr><td>MOV 200mg</td><td>6</td><td>6</td><td>6</td></tr>
<tr><td>MOV 400 mg</td><td>6</td><td>6</td><td>6</td></tr>
<tr><td>MOV 800 mg (fasted)</td><td>7</td><td>7</td><td>7</td></tr>
<tr><td>MOV 800 mg (fed)</td><td>7</td><td>6</td><td>6</td></tr>
<tr><td>MOV 1600 mg</td><td>6</td><td>6</td><td>6</td></tr>
<tr><td>Placebo</td><td>8</td><td>8</td><td>8</td></tr>
</table>
</td><td>Healthy male Japanese participants ≥20years of age
Part 1:
<table>
<tr><th>Group</th><th>Age Range (years)</th></tr>
<tr><td>MOV 200mg</td><td>52.5 (21 59)</td></tr>
<tr><td>MOV 400 mg</td><td>53.0 (31 57)</td></tr>
<tr><td>MOV 800 mg fasted</td><td>51.0 (24 57)</td></tr>
<tr><td>MOV 800 mg fed</td><td>48.5 (24 57)</td></tr>
<tr><td>MOV 1600 mg</td><td>53.5 (21 59)</td></tr>
</table>
</td><td>Part 1:
• AEs, vital signs, laboratory safety tests, 12-lead ECGs, physical examinations
• C_{max}, t_{max}, $t_{1/2}$, AUC_{0-12}, AUC_{0-last}, AUC_{0-inf}
Part 2:
• AEs, vital signs,</td></tr>
</table>

<table>
<tr><th>Study Number (Status) [CTD Location] Regions</th><th>Design</th><th>Number of Participants by Intervention Group</th><th>Study Population (N)</th><th>Primary Endpoint(s)</th></tr>
<tr>
<td></td>
<td></td>
<td>Part 2: multiple oral doses Q12H for 5.5 days
<table>
<tr><th>Group</th><th>R</th><th>T</th><th>C</th></tr>
<tr><td>MOV 400 mg</td><td>15</td><td>15</td><td>15</td></tr>
<tr><td>MOV 800 mg</td><td>15</td><td>15</td><td>15</td></tr>
<tr><td>Placebo</td><td>10</td><td>10</td><td>10</td></tr>
</table>
</td>
<td>
<table>
<tr><td>Placebo</td><td>51.0 (28 57)</td></tr>
</table>
Part 2:
<table>
<tr><th>Group</th><th>Age Range (years)</th></tr>
<tr><td>MOV 400 mg</td><td>42.0 (20 59)</td></tr>
<tr><td>MOV 800 mg</td><td>45.0 (21 57)</td></tr>
<tr><td>Placebo</td><td>49.5 (24 59)</td></tr>
</table>
</td>
<td>laboratory safety tests, 12-lead ECGs, physical examinations
• C_{trough}, C_{max}, t_{max}, AUCτ, AR for C_{max} and AUCτ (after first and last dose), $t_{1/2}$ (after last dose only)</td>
</tr>
<tr>
<td colspan="5">AE adverse event; AR accumulation ratio; AUC_{0-12} area under the concentration time curve from time 0 to 12 hours; AUC_{0-inf} area under the concentration time curve from time 0 extrapolated to infinity; AUC_{0-last} area under the concentration time curve from time 0 to the last quantifiable concentration; AUCτ area under the concentration time curve during the dosing interval; C completed; CL/F apparent total clearance of the drug from plasma; C_{max} maximum concentration; COVID 19 coronavirus disease 2019; CTCAE common terminology criteria for adverse events; CTD Common Technical Document; ECG electrocardiogram; F female; λ_z terminal rate constant; M male; MOV molnupiravir (MK 4482, EIDD 2801); N number of participants; PCR polymerase chain reaction; PK pharmacokinetics; Q12H every 12 hours; R randomized; RNA ribonucleic acid; RT PCR reverse transcriptase polymerase chain reaction; SAE serious adverse event; SARS CoV 2 severe acute respiratory syndrome coronavirus 2; T treated; $t_{1/2}$ terminal half life; TBD to be determined; t_{max} time to C_{max}; UK United Kingdom; V_z/F .
Source: [Ref. 5.3.5.1: P002V01MK4482] [Ref. 5.3.5.1: P002V03MK4482] [Ref. 5.3.5.1: P006MK4482] [Ref. 5.3.5.1: P001V01MK4482] [Ref. 5.3.3.1: P004MK4482] [Ref. 5.3.3.1: P012MK4482] [Ref. 5.3.3.3: P008MK4482]</td>
</tr>
</table>

1.6 Regulatory Guidance and Advice

Regulatory agency advice was obtained at key points during the development program. Formal guidance received from the US FDA, EMA, PMDA, and MHRA is summarized below [Table 2.5-covid19txallpop: 3].

Table 2.5-covid19txallpop: 3
Summary of Key Regulatory-Sponsor Interactions During Molnupiravir Clinical Development Program

Date	Type of Meeting/ Correspondence	Key Outcomes or Recommendations
Key Interactions with the US FDA		
[redacted]	[redacted]	On [redacted] on [redacted].
[redacted]	[redacted]	On [redacted]
[redacted]	[redacted]	On [redacted] On [redacted]

Date	Type of Meeting/ Correspondence	Key Outcomes or Recommendations
[redacted]	[redacted]	On [redacted]
[redacted]	[redacted]	On [redacted]
[redacted]	[redacted]	On [redacted]
[redacted]	[redacted]	[redacted]

Date	Type of Meeting/ Correspondence	Key Outcomes or Recommendations
[redacted]	[redacted]	On [redacted] On [redacted] On [redacted] On [redacted]
Key Interactions with EMA		
[redacted]	[redacted] Scientific Advice [redacted]	[redacted]

Date	Type of Meeting/ Correspondence	Key Outcomes or Recommendations
[redacted]	Scientific Advice [redacted]	[redacted]
[redacted]	[redacted]	On [redacted]
[redacted]	[redacted]	[redacted]

Date	Type of Meeting/ Correspondence	Key Outcomes or Recommendations
Key Interactions with PMDA		
[redacted]	[redacted] consultation	[redacted]
[redacted]	[redacted] consultation	[redacted]
[redacted]	[redacted] consultation	[redacted]
[redacted]	[redacted] consultation	[redacted]
03-DEC-2021	Submission of JNDA for special approval	On 24-DEC-2021, MHLW granted special approval to MOV for the treatment of infectious disease caused by SARS-CoV-2.
Key Interactions with MHRA		
[redacted]	[redacted]	On [redacted]

1.7 Good Clinical Practice

The clinical studies were conducted in accordance with current standard research approaches with regard to the design, conduct, and analysis of such studies including the archiving of essential documents. All studies were conducted following appropriate Good Clinical Practice standards and considerations for the ethical treatment of human participants that were in place at the time the studies were performed.

2 OVERVIEW OF BIOPHARMACEUTICS

This section presents an overview of the MOV biopharmaceutics program that characterizes the formulation development, bioavailability, and effect of food. Additional information on the biopharmaceutics program, including an overview of bioanalytical methods and an overview of drug solubility and permeability, is provided in [Sec. 2.7.1-covid19txallpop].

2.1 Formulation Development

MOV is classified as a high solubility and high permeability compound (BCS Class I). It has been formulated for commercial use as an immediate-release, 200 mg strength DFC intended for Q12H administration [Sec. 2.7.1-covid19txallpop: 1.1]. A [redacted]% w/w active loading was leveraged to achieve a target 200 mg strength in a size 0 hypromellose capsule shell containing a fill weight of 285.7 mg. MOV molecular formula is $C_{13}H_{19}N_3O_7$ and molecular weight is 329.31 g/mol. MOV has 2 known [redacted] forms, [redacted] and [redacted], and no known [redacted]. [redacted] is the thermodynamically more stable [redacted] phase with a crystalline melt onset of 161°C. [redacted] is the manufactured drug substance phase and has been used for drug product manufacture for clinical studies and therefore selected for commercial drug development.

Two formulations of MOV, a PIB solution ([redacted] mg/mL) and DFC formulation ([redacted], [redacted], and 200 mg strengths), were used in the clinical development program [Sec. 2.7.1-covid19txallpop: 1.1]. The PIB formulation of MOV (reconstituted on-site to a [redacted] mg/mL solution in water) was developed to support the initial Phase 1 clinical study (P004) [Ref. 5.3.3.1: P004MK4482]. In addition, 3 DFC formulations, [redacted], [redacted], and 200 mg strengths, were developed to support the clinical development program [Sec. 3.2.P.2.1-4482-capsule]. No changes in capsule fill excipients or their levels were made after the initial selection of the formulation used to support the initial safety and tolerability study (P004). The FMI has the same composition as the 200 mg DFC formulation used in the clinical development program, with the only difference being inclusion of ink marking to the outer surface of the capsule shell for product differentiation. Therefore, no clinical bridging studies were required.

2.2 Bioavailability and Food Effect

The bioavailability of MOV (the prodrug) is considered low due to rapid conversion to the primary circulating metabolite, NHC [Sec. 2.7.2-covid19txallpop: 2.1.1]. There have been no clinical studies to date dedicated to evaluating the absolute bioavailability of NHC following administration of MOV. PopPK modeling indicates no change in the bioavailability for the DFC relative to the PIB formulation [Sec. 2.7.1-covid19txallpop: 3.2].

Administration of MOV with food did not meaningfully affect the exposure (AUC) of NHC, which is the parameter most closely associated with efficacy [Sec. 2.7.1-covid19txallpop: 3.3]. A standard high-fat meal administered with a 200 mg dose (P004) or an 800 mg dose (P008) did not impact the AUC of NHC [Sec. 2.7.1-covid19txallpop: 2.3]. Administration of MOV with food appeared to slow the rate of absorption, as evidenced by a delay in NHC t_{max} and a reduction in geometric mean C_{max} (approximately 25 - 35%) in both P004 and P008. These findings are supported by a cross-study PopPK analysis, which indicated that a high-fat meal prior to dosing would increase the first-order absorption duration; however, dietary state was not a significant covariate on relative NHC bioavailability [Sec. 2.7.2-covid19txallpop: 2.5.2.2]. Together, these findings suggest that MOV can be taken without regard to food, with no meaningful clinical impact.

3 OVERVIEW OF CLINICAL PHARMACOLOGY

This section provides an overview of the clinical pharmacology program that evaluated the safety, tolerability, and PK of MOV or NHC. Additional information on the clinical pharmacology program, including results from individual Phase 1 studies, a summary of PopPK and exposure-response modeling, and an overview of pharmacodynamics and other safety endpoints, is provided in [Sec. 2.7.2-covid19txallpop].

3.1 Overview of Clinical Pharmacology Studies

Clinical pharmacology assessments include 3 Phase 1 studies in healthy participants [Sec. 2.7.2-covid19txallpop: 2.1]. P004 and P008 evaluated single doses up to 1600 mg and multiple doses up to 800 mg administered Q12H for 5.5 days in healthy participants and healthy Japanese participants, respectively. P012 evaluated multiple doses up to 800 mg administered Q12H for 10.5 days in healthy participants.

In addition to the Phase 1 clinical pharmacology studies, a number of model-based analyses were conducted to inform on the clinical pharmacology of MOV [Sec. 2.7.2-covid19txallpop: 2.5]. PopPK analyses were conducted using data obtained from P004, P001, P006, and P002. The PopPK analyses included covariate evaluation to inform on the effects of intrinsic and extrinsic factors [Ref. 5.3.5.3: 07ZXLB, 07ZRF9]. Exposure estimates in participants based on the PopPK model further informed E-R analyses for both virologic and clinical endpoints [Ref. 5.3.5.3: 08074R, 07YDDS]. A viral dynamics model explored the mechanism of action with regards to drug action on the viral infection and provided insights into determinants of response [Ref. 5.3.5.3: 05R5Z5].

3.2 Dose Selection and Comparability Bounds

The Phase 3 dose of 800 mg Q12H for 5 days was chosen at the time of the P002 IA2 based on the virologic data from all clinical studies (P004, P001, P006, and P002) and E-R modeling. E-R results from the Phase 2 studies (P001 Part 1 and P002 Part 1) for viral load and NGS error rate showed that the highest dose evaluated (800 mg) provided a larger drug effect than lower doses (200 mg and 400 mg). The overall trends also suggested that an 800 mg dose reduced infectivity faster, or to a greater extent, than the lower doses. Additional detail on the dose selection for Phase 3 is provided in [Sec. 2.7.2-covid19txallpop: 1.5.1].

The available efficacy and safety data and additional E-R modeling results from Phase 3 (P002 Part 2) further supported the proposed dose of 800 mg Q12H for 5 days. This dose was shown to reduce the incidence of hospitalization or death in non-hospitalized participants with mild or moderate COVID-19, compared with placebo. The E-R results also showed exposures produced by the 800 mg dose fall near the top of the E-R curves across clinical outcome and pharmacodynamic markers. No clinically meaningful trends were observed in AEs, SAEs, intervention-related AEs, discontinuations due to AEs, or clinical laboratory values as a function of dose or treatment. A full discussion around the justification for the proposed dose is provided in [Sec. 2.7.2-covid19txallpop: 1.5.3].

For the purposes of assessing the impact of intrinsic and extrinsic factors on the PK of NHC, the therapeutic window (comparability bounds) is defined as 0.7 to 2.0 fold of exposure (AUC) of the recommended clinical dose (800 mg Q12H). These bounds represent the range of exposures for which subpopulations can be expected to derive meaningful clinical benefit while ensuring that subpopulations are maintained within the range of clinical experience, at 800 mg Q12H for 5 days, known to be well-tolerated. For further details, see [Sec. 2.7.2-covid19txallpop: 1.5.3].

3.3 Pharmacokinetics in Humans

Following oral administration of MOV (the prodrug), MOV is only detected at very low levels in systemic circulation [Sec. 2.7.2-covid19txallpop: 2.1.1] due to rapid conversion to NHC (the circulating nucleoside analogue). NHC rapidly reaches peak concentrations at approximately 1.5 hours post-dose, followed by a biphasic decline with an effective $t_{1/2}$ of 3.3 hours. The geometric mean terminal $t_{1/2}$ was 20.6 hours after administration of 800 mg of MOV administered Q12H for 10.5 days [Sec. 2.7.2-covid19txallpop: 2.1]. Accumulation was minimal following Q12H dosing. NHC exposure increased in a manner that was approximately proportional to dose across the studies, with single-dose exposures being predictive of multiple-dose exposures. The PK of NHC was found to be similar between healthy participants and participants with COVID-19 [Sec. 2.7.2-covid19txallpop: 2.5.2]. No clinically meaningful food effect was observed following single MOV doses of either 200 or 800 mg [Sec. 2.5-covid19txallpop: 2.2].

Following uptake of NHC into cells, NHC is phosphorylated to the active triphosphate metabolite, NHC-TP. The $t_{1/2}$ of NHC-TP in PBMCs was consistent with the terminal $t_{1/2}$ of NHC in plasma [Sec. 2.7.2-covid19txallpop: 2.5.1] and >2-fold accumulation in NHC-TP AUC was observed with Q12H dosing. Additionally, a strong linear relationship was observed between $AUC_{0\ 12}$ exposures of NHC in the plasma and $AUC_{0\ 12}$ exposures of NHC-TP in PBMCs.

3.4 Intrinsic Factors

The 800 mg dose of MOV can be administered to patients with COVID-19 regardless of intrinsic factors. No dose adjustment is required based on age, sex, body weight, race, ethnicity, or geographic region [Sec. 2.7.2-covid19txallpop: 3.2]. Participants with BMI >40 kg/m^2 exhibited lower NHC exposures compared to participants with lower BMI; however, the GMR (90% CI) of these exposures fell within the established bounds for clinical significance [Sec. 2.7.2-covid19txallpop: 1.5.2, 3.2.3]. Therefore, no dose adjustment is recommended in this subpopulation.

Renal clearance is a very minor route of elimination for NHC based on preclinical and clinical data. In a PopPK analysis, mild (eGFR <90 to ≥60 mL/min/1.73 m^2) or moderate (eGFR <60 to ≥30 mL/min/1.73 m^2) renal impairment did not have a meaningful impact on the PK of NHC [Ref. 5.3.5.3: 07ZRF9]. The PK of MOV and NHC has not been evaluated in patients with eGFR <30 mL/min/1.73 m^2; however, extrapolation of the results in mild and moderate renally impaired participants, together with mechanism of NHC route of elimination, indicate that any increase in NHC exposure in patients with severe renal impairment would be unlikely to be clinically meaningful [Sec. 2.7.2-covid19txallpop: 3.2.5]. No dose adjustment is recommended in patients with any degree of renal impairment.

Hepatic elimination is not expected to be a major route of elimination for NHC based on preclinical data [Sec. 2.6.4: 6]. A PopPK analysis using a modified Child-Pugh score found minimal impact of mild hepatic impairment on NHC exposures (5% increase in NHC AUC in participants with mild impairment). Hepatic impairment is not expected to result in a clinically meaningful change in NHC exposure [Sec. 2.7.2-covid19txallpop: 1.3.1.2]. No dose adjustment is recommended in patients with any degree of hepatic impairment.

3.5 Extrinsic Factors

MOV is unlikely to be a victim or perpetrator of DDIs. 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 high-capacity host transporters and kinases important in the regulation of pyrimidine nucleotides [Sec. 2.7.2-covid19txallpop: 1.4.2], it is unlikely that other drugs will impact the exposure of NHC-TP in tissues. In addition, MOV and NHC did not inhibit or induce the activity of any of the major CYP enzymes tested in vitro [Sec. 2.7.2-covid19txallpop: 1.4.3], nor did they inhibit any of the major drug transporters tested in vitro [Sec. 2.7.2-covid19txallpop: 1.4.4]. These data suggest that the potential for DDIs between MOV/NHC and concomitant medications is low. Therefore, no clinical DDI studies were conducted. In a PopPK analysis, remdesivir coadministration was not found to affect the PK of NHC [Sec. 2.7.2-covid19txallpop: 3.3.1]. No PD interaction is expected between MOV and other commonly administered antivirals based on a lack of synergy or antagonism for antiviral activity in vitro against SARS-CoV-2.

3.6 Pharmacodynamics and Special Safety

Virological endpoints, including the viral load reduction, viral RNA mutation rate, and time to undetectable viral load, were evaluated in Phase 2 (P001, P006) and Phase 2/3 (P002) studies and are presented in [Sec. 2.7.3-covid19txallpop: 2]. Treatment with MOV was associated with a greater reduction in the mean change from baseline in SARS-CoV-2 viral load in NP samples by quantitative PCR compared with the placebo group at Days 3 and 5. Treatment with MOV was also associated with a higher mean SARS-CoV-2 RNA mutation rate across the viral genome, compared with placebo. Time to undetectable SARS-CoV-2 RNA was also shorter for the MOV 800 mg compared with the placebo group. Reduction in viral RNA was accompanied by the loss of recoverable infectious virus in samples from participants treated with MOV. Among participants with infectious virus detected at baseline, no MOV-treated participants had infectious virus detected on Day 3 or later compared with the placebo group wherein some participants had infectious virus detected up to Day 5 [Sec. 2.7.3-covid19txallpop: 2.2.1.2].

Throughout the MOV Phase 1 clinical development program there was no clinically meaningful intervention-related effect on the QT/QTc interval [Sec. 2.7.4-covid19txallpop: 4.3]. Furthermore, no safety concerns were observed regarding adverse events related to ECG findings in any of the Phase 2 or Phase 3 clinical studies [Sec. 2.7.4-covid19txallpop: 4.1, 4.2]. Based on an analysis of concentration-QTc data obtained in P004 (healthy adult participants) at single doses up to 1600 mg MOV, NHC did not have a clinically meaningful effect on the QTc interval as described in [Sec. 2.7.2-covid19txallpop: 2.4.1].

4 OVERVIEW OF EFFICACY

4.1 Efficacy Analyses and Statistical Methods

The efficacy endpoints, planned analyses, statistical methods, and determination of sample size for the studies are described in the final versions of the sSAP [Ref. 5.3.5.1: P002V03MK4482: 16.1.9] [Ref. 5.3.5.1: P006MK4482: 16.1.9] [Ref. 5.3.5.1: P001V01MK4482: 16.1.9] or are contained in the protocols [Ref. 5.3.5.1: P002V03MK4482: 16.1.1] [Ref. 5.3.5.1: P002V03MK4482: 16.1.1] [Ref. 5.3.5.1: P002V03MK4482: 16.1.1].

4.2 Relevance and Key Features of the Participant Population

The participants in P002 are representative of non-hospitalized patients with mild-to-moderate COVID-19 and support the proposed indication in patients from diverse geographic and ethnic backgrounds. P002 included participants from 18 to 94 years of age and from all racial and ethnic groups. Additionally, many of the participants had common risk factors for severe illness from COVID-19, including age >60 years, obesity (BMI ≥30 kg/m^2), diabetes mellitus, and serious heart condition (heart failure, coronary artery disease, or cardiomyopathies).

4.3 Efficacy Results

An overall description of all studies contributing efficacy data is provided in [Table 2.7.3-covid19txallpop: 1]. Efficacy results for each study are available in the individual CSRs [Ref. 5.3.5.1: P002V03MK4482] [Ref. 5.3.5.1: P002V01MK4482] [Ref. 5.3.5.1: P006MK4482] [Ref. 5.3.5.1: P001V01MK4482]. Additional virology data (including analyses of SARS-CoV-2 RNA, SARS-CoV-2 infectivity, and SARS-CoV-2 RNA sequences) from randomized participants in P002 Part 2 that were not presented in the P002 Part 2 CSR are presented in a separate Virology Report [Ref. 5.3.5.3: 07X2GY]; a summary of these results is in [Sec. 2.5-covid19txallpop: 4.3.1.2].

4.3.1 Phase 2/3 Study Results

4.3.1.1 P002 (Part 2)

4.3.1.1.1 Primary Efficacy Endpoint – Hospitalization or Death

Combined IA3/IA4

Hospitalization or death was selected as the primary endpoint because it combines key clinical outcomes of interest relevant to non-hospitalized patients with mild-to-moderate COVID-19. Evaluation of efficacy based on this endpoint provides a clinically meaningful assessment of the ability of MOV to reduce the risk of progression to severe COVID-19. The primary population for efficacy analyses was the MITT population, which consisted of all randomized participants who received at least 1 dose of study intervention and were not hospitalized before administration of the first dose of study intervention.

At the combined IA3/IA4 timepoint, MOV met the protocol-defined criterion (1-sided p-value boundary <0.0092) for demonstration of superiority to placebo for the primary efficacy endpoint [Table 2.5-covid19txallpop: 4].

- 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 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) [Table 2.5-covid19txallpop: 4].

- The 8 participants who died through Day 29 were all in the placebo group and were hospitalized before their death. No participants in the MOV group died [Table 2.5-covid19txallpop: 5].

Table 2.5-covid19txallpop: 4
Incidence of Hospitalization or Death Through Day 29
Modified Intent-To-Treat Population
MK-4482-002 (Combined IA3/IA4)

Treatment	N	n (%)	Treatment vs. Placebo		
			Unadjusted Difference	Adjusted Difference in Rates % (95% CI)[a]	p Value
MK 4482 800 mg	385	28 (7.3)	6.8	6.8 (11.3, 2.4)	0.0012
Placebo	377	53 (14.1)			

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

Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.

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

Table 2.5-covid19txallpop: 5
Summary of Hospitalization or Death Through Day 29
Modified Intent-To-Treat Population
MK-4482-002 (Combined IA3/IA4)

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

n number of participants with the corresponding event.

Every participant is counted a single time for each applicable row and column. Participants who died were hospitalized prior to death; such participants are counted once each in the hospitalization and death rows.

[a] Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death in the primary efficacy analysis.

Sensitivity Analyses

The results of sensitivity analyses for the primary endpoint were consistent with the results for the primary analysis at IA3/IA4. These analyses include time to event analyses, COVID-19-related hospitalization or death (as assessed by the investigator) and associated time to event analyses through Day 29, and an analysis excluding participants who received <5 doses of study intervention or were hospitalized or died before their 5th dose [Ref. 5.3.5.1: P002V03MK4482: Table 14.2-5] through [Ref. 5.3.5.1: P002V03MK4482: Table 14.2-9] [Ref. 5.3.5.1: P002V03MK4482: Figure 14.2-1, 14.2-2] [Ref. 5.3.5.1: P002V03MK4482: 11.1.1.1.1].

All Participants Randomized in Part 2

The efficacy results for all participants randomized in Part 2 and followed through Day 29 are included the P002 Part 2 CSR [Ref. 5.3.5.1: P002V03MK4482] and the Virology Report [Ref. 5.3.5.3: 07X2GY].

The results for all participants randomized in Part 2 support the benefit observed for MOV compared with placebo in reducing the incidence of hospitalization or death through Day 29 [Table 2.5-covid19txallpop: 6] [Table 2.5-covid19txallpop: 7] [Ref. 5.3.5.1: P002V03MK4482: 11.1.1.2].

- The percentage of participants who were hospitalized or died through Day 29 in the MOV group (6.8%) was lower compared with the placebo group (9.7%). Treatment with MOV resulted in a 3.0% reduction (95% CI: -5.9, -0.1) in the incidence of hospitalization or death through Day 29 compared with placebo (approximately 30% relative risk reduction) [Table 2.5-covid19txallpop: 6].

- Nine participants in the placebo group and 1 participant in the MOV group died through Day 29 [Table 2.5-covid19txallpop: 7].

Table 2.5-covid19txallpop: 6
Incidence of Hospitalization or Death Through Day 29
Modified Intent-To-Treat Population
MK-4482-002 Part 2 Day 29 DBL

Treatment	N	n (%)	Treatment vs. Placebo		
			Unadjusted Difference	Adjusted Difference in Rates % (95% CI)[a]	p Value
MK 4482 800 mg	709	48 (6.8)	3.0	3.0 (5.9, 0.1)	0.0218
Placebo	699	68 (9.7)			

[a] Adjusted differences, the corresponding confidence intervals and the one sided p values are based on Miettinen & Nurminen method stratified by randomization strata.
Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.
Nominal p value is presented in this table.

Source: [P002V03MK4482: adam adeff1]

Table 2.5-covid19txallpop: 7
Summary of Hospitalization or Death Through Day 29
Modified Intent-To-Treat Population
MK-4482-002 (Part 2 Day 29 DBL)

	MK 4482 800 mg		Placebo	
	n	(%)	n	(%)
Participants in population	709		699	
Hospitalization or Death	48	(6.8)	68	(9.7)
Hospitalization	48	(6.8)	67	(9.6)
Death	1	(0.1)	9	(1.3)
Unknown Day 29 Survival Status[a]	0	(0.0)	1	(0.1)

n number of participants with the corresponding event.
Every participant is counted a single time for each applicable row and column. Participants who died were hospitalized prior to death; such participants are counted once each in the hospitalization and death rows.
[a] Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death in the primary efficacy analysis.

Source: [P002V03MK4482: adam adsl; adeff1]

Sensitivity Analyses

The results of sensitivity analyses for the primary endpoint were consistent with the results for the primary analysis in all participants randomized in Part 2. These analyses included time to event analyses, COVID-19-related hospitalization or death (as assessed by the investigator) and associated time to event analyses through Day 29, an analysis excluding participants who received <5 doses of study intervention or were hospitalized or died before their 5th dose, an analysis imputing unknown hospitalization status as failure, and an analysis that included an additional stratification factor (geographic region) [Ref. 5.3.5.1: P002V03MK4482: Table 14.2-14] [Ref. 5.3.5.1: P002V03MK4482: Figure 14.2-3] [Table 2.5-covid19txallpop: 8] [Table 2.5-covid19txallpop: 9] [Ref. 5.3.5.1: P002V03MK4482: Table 14.2-18] [Ref. 5.3.5.1: P002V03MK4482: Figure 14.2-4] [Ref. 5.3.5.1: P002V03MK4482: Table 14.2-21, 14.2-22, 14.2-23] [Ref. 5.3.5.1: P002V03MK4482: 11.1.1.2.1].

Table 2.5-covid19txallpop: 8
Incidence of COVID-related Hospitalization or Death Through Day 29
Modified Intent-To-Treat Population
MK-4482-002 Part 2 Day 29 DBL

Treatment	N	n (%)	Treatment vs. Placebo	
			Unadjusted Difference	Adjusted Difference in Rates % (95% CI)[a]
MK 4482 800 mg	709	45 (6.3)	2.8	2.8 (5.7, 0.0)
Placebo	699	64 (9.2)		

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

Source: [P002V03MK4482: adam adeff3]

Table 2.5-covid19txallpop: 9
Summary of COVID-related Hospitalization or Death Through Day 29
Modified Intent-To-Treat Population
MK-4482-002 Part 2 Day 29 DBL

	MK 4482 800 mg		Placebo	
	n	(%)	n	(%)
Participants in population	709		699	
Hospitalization or Death	45	(6.3)	64	(9.2)
Hospitalization	45	(6.3)	64	(9.2)
Death	1	(0.1)	9	(1.3)

n number of participants with the corresponding event.
Every participant is counted a single time for each applicable row and column. Participants who died were hospitalized prior to death; such participants are counted once each in the hospitalization and death rows.

Source: [P002V03MK4482: adam adsl; adeff3]

Subgroup Analyses

Results of subgroup analyses of the primary endpoint based on most prespecified baseline characteristics, including updated virology characteristics, are presented in [Figure 2.7.3-covid19txallpop: 1] [Appendix 2.7.3-covid19txallpop: 1].

Summary of Differences Observed Between the Combined IA3/IA4 Analysis and the All Participants Randomized in Part 2 Analysis

A comprehensive assessment was performed to investigate the differences in efficacy observed at IA3/IA4 and the final analysis including all participants randomized in Part 2. Multiple factors were investigated as part of the comprehensive assessment to explore the difference in the point estimate of the primary efficacy endpoint observed in the IA3/IA4 and post-IA3/IA4 cohorts, including additional baseline serology testing, a detailed comparison of baseline characteristics (including demographic, clinical disease, and virologic characteristics), and an exploration of potential differences in standard of care by region and over time [Ref. 5.3.5.3: 07ZY5N].

While no single factor was identified that fully explains the differences in the incidence of hospitalization or death observed before and after IA3/IA4, a variety of factors were identified that could have contributed to the change in the treatment effect observed in the post-IA3/IA4 cohort. In comparing the results from IA3/IA4 to post-IA3/IA4, minor differences within and between treatment groups were observed in demographics (sex, age ≥75 years, racial groups, ethnicity, number of risk factors), regional enrollment, COVID-19 severity, and baseline virological characteristics (quantitative SARS-CoV-2 RNA and anti-SARS-CoV-2 neutralizing and nucleocapsid antibody status) [Ref. 5.3.5.3: 07ZY5N: Figure 1]. The cumulative effect of these factors, in combination with evolving external factors during the COVID-19 pandemic, may have resulted in the change in the point estimate of the primary efficacy endpoint observed in the post-IA3/IA4 cohort.

4.3.1.1.2 Secondary Efficacy Endpoints

To further evaluate the efficacy of MOV administered to non-hospitalized participants, additional endpoints were selected that are based on signs and symptoms associated with COVID-19 infection and other aspects of clinical progression of disease (ie, WHO 11-point ordinal outcomes scale) that are expected to improve with effective antiviral therapy [Ref. 5.3.5.1: P002V03MK4482: 16.1.1].

All Participants Randomized in Part 2

COVID-19 Signs and Symptoms

The analyses of self-reported signs and symptoms attributable to COVID-19 were based on data collected from a daily, 15-item paper symptom diary completed by the participant. The diary completion rates were comparable in the intervention groups, with greater than 92% completion for any sign/symptom through Day 29 [Ref. 5.3.5.1: P002V03MK4482: Table 14.2-25].

For most self-reported COVID-19 signs and symptoms, sustained resolution or improvement was more likely (indicated by a hazard ratio >1) for participants treated with MOV compared with placebo [Figure 2.5-covid19txallpop: 1]. A higher proportion 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 [Ref. 5.3.5.1: P002V03MK4482: Table 14.2-26] through [Ref. 5.3.5.1: P002V03MK4482: Table 14.2-41] and [Ref. 5.3.5.1: P002V03MK4482: Figure 14.2-7] through [Ref. 5.3.5.1: P002V03MK4482: Figure 14.2-22].

Progression (worsening) was less likely (indicated by a hazard ratio <1) for participants treated with MOV for most self-reported COVID-19 signs and symptoms compared with placebo [Figure 2.5-covid19txallpop: 2]. A lower proportion of participants reported progression in the MOV group compared with the placebo group for most self-reported COVID-19 signs and symptoms [Ref. 5.3.5.1: P002V03MK4482: Table 14.2-57] through [Ref. 5.3.5.1: P002V03MK4482: Table 14.2-72] and [Ref. 5.3.5.1: P002V03MK4482: Figure 14.2-24] through [Ref. 5.3.5.1: P002V03MK4482: Figure 14.2-39].

Figure 2.5-covid19txallpop: 1
Hazard Ratio of Time to Sustained Improvement or Resolution of Signs and Symptoms Through Day 29
Modified Intent-To-Treat Population
MK-4482-002 Part 2 Day 29 DBL

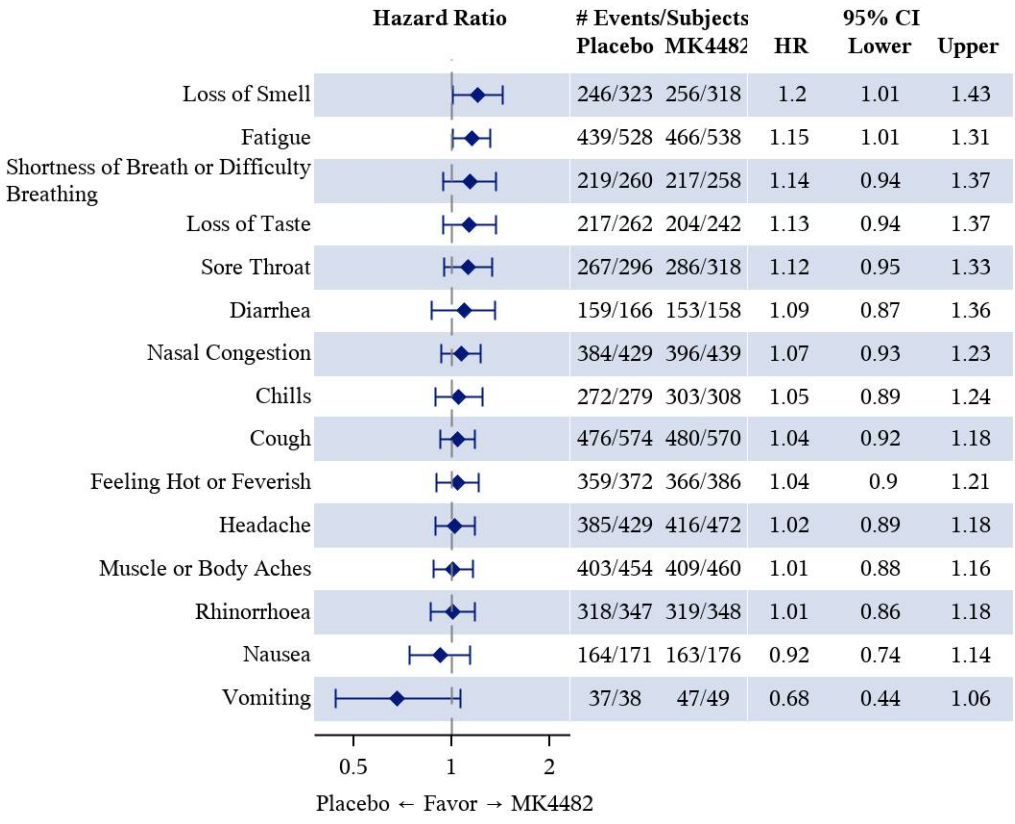
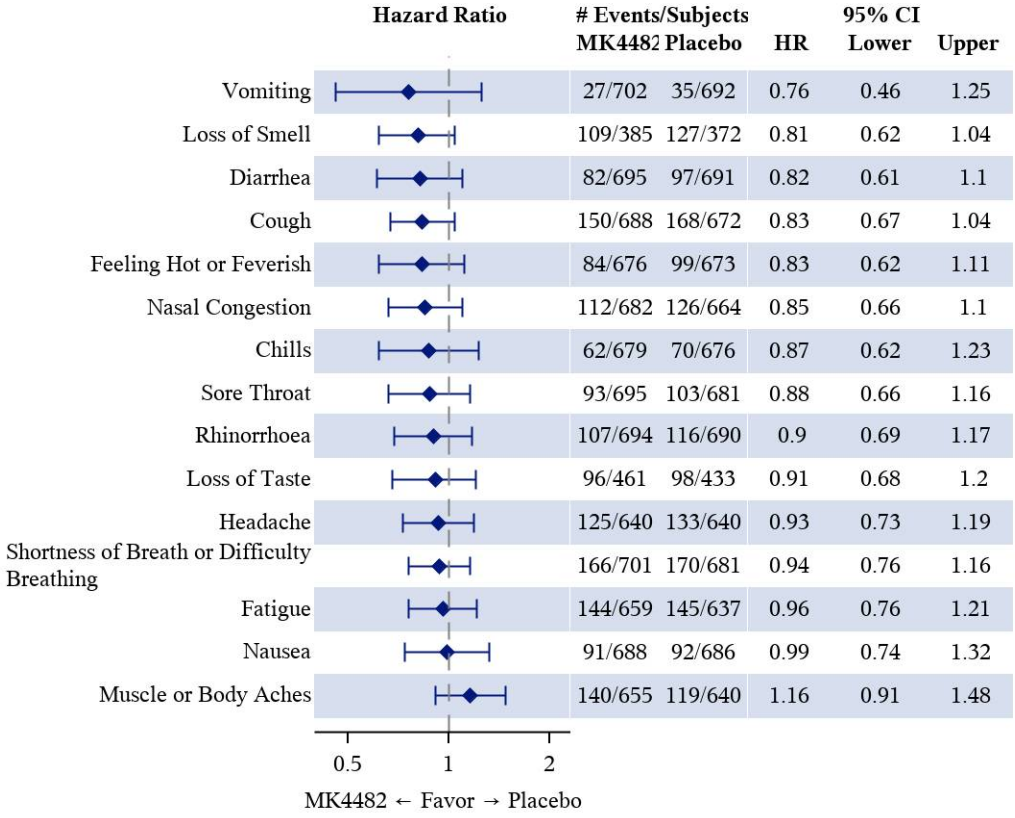


Figure 2.5-covid19txallpop: 2
Hazard Ratio of Time to Progression of Signs and Symptoms Through Day 29
Modified Intent-To-Treat Population
MK-4482-002 Part 2 Day 29 DBL



WHO 11-Point Scale Score

The WHO 11-point ordinal outcome scale was used to assess COVID-19-associated symptom burden (severity and duration), hospitalization, and death through Day 29. This scale provides a measure of illness severity across a range from 0 (not infected) to 10 (dead) [Ref. 5.4: 0806GL].

A lower percentage of participants who received MOV showed worse outcomes on the WHO 11-point ordinal scale compared with those who received placebo; the largest observed differences occurred at Days 10 and 15 [Ref. 5.3.5.1: P002V03MK4482: Table 14.2-92] [Ref. 5.3.5.1: P002V03MK4482: Figure 14.2-40]. When the WHO 11-point ordinal scale scores were grouped by category (0 [Uninfected], 1-3 [ambulatory, mild disease], 4-5 [hospitalized, moderate disease], 6-9 [hospitalized, severe disease], 10 [Death]), the odds of an improved outcome were 1.58 times higher after treatment with MOV compared with placebo at Day 10 [Ref. 5.3.5.1: P002V03MK4482: Table 14.2-91] [Ref. 5.3.5.1: P002V03MK4482: 11.1.2.2]. These data reflect the potential positive impact of MOV on important clinical measures used to monitor patient improvement over the course of illness.

4.3.1.1.3 Exploratory Endpoints

All Participants Randomized in Part 2

Acute Care Visits

The percentage of participants who had any acute care visit or any COVID-19-related acute care visit was assessed through Day 29. An acute care visit is defined as any hospitalization (any amount of time in a hospital or similar acute care facility, including emergency rooms or facilities created to address hospitalization needs during the COVID-19 pandemic) or emergency room visit or any other acute care visit (including an urgent care visit or visit with any healthcare provider for acute care needs) from randomization through Day 29.

A lower percentage of participants in the MOV group compared with the placebo group had an acute care visit (MOV: 7.2%; placebo: 10.6%) or COVID-19-related acute care visit (MOV: 6.6%; placebo: 10.0%) through Day 29 [Ref. 5.3.5.1: P002V03MK4482: Table 14.2-94, 14.2-95].

Virology Outcomes

The virology endpoints were selected to assess the activity of MOV against SARS-CoV-2 (ie, the reduction of infectious virus and viral RNA titer and the increase in the rate of viral mutagenesis) in participants and were assessed through Day 29. Reducing SARS-CoV-2 viral replication and eradicating the virus are important to recovery and have implications for transmission and infection control strategies.

Virology data from the combined IA3/IA4 timepoint are presented in the P002 Part 2 CSR [Ref. 5.3.5.1: P002V03MK4482].

Virology data from all randomized participants in Part 2 are presented in a separate Virology Report [Ref. 5.3.5.3: 07X2GY] and a summary of these results is included below.

SARS-CoV-2 RNA

Treatment with MOV was associated with a greater reduction in SARS-CoV-2 RNA titer compared with the placebo group, as measured by the mean change from baseline at Days 3, 5, and 10 [Table 2.7.3-covid19txallpop: 8] [Ref. 5.3.5.3: 07X2GY: Table 4] [Ref. 5.3.5.3: 07X2GY: Figure 1]. The adjusted mean difference in SARS-CoV-2 RNA (in $\log_{10}$ scale; MOV minus placebo) was -0.21 [95% CI: -0.36, -0.05] at Day 3, -0.30 [95% CI: -0.46, -0.14] at Day 5, and -0.16 [95% CI: -0.29, -0.02] at Day 10, which corresponds to a relative reduction in the geometric mean SARS-CoV-2 RNA titer of 38% [95% CI: 11%, 56%], 50% [95% CI: 28%, 65%], and 31% [95% CI: 5%, 49%] for the MOV group compared with the placebo group, respectively [Ref. 5.3.5.3: 07X2GY: Table 4] [Ref. 5.3.5.3: 07X2GY: Figure 2]. Viral RNA reductions at Days 15 and 29 were generally comparable between MOV and placebo groups [Table 2.7.3-covid19txallpop: 8] [Ref. 5.3.5.3: 07X2GY: Table 4] [Ref. 5.3.5.3: 07X2GY: Figure 1, 2].

Results for participants stratified by high and low baseline SARS-CoV-2 viral load were generally consistent with the overall results for the mean change from baseline in SARS-CoV-2 RNA [Table 2.7.3-covid19txallpop: 8]. Among participants with a lower viral load at baseline, after adjusting for baseline RNA titer, the largest difference (-0.27 [95% CI: -0.53, -0.01], in $\log_{10}$ scale) was observed at Day 3, which corresponds to a 46% (95% CI: 2%, 70%) relative reduction in the geometric mean SARS-CoV-2 RNA titer for the MOV group compared with the placebo group [Ref. 5.3.5.3: 07X2GY: Table 5] [Ref. 5.3.5.3: 07X2GY: Figure 3]. Among participants with a high viral load at baseline, the largest difference (-0.36 [95% CI: -0.56, -0.16], in $\log_{10}$ scale) was observed at Day 5, which corresponds to a 56% (95% CI: 31%, 73%) relative reduction in the geometric mean SARS-CoV-2 RNA titer for the MOV group compared with the placebo group [Ref. 5.3.5.3: 07X2GY: Table 6] [Ref. 5.3.5.3: 07X2GY: Figure 4].

The proportion of participants who achieved undetectable SARS-CoV-2 RNA in NP samples over time was assessed by a qualitative PCR assay. Among participants with detectable SARS-CoV-2 RNA at baseline, the proportion of participants who achieved undetectable SARS-CoV-2 RNA in NP samples by qualitative PCR increased over time and was comparable between the intervention groups through Day 29 with approximately 75% of participants having undetectable RNA by Day 29. Results were comparable between intervention groups regardless of baseline RNA titer ($>10^6$ and $\leq 10^6$ copies/mL) [Table 2.7.3-covid19txallpop: 9] [Ref. 5.3.5.3: 07X2GY: Figure 5].

SARS-CoV-2 Infectivity

Infectious SARS-CoV-2 virus was predominately detected in NP samples obtained from participants within 10 days or less from symptom onset [Ref. 5.3.5.3: 07X2GY: Figure 6] and with negative SARS-CoV-2 nucleocapsid antibodies at baseline [Ref. 5.3.5.3: 07X2GY: Figure 7, 8].

Among participants with infectious virus detected at baseline, no MOV-treated participant had infectious virus detected at Day 3 or later. In the placebo group, infectious virus was detected at Day 3 (20.8% of participants [(20/96]) and EOT (Day 5; 2.2% of participants [2/89]) but not at later timepoints [Ref. 5.3.5.3: 07X2GY: Table 15].

SARS-CoV-2 RNA Sequences

Consistent with the mechanism of action for MOV (viral error catastrophe), treatment with MOV was associated with a higher viral error rate across the viral genome, and was observed in a higher proportion of participants in the MOV group compared with placebo. Among participants with paired baseline and post-baseline next-generation sequencing data, a higher mean mutation rate (number of nucleotide changes per 10,000 bases) of SARS-CoV-2 RNA was observed at Day 5 in the MOV group (7.3) compared with the placebo group (2.9). The small number of participants with samples that met the criteria for analyses at the later time points (Days 10, 15, and 20) prevent any meaningful interpretation of the data [Table 2.7.3-covid19txallpop: 11]. Consistent with the higher mean mutation rates observed in the MOV group, there was a higher proportion of participants in the MOV group with >3, >6 or >9

mutations per 10,000 bases at Days 5 compared with the placebo group [Table 2.7.3-covid19txallpop: 12].

4.3.1.1.4 Post-Hoc Efficacy Analyses

All Participants Randomized in Part 2

Mortality

The percentage of participants who died through Day 29 was lower in the MOV group (0.1%) compared with the placebo group (1.3%). Treatment with MOV resulted in a 1.1 percentage point reduction in the incidence of death (approximately 89% estimated relative risk reduction) [Ref. 5.3.5.1: P002V03MK4482: Table 14.2-109].

Oxygen Therapy

The percentage of participants requiring supplemental oxygen therapy through Day 29 was lower in the MOV group (5.9%) compared with the placebo group (9.0%), including use of invasive mechanical ventilation (MOV: 0.6%; placebo: 1.6%) [Ref. 5.3.5.1: P002V03MK4482: Table 14.2-110]. In participants with hospitalization or death observed through Day 29, the percentage of participants requiring supplemental oxygen therapy was lower in the MOV group (64.6%) compared with the placebo group (82.1%), including use of invasive mechanical ventilation (MOV: 8.3%; placebo: 16.4%) [Ref. 5.3.5.1: P002V03MK4482: Table 14.2-111]. Summaries of supplemental oxygen therapy by highest level of oxygen need also show that participants in the MOV group had less requirement for any supplemental oxygen therapy compared with the placebo group [Ref. 5.3.5.1: P002V03MK4482: Table 14.2-112, 14.2-113].

Hospital Length of Stay

In participants with hospitalization observed through Day 29, the median time to hospital discharge was shorter in the MOV group (9.0 days) compared with the placebo group (12.0 days) [Ref. 5.3.5.1: P002V03MK4482: Table 14.2-114].

4.3.1.2 P002 (Part 1)

The efficacy results for Part 1 of P002 that are presented in this application comprises results primarily from IA2 (for dose selection, which occurred at the completion of Phase 2 after approximately 300 participants completed Day 29) and are included in the P002 Part 1 CSR [Ref. 5.3.5.1: P002V01MK4482]. Additional virology data that were not presented in the P002 Part 1 CSR are presented in [Sec. 2.5-covid19txallpop: 4.3.1.3.2].

4.3.1.2.1 Clinical Outcomes

In Part 1 of P002, the number of hospitalizations was low and comparable for all intervention groups through Day 29 [Ref. 5.3.5.1: P002V01MK4482: Table 11-1]. All 11 participants who were hospitalized had at least 1 risk factor for severe illness from COVID-19, including obesity (n 8), >60 years of age (n 5), and diabetes mellitus (n 5)

[Ref. 5.3.5.1: P002V01MK4482: 16.2.7.2]. No participant in any group died through Day 29; one participant who became hospitalized in the placebo group died on Day 36 (30 days after the last administration of study intervention) [Ref. 5.3.5.1: P002V01MK4482: 11.1.1].

In order to identify patient subgroups who were most likely to benefit from treatment with MOV, post-hoc subgroup analyses of the primary endpoint were conducted for the following groups:

- Participants >60 years of age
- Participants at increased risk for severe illness from COVID-19
- Participants with ≤5 days from symptom onset to randomization and at increased risk for severe illness from COVID-19
- Participants with ≤5 days from symptom onset to randomization

Results of these subgroup analyses suggested improved outcomes with MOV treatment compared with placebo and that treatment with MOV is more likely to be beneficial if started early (ie, ≤5 days after symptom onset) in the COVID-19 disease course [Ref. 5.3.5.1: P002V01MK4482: Table 14.2-45] through [Ref. 5.3.5.1: P002V01MK4482: Table 14.2-48]. For participants randomized ≤5 days from symptom onset and at increased risk for severe illness from COVID-19, the percentage of hospitalizations was 3.7% (4/107) in the combined MOV groups and 11.8% (4/34) in the placebo group [Ref. 5.3.5.1: P002V01MK4482: Table 14.2-47].

No clear evidence of a treatment effect for MOV (any dose) compared with placebo was observed as assessed by the self-reported signs/symptoms of COVID-19 and the WHO 11-point ordinal scale [Ref. 5.3.5.1: P002V01MK4482: 11.1.2.1, 11.1.2.2].

4.3.1.2.2 Virology Outcomes

SARS-CoV-2 RNA

Decreases in mean SARS-CoV-2 RNA titer relative to baseline (NP and OP samples) were comparable across intervention groups at all timepoints [Ref. 5.3.5.1: P002V01MK4482: 11.1.3.1]. However, for participants with $>10^6$ copies/mL SARS-CoV-2 RNA at baseline, the results of a post-hoc analysis of participants with ≤5 days from symptom onset to randomization showed a greater decrease in the mean change from baseline in SARS-CoV-2 RNA titer at Day 5 and Day 10 for the MOV 800 mg group compared with the placebo group [Ref. 5.3.5.1: P002V01MK4482: Table 14.2-52]. Results from additional subgroup analyses were consistent with the results in the overall population [Ref. 5.3.5.1: P002V01MK4482: 11.1.3.1].

Detection of SARS-CoV-2 RNA using a qualitative assay showed that for participants with detectable SARS-CoV-2 RNA in NP samples at baseline, a higher proportion of participants in the 400 mg and 800 mg groups had undetectable RNA results compared with placebo at Days 5 (EOT), 10, 15, and 29 [Ref. 5.3.5.1: P002V01MK4482: Table 14.2-43]. Results of post-hoc subgroup analyses were consistent with results in the overall population [Ref. 5.3.5.1: P002V01MK4482: 11.1.3.2].

SARS-CoV-2 Infectivity

In participants with positive baseline infectivity, no infectious virus was detected by Day 5 in any NP sample in the MOV-treatment groups; samples from 2 participants in the placebo group remained positive for infectious virus [Appendix 2.7.3-covid19txallpop: 6]. Notably, positive infectivity was only detected in NP samples from participants with negative SARS-CoV-2 antibodies at baseline [Appendix 2.7.3-covid19txallpop: 2] [Appendix 2.7.3-covid19txallpop: 3].

SARS-CoV-2 RNA Sequences

Consistent with the mechanism of action for MOV (viral error catastrophe), comparison of baseline and post-baseline sequences showed the highest RNA mutation rate was in the MOV 800 mg group in NP samples. [Ref. 5.3.5.1: P002V01MK4482: Table 14.2-38]. A higher proportion of participants in the MOV 800 mg group at Day 5 had >6 or >9 mutations per 10,000 bases compared with placebo [Ref. 5.3.5.1: P002V01MK4482: Table 14.2-41].

4.3.2 Phase 2a Study Results

4.3.2.1 P006

A full analysis and summary of efficacy results are included in the final version of the P006 CSR [Ref. 5.3.5.1: P006MK4482].

4.3.2.1.1 Clinical Outcomes

There was no clinically meaningful difference in clinical outcomes between groups based on self-reported signs/symptoms recorded in participant diaries, hospitalization for COVID-19-related illness [Ref. 5.3.5.1: P006MK4482: 11.4.1.5, 11.4.1.6].

4.3.2.1.2 Virology Outcomes

SARS-CoV-2 RNA

Time to undetectable SARS-CoV-2 RNA (median [95% CI]) was shorter for the MOV 800 mg group (14 days [13, 14]) compared with the placebo group (15 days [15, 27]) [Ref. 5.3.5.1: P006MK4482: Table 4] [Ref. 5.3.5.1: P006MK4482: Figure 2]. The proportion of participants who achieved undetectable SARS-CoV-2 RNA by the end of the study was greater for those who received MOV 800 mg (92.5%) compared with those who received placebo (80.3%) [Ref. 5.3.5.1: P006MK4482: Table 4]. The proportion of participants who achieved undetectable SARS-CoV-2 RNA at Days 3, 5, 7, 14, and 28 was also greater in the

MOV 800 mg group compared with the placebo group, with the greatest differences observed at Day 5 (30.2% vs 13.1%) and Day 28 (95.8% vs 82.1%) [Ref. 5.3.5.1: P006MK4482: Table 5].

Analysis of change from baseline in SARS-CoV-2 viral load (log10 copies/mL) showed a larger decrease in the MOV 800 mg group compared with any of the other treatment groups from Days 3 to 28. The largest difference between the MOV 800 mg group and the placebo group was observed at Day 5 [Ref. 5.3.5.1: P006MK4482: Table 4, 8] [Ref. 5.3.5.1: P006MK4482: Figure 3].

SARS-CoV-2 Infectivity

Treatment with MOV 800 mg resulted in a smaller proportion of participants with detectable infectious virus compared with the placebo, MOV 200 mg, and MOV 400 mg groups. On Day 3, the proportion of participants with positive infectivity results was 1/53 (1.9%) in the MOV 800 mg group compared with 9/54 (16.7%) in the placebo group. All participants who received MOV 400 mg or 800 mg cleared infectious virus by Day 5, whereas 1/22 (4.5%) of participants in the MOV 200 mg group and 6/54 (11.1%) in the placebo group still had infectious virus on Day 5 [Ref. 5.3.5.1: P006MK4482: Table 6].

SARS-CoV-2 RNA Sequences

The MOA of MOV (viral error catastrophe) was supported by the results of next-generation sequencing analysis of SARS-CoV-2 RdRp at Baseline and Day 5 (EOT) [Ref. 5.3.5.1: P006MK4482: 11.4.1.4]. For MOV-treated participants (all MOV doses) with paired baseline and Day 5 (EOT) sequence data, a mean (SD) of 10.9 (15.05) nucleotide changes in the RdRp for MOV-treated participants compared with 5.7 (6.24) nucleotide changes in the RdRp for placebo-treated participants [Ref. 5.3.5.1: P006MK4482: Table 14.2.14.1] was observed.

Analysis of amino acid changes between the posttreatment and baseline samples showed an increased mean (SD) number of changes throughout the RdRp gene for MOV-treatment participants of 7.5 (10.60) compared with 4.2 (4.39) for placebo-treated participants [Ref. 5.3.5.1: P006MK4482: Table 14.2.13.1] [Ref. 5.3.5.1: P006MK4482: Table 14.2.11.1].

4.3.3 Phase 2 Study Results

4.3.3.1 P001 (Part 1)

The efficacy results for P001 that are presented in this application are primarily comprises results from IA2 (for dose selection, which occurred at the completion of Phase 2 after approximately 300 participants completed Day 29) and are included in the P001 CSR [Ref. 5.3.5.1: P001V01MK4482]. Additional virology data that were not presented in the P001 CSR are presented in [Sec. 2.5-covid19txallpop: 4.3.3.1.2].

4.3.3.1.1 Clinical Outcomes

No clear effect of MOV treatment was observed for the primary endpoint of time to sustained recovery in these hospitalized participants [Ref. 5.3.5.1: P001V01MK4482: Table 11-1] [Ref. 5.3.5.1: P001V01MK4482: Figure 14.2-1]. The rate of sustained recovery through Day 29 was high (>81%) and comparable across groups.

Of the 17 participants who died in P001, a higher proportion occurred in the MOV 200 mg, 400 mg, and 800 mg groups (n 4 [5.5%], n 8 [11.0%], n 3 [4.2%], respectively) compared with placebo (n 2 [2.7%]). There was no clear evidence of a drug or dose effect based on the evaluation of the mortality results. The number of deaths was small and the 95% CIs for the treatment differences included zero for the MOV 200 mg and 800 mg groups compared with the placebo group. Additionally, survival status at Day 29 was unknown for 4 of 8 participants counted as deaths in the MOV 400 mg group and 1 of 2 participants in the placebo group [Ref. 5.3.5.1: P001V01MK4482: Table 14.2-6] [Ref. 5.3.5.1: P001V01MK4482: 11.1.2.1]. None of the deaths were considered related to study intervention by the investigator [Ref. 5.3.5.1: P001V01MK4482: 12.2.1.1].

Results for other secondary efficacy endpoints (pulmonary and pulmonary+ scores, NEWS, and WHO 11-point ordinal scale score) were comparable across intervention groups with generally improved outcomes over time with no observed dose-response for MOV [Ref. 5.3.5.1: P001V01MK4482: 11.1.2.2, 11.1.2.3, 11.1.2.4] [Ref. 5.3.5.1: P001V01MK4482: 11.1.2.5].

4.3.3.1.2 Virology Outcomes

SARS-CoV-2 RNA

Comparable decreases from baseline in mean SARS-CoV-2 RNA titers were observed for all MOV groups and placebo at all timepoints in NP and OP samples [Ref. 5.3.5.1: P001V01MK4482: 11.1.3.1]. The proportion of participants with undetectable SARS-CoV-2 RNA over time was comparable across all intervention groups [Ref. 5.3.5.1: P001V01MK4482: 11.1.3.2].

SARS-CoV-2 Infectivity

NP samples with viral RNA titers ≥100,000 copies/mL were evaluated at baseline and through Day 29 for the presence of infectious virus (plaque assay in Vero cells). NP samples with viral RNA <100,000 copies/mL were not evaluated and were imputed as negative based on the lack of positive results in samples $<10^6$ copies/mL [Appendix 2.7.3-covid19txallpop: 16] [Appendix 2.7.3-covid19txallpop: 14] [Appendix 2.7.3-covid19txallpop: 15]. Eleven of the 200 (5.5%) participants in the combined MOV groups and 3 of the 69 (4.3%) participants in the placebo group had positive viral infectivity at baseline (NP samples). No participant in the MOV groups had detectable infectious virus on Day 3 to 29. In the placebo group, infectious virus remained detectable in 2 of 3 participants on Day 3 and 1 of 3 participants on Day 5 [Appendix 2.7.3-covid19txallpop: 14] [Appendix 2.7.3-covid19txallpop: 15]. Positive infectivity results were primarily observed in samples with a higher viral load ($>10^6$ copies/mL), participants with symptom onset ≤5 days from randomization, and participants

with negative baseline SARS-CoV-2 antibodies [Appendix 2.7.3-covid19txallpop: 16] [Appendix 2.7.3-covid19txallpop: 17] [Appendix 2.7.3-covid19txallpop: 18].

SARS-CoV-2 RNA Sequences

Consistent with the mechanism of action of MOV (viral error catastrophe), evidence for an increased SARS-CoV-2 mutation rate was observed in NP swabs from participants who received MOV compared with placebo [Ref. 5.3.5.1: P001V01MK4482: Table 14.2-44]. A trend toward a higher proportion of participants with >3 or >6 (per 10,000 bases) SARS-CoV-2 mutations was observed for MOV groups compared with placebo from NP samples [Ref. 5.3.5.1: P001V01MK4482: Table 14.2-45].

4.4 Rationale for Applicability of Foreign Data to the United States Population

As highlighted in [Sec. 2.5-covid19txallpop: 4.2], the MOV clinical development program included a wide age range of participants from all racial and ethnic groups, many of which had medical conditions that put them at risk for severe illness from COVID-19. Results of subgroup analyses of the primary endpoint in P002 based on most prespecified baseline characteristics, including geographic region, were consistent with the results of the primary analysis [Sec. 2.5-covid19txallpop: 3.1.1.1]. Additionally, in P002, MOV was generally well tolerated in participants from all geographic regions with no clinically meaningful differences identified in patterns of specific AEs observed between study intervention groups when analyzed by geographic region [Sec. 2.5-covid19txallpop: 5.2.4.2.1]. The applicant considers foreign data to be applicable to the population in the United States.

4.5 Summary of Key Efficacy Results

Based on the results from Part 2 of P002, the following conclusion may be made in non-hospitalized, adult patients with mild or moderate laboratory-confirmed COVID-19 at high risk for disease progression:

- MOV (800 mg Q12H for 5 days) is superior to placebo in reducing the risk of hospitalization or death through Day 29

The following key results were also observed in P002, P006, and/or P001:

- Treatment with MOV was associated with a relative reduction in risk of death compared with placebo (P002 Part 2)
- Treatment with MOV was associated with improved clinical outcomes based on self-reported signs/symptoms and as assessed by the WHO-11 point ordinal scale compared with placebo (P002 Part 2)
- Clinically relevant markers of improvement and healthcare utilization outcomes (eg, acute care visits, supplemental oxygen use, and hospital length of stay) support the beneficial impact of treatment with MOV compared with placebo (P002 Part 2)

- Treatment with MOV was associated with a greater reduction in the mean change from baseline in SARS-CoV-2 RNA titer from baseline compared with placebo (P002 Parts 1 and 2, P006)

- Treatment with MOV was associated with a reduced percentage of participants with infectious virus compared with placebo (P002 Parts 1 and 2, P006, P001)

- Treatment with MOV was associated with a higher SARS-CoV-2 RNA mutation rate compared with placebo, consistent with the mechanism of action of MOV (viral error catastrophe) (P002 Parts 1 and 2, P006, P001)

5 OVERVIEW OF SAFETY

5.1 Overall Safety Evaluation and Plan

The clinical safety assessment of MOV is based on safety results from 8 clinical studies, 5 of which have completed and 3 are ongoing. One of the 3 ongoing studies is the pivotal Phase 2/3 study, MK-4482-002 (P002). Enrollment in P002 is completed and data (through Day 29) are complete and unblinded. A total of 1468 adult participants received at least 1 dose of MOV in the in studies where enrollment is completed; 944 of these participants received at least 1 dose of MOV 800 mg Q12H for at least 5 days [Table 2.5-covid19txallpop: 10].

Safety was evaluated in the MOV clinical studies by collection of AEs, clinical laboratory evaluations, and physical examinations (including vital signs). AEs were assessed from the time of intervention randomization through 14 days after cessation of study intervention. Safety analyses are based on the APaT population, which includes all randomized participants who received at least 1 dose of study intervention. Participants are included in the intervention group corresponding to the study intervention they received. Safety results are shown separately for each of the clinical studies due to differences in the study populations. For P002, the unblinded safety data from Phase 2 (Part 1) and Phase 3 (Part 2) are combined and show for MOV 800 mg and placebo in the ISS [Sec. 5.3.5.3.3-covid19txallpop]. Key tables for these combined data are included in this Clinical Overview and the Clinical Summary of Safety [Sec. 2.7.4-covid19txallpop]. These Phase 2/3 data provide the largest pool of MOV 800 mg/placebo data available for analysis from a single study population. A complete reporting of results from each unblinded part of P002 is available in the respective CSRs [Ref. 5.3.5.1: P002V01MK4482] [Ref. 5.3.5.1: P002V03MK4482].

The safety endpoints, planned analyses, and statistical methods are described in the final version of the protocol-specific SAP/sSAP or are contained in the clinical study protocols for the 6 studies with completed enrollment. Listings and narratives for participants with protocol-specified ECI, study intervention-related AEs, SAEs, study intervention-related SAEs, AEs leading to discontinuation of study intervention, and AEs resulting in death are provided in the CSRs for these studies.

Table 2.5-covid19txallpop: 10
Participants Who Received MOV (P002, P006, P001, P004, P012, and P008)

Protocol Number (Phase)	Number of Participants	
	APaT (Any Dose of MOV)	MOV 800 mg[a] Q12H
P002 (Phase 3)	Part 2: 710	Part 2: 710[a]
P002 (Phase 2)	Part 1: 225	Part 1: 74[a]
P006 (Phase 2a)	140	55[a]
P001 (Phase 2)	218	72[a]
P004 (Phase 1)	100	6[a]
P012 (Phase 1)	24	12[b]
P008 (Phase 1)	51	15[a]
Total	1468	944

APaT=all participants as treated; MOV=molnupiravir; Q12H=once every 12 hours.

[a] Participants received at least 1 dose of MOV 800 mg Q12H for 5 days.

[b] Participants received at least 1 dose of MOV 800 mg in a dosing regimen of Q12H for 10.5 days.

Source: [Ref. 5.3.5.1: P002V03MK4482: Table 10 2] [Ref. 5.3.5.1: P002V01MK4482: Table 10 1] [Ref. 5.3.5.1: P006MK4482: Table 2] [Ref. 5.3.5.1: P001V01MK4482: Table 10 1] [Ref. 5.3.3.1: P004MK4482: Table 14.1 1.1, 14.1 1.3] [Ref. 5.3.3.1: P012MK4482: Table 10 1] [Ref. 5.3.3.3: P008MK4482: 16.1.7]

5.2 Safety Results

Unless otherwise indicated, safety results in this Overview of Safety are presented by study phase, as follows:

- Phase 2/3: P002 (Part 1 [MOV 800 mg/placebo] and Part 2 combined)
- Phase 2: P002 Part 1, P006, and P001 Part 1
- Phase 1: P004, P012, and P008

5.2.1 Overall Extent of Exposure

5.2.1.1 Disposition of Participants

5.2.1.1.1 Phase 2/3: P002 (Part 1 [MOV 800 mg/Placebo] and Part 2 Combined)

The disposition of participants in P002 (Part 1 and Part 2 combined) was comparable between the 2 intervention groups. Most participants completed the study through Day 29 (95.8% MOV, 96.0% placebo) [Table 2.7.4-covid19txallpop: 3]. More participant deaths were reported for the placebo group compared with the MOV 800 mg group; deaths are discussed further in [Sec. 2.5-covid19txallpop: 5.2.2.1.2].

5.2.1.1.2 Phase 2 (P002 Part 1, P006, and P001 Part 1)

The disposition of participants enrolled in the Phase 2 studies was comparable across intervention groups in each study. A total of 810 participants were randomized to MOV (n 596 all doses) or placebo (n 214) in these studies [Table 2.7.4-covid19txallpop: 2]. Of these, 794 (98.0%; n 583 MOV, n 211 placebo) participants received at least 1 dose of study intervention and 742 (93.7%; n 539 MOV, n 203 placebo) completed the study.

The disposition of participants is shown in the CSR for that study [Ref. 5.3.5.1: P002V01MK4482: Table 10-1] [Ref. 5.3.5.1: P006MK4482: Table 14.1.1.1] [Ref. 5.3.5.1: P001V01MK4482: Table 10-1].

5.2.1.1.3 Phase 1 (P004, P012, and P008)

The disposition of participants enrolled in the Phase 1 studies was comparable across intervention groups in each study [Table 2.7.4-covid19txallpop: 2]. A total of 227 participants (n 175 MOV, n 56 placebo) were randomized, received at least 1 dose of study intervention, and completed the study. Some participants received both MOV and placebo due to cross-over design in certain studies. Two participants discontinued study intervention due to an AE (1 in P004 and 1 in P008) and 2 participants withdrew consent from study intervention (both in P008). All 4 participants continued with study procedures and completed the study.

The disposition of participants in each study is shown in the CSR for that study: P004 [Ref. 5.3.3.1: P004MK4482: 10.1] [Ref. 5.3.3.1: P004MK4482: Table 14.1-1.1, 14.1-1.2, 14.1-1.3], P012 [Ref. 5.3.3.1: P012MK4482: Table 10-1], and P008 [Ref. 5.3.3.3: P008MK4482: 10.6] [Ref. 5.3.3.3: P008MK4482: Table 10-1, 10-2].

5.2.1.2 Duration of Exposure

5.2.1.2.1 Phase 2/3: P002 (Part 1 [MOV 800 mg/Placebo] and Part 2 Combined)

The duration of exposure to study intervention in P002 (Part 1 [MOV 800 mg] and Part 2 combined) was comparable in both intervention groups [Ref. 5.3.5.3.3-covid19txallpop: 2]. Most participants (95.2% MOV, 94.6% placebo) received 9 to 10 doses with a mean duration of treatment of approximately 4.4 days in both intervention groups. Compliance with the study intervention regimen was high and comparable between intervention groups. Most participants were 100% compliant with the protocol-defined regimen [Ref. 5.3.5.3.3-covid19txallpop: 3].

5.2.1.2.2 Phase 2 (P002 Part 1, P006, and P001 Part 1)

Most (>89%) participants in each study intervention group took 9 of 10 doses of either MOV (200, 400, or 800 mg) or placebo in the Phase 2 studies [Ref. 5.3.5.1: P002V01MK4482: Table 14.1-7] [Ref. 5.3.5.1: P006MK4482: Table 14.1.5.1.1] [Ref. 5.3.5.1: P001V01MK4482: Table 14.1-5].

5.2.1.2.3 Phase 1 (P004, P012, and P008)

Duration of exposure in the Phase 1 studies ranged from single doses in P004 (Parts 1 and 2) and P008 (Part 1) to multiple doses (administered Q12H) for approximately 5 days in P004 (Part 3) and P008 (Part 2), and approximately 10 days in P012 [Ref. 5.3.3.1: P004MK4482: 10.5] [Ref. 5.3.3.3: P008MK4482: Table 9-3] [Ref. 5.3.3.3: P008MK4482: 16.1.7] [Ref. 5.3.3.1: P012MK4482: 10.6].

5.2.2 Summary of Adverse Events

Note: MedDRA coded worsening of COVID-19 to the preferred term “COVID-19”.

5.2.2.1 Phase 2/3: P002 (Part 1 [MOV 800 mg/Placebo] and Part 2 Combined)

The proportions of participants with AEs (overall and by category) were generally comparable for the MOV 800 mg and placebo groups in P002 (Part 1 [MOV 800 mg and placebo] and Part 2 combined) [Table 2.5-covid19txallpop: 11].

The proportion of participants who had AEs leading to death in the MOV group (n 2, 0.3%) was lower than in the placebo group (n 13, 1.7%). AEs leading to death are discussed further in [Sec. 2.5-covid19txallpop: 5.2.2.1.2]. None of the deaths were considered to be related to study intervention by the investigator. AEs considered related to study intervention and overall SAEs were reported for <10% of participants in both groups. One SAE (in the placebo group) was classified as related to study intervention. Discontinuation of study intervention due to an AE was infrequent (<3%) in both intervention groups.

The proportions of participants with AEs by SOC and preferred term were comparable in both study intervention groups [Table 5.3.5.3.3-covid19txallpop: 7] [Figure 5.3.5.3.3-covid19txallpop: 1].

Table 2.5-covid19txallpop: 11
Analysis of Adverse Event Summary During Treatment and 14-Day Follow-Up Period
All Participants as Treated Population
MK-4482-002 (Part 1 and Part 2 Combined)

	MK 4482 800 mg		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[a]
Participants in population	784		775		
with one or more adverse events	245	(31.3)	259	(33.4)	2.2 (6.8, 2.5)
with no adverse event	539	(68.8)	516	(66.6)	2.2 (2.5, 6.8)
with drug related[b] adverse events	61	(7.8)	64	(8.3)	0.5 (3.2, 2.2)
with serious adverse events	53	(6.8)	71	(9.2)	2.4 (5.1, 0.3)
with serious drug related adverse events	0	(0.0)	1	(0.1)	0.1 (0.7, 0.4)
who died	2	(0.3)	13	(1.7)	1.4 (2.6, 0.5)
discontinued drug due to an adverse event	13	(1.7)	21	(2.7)	1.1 (2.6, 0.4)
discontinued drug due to a drug related adverse event	4	(0.5)	4	(0.5)	0.0 (0.9, 0.8)
discontinued drug due to a serious adverse event	7	(0.9)	13	(1.7)	0.8 (2.1, 0.4)
discontinued drug due to a serious drug related adverse event	0	(0.0)	0	(0.0)	0.0 (0.5, 0.5)

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

Source: [ISS: adam adsl; adae]

5.2.2.1.1 Common Adverse Events

Most Frequently Reported Adverse Events

The percentage of participants in P002 (Part 1 [MOV 800 mg/placebo] and Part 2 combined) with 1 or more AEs was comparable in both intervention groups (31.3% MOV, 33.4% placebo) [Table 5.3.5.3.3-covid19txallpop: 9, 10]. COVID-19, COVID pneumonia, and diarrhea were the most frequently reported AEs (≥2% in either group) [Table 2.5-covid19txallpop: 12]. COVID-19 pneumonia and cough were reported more frequently in the placebo group compared with the MOV group [Table 5.3.5.3.3-covid19txallpop: 10].

Table 2.5-covid19txallpop: 12
Participants with Adverse Events During Treatment and 14-Day Follow-Up Period
(Incidence ≥2% in 1 or More Treatment Groups)
All Participants as Treated Population
MK-4482-002 (Part 1 and Part 2 Combined)

	MK 4482 800 mg		Placebo	
	n	(%)	n	(%)
Participants in population	784		775	
with one or more adverse events	245	(31.3)	259	(33.4)
with no adverse events	539	(68.8)	516	(66.6)
Gastrointestinal disorders	**50**	**(6.4)**	**62**	**(8.0)**
Diarrhoea	18	(2.3)	25	(3.2)
Infections and infestations	**104**	**(13.3)**	**127**	**(16.4)**
COVID 19	58	(7.4)	74	(9.5)
COVID 19 pneumonia	49	(6.3)	70	(9.0)
Investigations	**39**	**(5.0)**	**56**	**(7.2)**
Metabolism and nutrition disorders	**19**	**(2.4)**	**14**	**(1.8)**
Nervous system disorders	**21**	**(2.7)**	**14**	**(1.8)**
Respiratory, thoracic and mediastinal disorders	**13**	**(1.7)**	**29**	**(3.7)**

Participants With Adverse Events During Treatment and 14-Day Follow-Up Period
(Incidence ≥ 2% in One or More Treatment Groups)
All Participants as Treated Population
MK-4482-002 (Part 1 and Part 2 Combined)

	MK 4482 800 mg		Placebo	
	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**17**	**(2.2)**	**8**	**(1.0)**

Every participant is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Adverse event terms are from MedDRA Version 24.1.

Source: [ISS: adam adsl; adae]

Adverse Events Related to Study Intervention

Phase 2/3: P002 (Part 1 [MOV 800 mg/placebo] and Part 2 Combined)

The proportion of participants in P002 (Part 1 [MOV 800 mg/placebo] and Part 2 combined) with AEs considered related to study intervention by the investigator were comparable in both intervention groups [Table 2.7.4-covid19txallpop: 7] [Table 5.3.5.3.3-covid19txallpop: 12] [Figure 5.3.5.3.3-covid19txallpop: 2]. Diarrhea and nausea were the only intervention-related AEs reported with an incidence ≥1% in either group. Most events were reported as resolved by Day 29 [Ref. 5.3.5.1: P002V01MK4482: 16.2.7.1.1] [Ref. 5.3.5.1: P002V03MK4482: 16.2.7.1.3].

Table 2.5-covid19txallpop: 13
Participants with Drug-Related Adverse Events During Treatment and 14-Day Follow-Up Period
(Incidence ≥1% in 1 or More Treatment Groups)
All Participants as Treated Population
MK-4482-002 (Part 1 and Part 2 Combined)

	MK 4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	784		775		1,559	
with one or more drug related adverse events	61	(7.8)	64	(8.3)	125	(8.0)
with no drug related adverse events	723	(92.2)	711	(91.7)	1,434	(92.0)
Gastrointestinal disorders	**30**	**(3.8)**	**34**	**(4.4)**	**64**	**(4.1)**
Diarrhoea	13	(1.7)	17	(2.2)	30	(1.9)
Nausea	11	(1.4)	6	(0.8)	17	(1.1)
Investigations	**8**	**(1.0)**	**14**	**(1.8)**	**22**	**(1.4)**
Nervous system disorders	**11**	**(1.4)**	**6**	**(0.8)**	**17**	**(1.1)**
Skin and subcutaneous tissue disorders	**9**	**(1.1)**	**5**	**(0.6)**	**14**	**(0.9)**

Every participant is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Adverse event terms are from MedDRA Version 24.1.

Source: [ISS: adam adsl; adae]

Phase 3: P002 (Part 2)

AEs considered related to study intervention were reported for approximately 8% of participants in either intervention group in P002 Part 2 [Ref. 5.3.5.1: P002V03MK4482: Table 14.3-8]. Diarrhea (1.7% MOV vs 2.1% placebo), nausea (1.4% MOV vs 0.7% placebo), and dizziness (1.0% MOV vs 0.7% placebo) were the only intervention-related AEs reported with an incidence ≥1% in either group. Study intervention-related SAEs were not reported in the MOV group and were reported in 0.1% of participants in the placebo group. A higher proportion of participants had AEs leading to death in the placebo group compared with the MOV group (1.7% placebo, 0.3% MOV). A complete reporting of results from P002 (Part 2) is in the CSR [Ref. 5.3.5.1: P002V03MK4482].

Study Intervention-related Adverse Events by Toxicity Grade

Phase 2/3: P002 (Part 1 [MOV 800 mg/placebo] and Part 2 Combined)

Of the participants reporting 1 or more study intervention-related AE, most participants reported AEs of Grade 1 or Grade 2 [Table 5.3.5.3.3-covid19txallpop: 13]. Five participants had a Grade 3 study intervention-related AE (n 2 [0.3%] MOV, n 3 [0.4%] placebo).

5.2.2.1.2 Deaths

AEs leading to death in P002 (Part 1 [MOV 800 mg/placebo] and Part 2 combined] were reported for 15 participants; 2 (0.3%) participants in the MOV group and 13 (1.7%) participants in the placebo group [Table 2.5-covid19txallpop: 14]. None of the deaths were considered to be related to study intervention by the investigator [Ref. 5.3.5.1: P002V01MK4482: 16.2.7.2] [Ref. 5.3.5.1: P002V03MK4482: 16.2.7.1.4].

The analysis of AEs resulting in death includes participants who died due to an AE regardless of the timing of death, provided the AE onset occurred during the study intervention period through 14 days after completion of study intervention. Among the 15 deaths reported in P002 (Part 1 [MOV 800 mg/placebo] and Part 2 combined), 1 was a participant from Part 1 (placebo group, on Day 36). Of the 14 deaths included in the safety analysis, 10 were also included in the efficacy analysis (based on timing of the death occurring on or before Day 29); the remaining 4 deaths included in the safety analysis had AE onset dates within the period for AE reporting but occurred after Day 29.

Table 2.5-covid19txallpop: 14
Participants with Adverse Events Resulting in Death During Treatment and 14-Day Follow-Up Period
(Incidence >0% in 1 or More Treatment Groups)
All Participants as Treated Population
MK-4482-002 (Part 1 and Part 2 Combined)

	MK 4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	784		775		1,559	
with one or more adverse events resulting in death	2	(0.3)	13	(1.7)	15	(1.0)
with no adverse events resulting in death	782	(99.7)	762	(98.3)	1,544	(99.0)
Infections and infestations	**2**	**(0.3)**	**11**	**(1.4)**	**13**	**(0.8)**
COVID 19	1	(0.1)	9	(1.2)	10	(0.6)
COVID 19 pneumonia	1	(0.1)	6	(0.8)	7	(0.4)
Pneumonia	2	(0.3)	0	(0.0)	2	(0.1)
Septic shock	0	(0.0)	1	(0.1)	1	(0.1)
Staphylococcal sepsis	0	(0.0)	1	(0.1)	1	(0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**(0.0)**	**1**	**(0.1)**	**1**	**(0.1)**
Metastases to lung	0	(0.0)	1	(0.1)	1	(0.1)
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**3**	**(0.4)**	**3**	**(0.2)**
Acute respiratory failure	0	(0.0)	1	(0.1)	1	(0.1)

Participants With Adverse Events Resulting in Death During Treatment and 14-Day Follow-Up Period
(Incidence > 0% in One or More Treatment Groups)
All Participants as Treated Population
MK-4482-002 (Part 1 and Part 2 Combined)

	MK 4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**3**	**(0.4)**	**3**	**(0.2)**
Respiratory failure	0	(0.0)	2	(0.3)	2	(0.1)

Every participant is counted a single time for each applicable row and column.
Adverse event terms are from MedDRA Version 24.1.

Source: [ISS: adam adsl; adae]

5.2.2.1.3 Serious Adverse Events

SAEs were reported for 53 (6.8%) participants in the MOV group and 71 (9.2%) participants in the placebo group in P002 (Part 1 [MOV 800 mg/placebo] and Part 2 combined) [Table 2.5-covid19txallpop: 15] [Figure 5.3.5.3.3-covid19txallpop: 3].

The most commonly reported (≥2% in any group) SAEs were COVID-19 and COVID-19 pneumonia. One SAE (pancreatitis, placebo group) was considered to be related to study intervention by the investigator.

Discontinuation from study intervention due to an SAE was comparable in both groups (0.9% MOV, 1.7% placebo) [Table 2.7.4-covid19txallpop: 5].

Table 2.5-covid19txallpop: 15
Participants with Serious Adverse Events During Treatment and 14-Day Follow-Up Period
(Incidence >0% in 1 or More Treatment Groups)
All Participants as Treated Population
MK-4482-002 (Part 1 and Part 2 Combined)

	MK 4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	784		775		1,559	
with one or more serious adverse events	53	(6.8)	71	(9.2)	124	(8.0)
with no serious adverse events	731	(93.2)	704	(90.8)	1,435	(92.0)
Blood and lymphatic system disorders	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**
Thrombocytopenia	1	(0.1)	0	(0.0)	1	(0.1)
Cardiac disorders	**0**	**(0.0)**	**2**	**(0.3)**	**2**	**(0.1)**
Acute myocardial infarction	0	(0.0)	1	(0.1)	1	(0.1)
Atrial flutter	0	(0.0)	1	(0.1)	1	(0.1)
Gastrointestinal disorders	**1**	**(0.1)**	**1**	**(0.1)**	**2**	**(0.1)**
Pancreatitis	0	(0.0)	1	(0.1)	1	(0.1)
Pancreatitis acute	1	(0.1)	0	(0.0)	1	(0.1)
General disorders and administration site conditions	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**
Oedema peripheral	1	(0.1)	0	(0.0)	1	(0.1)
Infections and infestations	**47**	**(6.0)**	**63**	**(8.1)**	**110**	**(7.1)**

Participants With Serious Adverse Events During Treatment and 14-Day Follow-Up Period
(Incidence > 0% in One or More Treatment Groups)
All Participants as Treated Population
MK-4482-002 (Part 1 and Part 2 Combined)

	MK 4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Infections and infestations	**47**	**(6.0)**	**63**	**(8.1)**	**110**	**(7.1)**
Anal abscess	1	(0.1)	0	(0.0)	1	(0.1)
COVID 19	35	(4.5)	54	(7.0)	89	(5.7)
COVID 19 pneumonia	30	(3.8)	44	(5.7)	74	(4.7)
Lung abscess	1	(0.1)	0	(0.0)	1	(0.1)
Peritonsillitis	1	(0.1)	0	(0.0)	1	(0.1)
Pneumonia	3	(0.4)	0	(0.0)	3	(0.2)
Pneumonia aspiration	1	(0.1)	0	(0.0)	1	(0.1)
Pneumonia bacterial	3	(0.4)	2	(0.3)	5	(0.3)
Pneumonia haemophilus	0	(0.0)	1	(0.1)	1	(0.1)
Septic shock	0	(0.0)	1	(0.1)	1	(0.1)
Staphylococcal sepsis	0	(0.0)	1	(0.1)	1	(0.1)
Metabolism and nutrition disorders	**1**	**(0.1)**	**4**	**(0.5)**	**5**	**(0.3)**
Diabetic ketoacidosis	1	(0.1)	1	(0.1)	2	(0.1)
Diabetic metabolic decompensation	0	(0.0)	2	(0.3)	2	(0.1)
Type 2 diabetes mellitus	0	(0.0)	1	(0.1)	1	(0.1)

Participants With Serious Adverse Events During Treatment and 14-Day Follow-Up Period
(Incidence > 0% in One or More Treatment Groups)
All Participants as Treated Population
MK-4482-002 (Part 1 and Part 2 Combined)

	MK 4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**(0.0)**	**1**	**(0.1)**	**1**	**(0.1)**
Metastases to lung	0	(0.0)	1	(0.1)	1	(0.1)
Nervous system disorders	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**
Cerebral haemorrhage	1	(0.1)	0	(0.0)	1	(0.1)
Renal and urinary disorders	**0**	**(0.0)**	**1**	**(0.1)**	**1**	**(0.1)**
Acute kidney injury	0	(0.0)	1	(0.1)	1	(0.1)
Respiratory, thoracic and mediastinal disorders	**9**	**(1.1)**	**19**	**(2.5)**	**28**	**(1.8)**
Acute respiratory failure	0	(0.0)	2	(0.3)	2	(0.1)
Cough	0	(0.0)	1	(0.1)	1	(0.1)
Dyspnoea	0	(0.0)	1	(0.1)	1	(0.1)
Hiccups	0	(0.0)	1	(0.1)	1	(0.1)
Hypoxia	1	(0.1)	1	(0.1)	2	(0.1)
Pneumomediastinum	0	(0.0)	1	(0.1)	1	(0.1)
Pneumothorax	1	(0.1)	0	(0.0)	1	(0.1)
Pulmonary embolism	1	(0.1)	1	(0.1)	2	(0.1)

Participants With Serious Adverse Events During Treatment and 14-Day Follow-Up Period
(Incidence > 0% in One or More Treatment Groups)
All Participants as Treated Population
MK-4482-002 (Part 1 and Part 2 Combined)

	MK 4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Respiratory, thoracic and mediastinal disorders	**9**	**(1.1)**	**19**	**(2.5)**	**28**	**(1.8)**
Pulmonary hypertension	0	(0.0)	1	(0.1)	1	(0.1)
Respiratory distress	0	(0.0)	1	(0.1)	1	(0.1)
Respiratory failure	6	(0.8)	9	(1.2)	15	(1.0)
Vascular disorders	**1**	**(0.1)**	**1**	**(0.1)**	**2**	**(0.1)**
Peripheral vascular disorder	0	(0.0)	1	(0.1)	1	(0.1)
Shock	1	(0.1)	0	(0.0)	1	(0.1)

Every participant is counted a single time for each applicable row and column.
Adverse event terms are from MedDRA Version 24.1.

Source: [ISS: adam adsl; adae]

Confidential

5.2.2.1.4 Other Significant Adverse Events

Adverse Events Leading to Discontinuation of Study Intervention

Overall, the proportions of participants with 1 or more AEs leading to study intervention discontinuation were low and comparable in both intervention groups [Table 2.5-covid19txallpop: 16]. Eight participants, 4 (0.5%) in each group, discontinued study intervention due to an AE considered related to study intervention [Table 2.7.4-covid19txallpop: 12].

Table 2.5-covid19txallpop: 16
Participants with Adverse Events Leading to Discontinuation of Treatment (Incidence >0% in 1 or More Treatment Groups)
All Participants as Treated Population
MK-4482-002 (Part 1 and Part 2 Combined)

	MK 4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	784		775		1,559	
with one or more adverse events leading to discontinuation	13	(1.7)	21	(2.7)	34	(2.2)
with no adverse events leading to discontinuation	771	(98.3)	754	(97.3)	1,525	(97.8)
Eye disorders	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**
Vision blurred	1	(0.1)	0	(0.0)	1	(0.1)
Gastrointestinal disorders	**2**	**(0.3)**	**5**	**(0.6)**	**7**	**(0.4)**
Abdominal pain lower	0	(0.0)	1	(0.1)	1	(0.1)
Abdominal pain upper	0	(0.0)	2	(0.3)	2	(0.1)
Diarrhoea	0	(0.0)	4	(0.5)	4	(0.3)
Faeces discoloured	0	(0.0)	1	(0.1)	1	(0.1)
Nausea	2	(0.3)	0	(0.0)	2	(0.1)
Vomiting	2	(0.3)	1	(0.1)	3	(0.2)
General disorders and administration site conditions	**1**	**(0.1)**	**1**	**(0.1)**	**2**	**(0.1)**
Chest discomfort	0	(0.0)	1	(0.1)	1	(0.1)
Fatigue	1	(0.1)	0	(0.0)	1	(0.1)

Participants With Adverse Events Leading to Discontinuation of Treatment
(Incidence > 0% in One or More Treatment Groups)
All Participants as Treated Population
MK-4482-002 (Part 1 and Part 2 Combined)

	MK 4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Infections and infestations	**6**	**(0.8)**	**12**	**(1.5)**	**18**	**(1.2)**
COVID 19	3	(0.4)	10	(1.3)	13	(0.8)
COVID 19 pneumonia	3	(0.4)	7	(0.9)	10	(0.6)
Peritonsillitis	1	(0.1)	0	(0.0)	1	(0.1)
Tonsillitis	1	(0.1)	0	(0.0)	1	(0.1)
Investigations	**0**	**(0.0)**	**1**	**(0.1)**	**1**	**(0.1)**
Alanine aminotransferase increased	0	(0.0)	1	(0.1)	1	(0.1)
Aspartate aminotransferase increased	0	(0.0)	1	(0.1)	1	(0.1)
Metabolism and nutrition disorders	**0**	**(0.0)**	**1**	**(0.1)**	**1**	**(0.1)**
Diabetic metabolic decompensation	0	(0.0)	1	(0.1)	1	(0.1)
Musculoskeletal and connective tissue disorders	**0**	**(0.0)**	**1**	**(0.1)**	**1**	**(0.1)**
Myalgia	0	(0.0)	1	(0.1)	1	(0.1)
Nervous system disorders	**3**	**(0.4)**	**0**	**(0.0)**	**3**	**(0.2)**
Dizziness	1	(0.1)	0	(0.0)	1	(0.1)
Headache	1	(0.1)	0	(0.0)	1	(0.1)

Participants With Adverse Events Leading to Discontinuation of Treatment
(Incidence > 0% in One or More Treatment Groups)
All Participants as Treated Population
MK-4482-002 (Part 1 and Part 2 Combined)

	MK 4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Nervous system disorders	**3**	**(0.4)**	**0**	**(0.0)**	**3**	**(0.2)**
Hypoaesthesia	1	(0.1)	0	(0.0)	1	(0.1)
Psychiatric disorders	**1**	**(0.1)**	**1**	**(0.1)**	**2**	**(0.1)**
Insomnia	1	(0.1)	1	(0.1)	2	(0.1)
Respiratory, thoracic and mediastinal disorders	**1**	**(0.1)**	**1**	**(0.1)**	**2**	**(0.1)**
Hiccups	0	(0.0)	1	(0.1)	1	(0.1)
Hypoxia	1	(0.1)	0	(0.0)	1	(0.1)
Skin and subcutaneous tissue disorders	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**
Urticaria	1	(0.1)	0	(0.0)	1	(0.1)

Every participant is counted a single time for each applicable row and column.
Adverse event terms are from MedDRA Version 24.1.

Source: [ISS: adam adsl; adae]

Confidential

Events of Clinical Interest

No participants had laboratory values that met the predefined ECI criteria for potential DILI (defined as post-baseline elevated AST or ALT ≥3 × ULN and elevated total bilirubin ≥2 × ULN and alkaline phosphatase <2 × ULN) in P002 (Part 1 [MOV 800 mg/placebo] and Part 2 combined) [Table 5.3.5.3.3-covid19txallpop: 20]. One participant in each intervention group had laboratory values that met the predefined ECI criteria of post-baseline platelet value. The events were not considered by the investigator to be related to study intervention [Ref. 5.3.5.1: P002V03MK4482: 16.2.7.1.6, 16.2.7.2]. The post-baseline platelet value of <50,000/μL was reported on Day 13 in a participant from the MOV group who was hospitalized with worsening COVID-19 and subsequently diagnosed COVID-19 pneumonia; the participant received multiple antibacterial drugs, remdesivir, and enoxaparin as well as hemoperfusion. The event was assessed by a hematology consultant as hemoperfusion-related thrombocytopenia [Ref. 5.3.5.1: P002V03MK4482: 16.2.7.2].

Events of Pregnancy

No pregnancies were reported in P002 (Part 1 [MOV 800 mg/placebo] and Part 2 combined) through Day 29 [Ref. 5.3.5.1: P002V01MK4482: 12.2.3.2] [Ref. 5.3.5.1: P002V03MK4482: 12.2.3.2].

Hypersensitivity and Allergic Reactions

AEs that may indicate hypersensitivity when using the standardized MedDRA queries for "anaphylactic reaction" (narrow), "hypersensitivity" (narrow), and "angioedema" (narrow) were reported for 14 (1.8%) participants in the MOV group and 6 (0.8%) participants in the placebo group [Table 2.7.4-covid19txallpop: 13]. An AE of bronchospasm and an SAE of shock, reported by 2 different participants in the MOV 800 mg group, were assessed as unrelated to study intervention by the investigator [Ref. 5.3.5.1: P002V03MK4482: 16.2.7.1.2].

The majority of the participants who reported AEs potentially indicating hypersensitivity reported AEs in the SOC of skin and subcutaneous tissue disorders. Overall, 9 (1.1%) participants in the MOV group and 5 (0.6%) participants in the placebo group reported AEs assessed by the investigator as study intervention-related [Table 2.5-covid19txallpop: 13]. One participant (MOV group) reported an AE of urticaria that was Grade 3 and study intervention-related, as assessed by the investigator; the remaining AEs in the skin and subcutaneous SOC were Grade 1 or Grade 2 [Table 5.3.5.3.3-covid19txallpop: 14]. This Grade 3 urticaria event was not considered serious but resulted in discontinuation of study intervention [Ref. 5.3.5.1: P002V03MK4482: 16.2.7.1.5]. The angioedema reported by a participant in the MOV group on Day 2 was of Grade 1 intensity, assessed as study intervention-related by the investigator, did not result in discontinuation of study intervention, and resolved at the end of therapy [Ref. 5.3.5.1: P002V03MK4482: 16.2.7.1.1]. Anaphylaxis was not reported in any participant [Table 5.3.5.3.3-covid19txallpop: 14].

5.2.2.2 Phase 2 (P002 Part 1, P006, and P001 Part 1)

5.2.2.2.1 P002 Part 1

The AE profiles observed in P002 Part 1 were comparable across intervention groups (MOV 200, 400, 800 mg/placebo) [Ref. 5.3.5.1: P002V01MK4482: Table 12-1]. One participant had an AE leading to death (placebo group, Day 36) [Ref. 5.3.5.1: P002V01MK4482: Table 14.3-6] [Ref. 5.3.5.1: P002V01MK4482: 16.2.7.2].

The following key results were also observed:

- The most frequently reported AEs (≥5%) were COVID-19 pneumonia in the MOV 800 mg group; and diarrhea and COVID-19 in the placebo group [Ref. 5.3.5.1: P002V01MK4482: Table 14.3-5].

- SAEs were reported for 3.6% of participants in the MOV groups (combined) and 5.4% of participants in the placebo group [Ref. 5.3.5.1: P002V01MK4482: Table 14.3-8]. None were considered study intervention-related by the investigator [Ref. 5.3.5.1: P002V01MK4482: Table 14.3-7].

- AEs leading to study intervention discontinuation were reported for 1.3% of participant in the MOV groups (combined) (none were study intervention-related) and 1.4% in the placebo group (study intervention-related) [Ref. 5.3.5.1: P002V01MK4482: Table 14.3-11, 14.3-12].

5.2.2.2.2 P006

The AE profiles observed in P006 were generally comparable across intervention groups [Ref. 5.3.5.1: P006MK4482: 13.1.2.2]. No participants died while enrolled in the study [Ref. 5.3.5.1: P006MK4482: 12.3.1.1]. One participant in the placebo group died 31 days after discontinuation from the study.

The following key safety results were observed:

- The only AE reported in more than 5% of participants in either the combined MOV group or the placebo group was insomnia (2.9% combined MOV group, 6.5% placebo) [Ref. 5.3.5.1: P006MK4482: 12.2.2.1].

- SAEs were reported for 4 participants (3 participants in the MOV groups combined and 1 in the placebo group). None were considered drug-related per the investigator [Ref. 5.3.5.1: P006MK4482: 12.3.1.2].

- AEs leading to study intervention discontinuation were reported for 2 participants in the MOV groups (combined) and 1 participant in the placebo group. None were considered related to study intervention by the investigator [Ref. 5.3.5.1: P006MK4482: 12.3.1.3.1].

5.2.2.2.3 P001 (Part 1)

Overall safety profiles observed in P001 were generally comparable across intervention groups [Ref. 5.3.5.1: P001V01MK4482: Table 12-1]. AEs leading to death were reported for 16 participants (14 in the MOV groups [combined], 2 in placebo) [Ref. 5.3.5.1: P001V01MK4482: Table 14.3-8]. Most deaths occurred in participants who had severe COVID-19 at baseline (12 of 16 participants), were >60 years of age (13 of 16 participants), had underlying comorbidities (14 of 16 participants), and/or had duration of COVID-19 symptoms >5 days before randomization (12 of 16 participants). None of the deaths was considered to be related to study intervention by the investigator [Ref. 5.3.5.1: P001V01MK4482: 16.2.7.1.6].

The following key safety results were observed:

- The most frequently reported AEs (≥5%) in any MOV group were COVID-19, AST/ALT elevations, constipation, bacterial pneumonia, hyperglycemia, and respiratory failure [Ref. 5.3.5.1: P001V01MK4482: Table 14.3-3]. The most frequently reported AEs (≥5%) in the placebo group were constipation, COVID-19, COVID-19 pneumonia, ALT increased, and respiratory failure.

- SAEs were reported for 15.4% of participants (15.1% of participants in the MOV groups [combined] and 16.0% of participants in placebo group) [Ref. 5.3.5.1: P001V01MK4482: Table 14.3-9]. One SAE of Grade 3 urticaria was considered to be related to study intervention (MOV 200 mg) [Ref. 5.3.5.1: P001V01MK4482: Table 14.3-10].

- AEs leading to study intervention discontinuation were reported for 1 participant in the MOV 400 mg group (not intervention-related) [Ref. 5.3.5.1: P001V01MK4482: Table 14.3-11].

- One participant (MOV 400 mg) discontinued study intervention due to an SAE of respiratory failure (not related to study intervention) [Ref. 5.3.5.1: P001V01MK4482: Table 14.3-11].

5.2.2.3 Phase 1 (P004, P012, and P008)

In the Phase 1 studies, single doses of MOV ranging from 50 to 1600 mg or multiple doses ranging from 50 to 800 mg (Q12H for 5.5 or 10.5 days) were generally well tolerated in healthy participants. No SAEs or deaths were reported in any of the Phase 1 studies [Ref. 5.3.3.1: P004MK4482: 12.1.2, 12.1.3] [Ref. 5.3.3.1: P012MK4482: 12.1] [Ref. 5.3.3.3: P008MK4482: 12.5]. No ECIs were reported in P012 or P008.

The following key safety results were observed:

- For participants receiving single or multiple doses of study intervention, at least 1 AE was reported for up to 35.4% and 87.5% of participants in the MOV groups and up to 43.8% and 75.0% of participants in the placebo groups. Study intervention-related AEs were reported for 0% to 33.3% of participants receiving MOV and 0% to 12.5% of participants receiving placebo.

- All AEs were mild in intensity with the exception of 2 moderate AEs reported for 2 participants (dermatitis and toxic skin eruption).

- One participant discontinued study intervention after receiving 5 days of MOV 800 mg Q12H due to moderate toxic skin eruption, which was treated and resolved by the end of the study. Moderate dermatitis was reported for 1 participant who received a single dose of MOV 200 mg in Period 1 of Part 1; this participant subsequently received a single dose of MOV 1600 mg in Period 2 of Part 1 without recurrence of dermatitis. Moderate toxic skin eruption was reported for 1 participant who received MOV 800 mg Q12H for 5 days in Part 2 before discontinuation of study intervention. These AEs were treated topically and resolved before the end of the study.

5.2.2.4 Blinded Safety Data from Ongoing Studies: Phases 1 and 2

P005 and P007 are ongoing and remain blinded (except for Part 1 of P005, which is unblinded). Safety data are consistent with completed studies and do not indicate any safety signals.

5.2.3 Laboratory, Vital Signs, and Other Observations Related to Safety

5.2.3.1 Overview of Laboratory Events

5.2.3.1.1 Phase 2/3: P002 (Part 1 [MOV 800 mg/Placebo] and Part 2 Combined)

No evidence of hematologic, hepatic, or other toxicity were observed for participants in the MOV group in P002 (Part 1 [MOV 800 mg/placebo] and Part 2 combined). Overall, comparable proportions of participants in each intervention group had laboratory values that met PDLC, as summarized by toxicity grade in [Table 5.3.5.3.3-covid19txallpop: 27] [Table 5.3.5.3.3-covid19txallpop: 25] [Table 5.3.5.3.3-covid19txallpop: 26]. Overall mean changes in laboratory values from baseline over time were comparable for both groups [Table 5.3.5.3.3-covid19txallpop: 28].

5.2.3.2 Hematology

5.2.3.2.1 Phase 2/3: P002 (Part 1 and Part 2 Combined)

No evidence of hematologic toxicity was observed for participants in the MOV group in P002 (Part 1 [MOV 800 mg/placebo] and Part 2 combined). Overall, comparable proportions of participants in each intervention group had laboratory values that met PDLC, as summarized by [Table 5.3.5.3.3-covid19txallpop: 27] [Table 5.3.5.3.3-covid19txallpop: 25] [Table 5.3.5.3.3-covid19txallpop: 26]. Overall, mean changes in laboratory from baseline in laboratory values over time were comparable for both intervention groups [Table 5.3.5.3.3.-covid19txallpop: 28]. There were no notable between-group differences in mean changes from baseline over time for hemoglobin, neutrophils, or platelets [Table 2.7.4-covid19txallpop: 14]. Hematology-related ECIs are described in [Sec. 2.5-covid19txallpop: 5.2.2.1.4].

5.2.3.2.2 Phase 2 (P002 Part 1, P006, P001 Part 1)

There were no clinically meaningful treatment- or dose-related changes in hematology values observed in Phase 2 studies [Ref. 5.3.5.1: P006MK4482: 12.4.2.1.1] [Ref. 5.3.5.1: P001V01MK4482: Table 14.3-15] [Ref. 5.3.5.1: P002V01MK4482: Table 14.3-13, 14.3-16]. One participant (placebo group) in P001 had a confirmed platelet value <50,000 μL on Day 10 [Sec. 2.5-covid19txallpop: 5.2.2.2]. This participant was receiving antibacterial therapies and developed fatal septic shock due to bacterial pneumonia requiring intubation on Day 11 [Ref. 5.3.5.1: P001V01MK4482: 16.2.7.2].

5.2.3.2.3 Phase 1 (P004, P012, and P008)

There were no study intervention-related clinically meaningful changes in hematology values observed as a function of dose or treatment in studies conducted in healthy participants who received MOV up to 10.5 days (Q12H) (P004 [Ref. 5.3.3.1: P004MK4482: 12.3], P012 [Ref. 5.3.3.1: P012MK4482: 12.3.1, 12.3.2], and P008 [Ref. 5.3.3.3: P008MK4482: 12.5]).

5.2.3.3 Chemistry

5.2.3.3.1 Phase 2/3: P002 (Part 1 and Part 2 Combined)

The proportions of participants from P002 (Part 1 [MOV 800 mg/placebo] and Part 2 combined) with Grade 3 or Grade 4 chemistry PDLC findings were low and comparable in both intervention groups [Table 5.3.5.3.3-covid19txallpop: 25]. The percentage of participants who met predetermined criteria for Grade 3 or Grade 4 ALT (1.2% MOV, 1.6% placebo) and lipase (0.6% MOV, 1.0% placebo) were low and comparable in both intervention groups [Table 5.3.5.3.3-covid19txallpop: 25].

5.2.3.3.2 Phase 2 (P002 Part 1, P006, and P001 Part 1)

Overall, there were no clinically meaningful treatment- or dose-related changes in chemistry values observed in Phase 2 studies [Ref. 5.3.5.1: P001V01MK4482: Table 14.3-15] [Ref. 5.3.5.1: P001V01MK4482: Table 14.3-15, 14.3-16] [Ref. 5.3.5.1: P006MK4482: 12.4.2.1.1]. One participant (MOV 800 mg) in P001 Part 1 had post-baseline elevated AST or ALT ≥3 × ULN and elevated total bilirubin ≥2 × ULN and alkaline phosphatase <2 × ULN (satisfying the criteria for potential DILI) on Day 14. The potential DILI criteria were no longer satisfied on Day 15 when alkaline phosphatase became >2 × ULN. The laboratory parameters were considered to be secondary to fatal septic shock and cholestasis and not considered DILI [Ref. 5.3.5.1: P001V01MK4482: 16.2.7.2].

5.2.3.3.3 Phase 1 (P004, P012, and P008)

No study intervention-related clinically meaningful changes in chemistry laboratory values were observed as a function of dose or treatment in studies conducted in healthy participants (P004 [Ref. 5.3.3.1: P004MK4482: 12.3], P012 [Ref. 5.3.3.1: P012MK4482: 12.3.1, 12.3.2], and P008 [Ref. 5.3.3.3: P008MK4482: 12.5]).

5.2.3.4 Other Laboratory Values

5.2.3.4.1 Phase 2/3: P002 (Part 1 and Part 2 Combined)

Mean C-reactive protein levels decreased beginning on Day 3 for participants who received MOV, as compared with Day 10 for participants in the placebo group, suggesting earlier resolution of inflammation in participants in the MOV group compared with the placebo group [Table 5.3.5.3.3-covid19txallpop: 31].

5.2.3.4.2 Phase 2 (P002 Part 1, P006, and P001 Part 1)

There were no clinically meaningful findings in other laboratory values (ie, lipase [P001 and P002] or amylase [P001]) that met PDLC in Part 1 of P001 or P002 (Part 1 [MOV 200, 400, 800 mg/placebo]) [Ref. 5.3.5.1: P001V01MK4482: Table 14.3-15] [Ref. 5.3.5.1: P002V03MK4482: Table 14.3-15]. There were no treatment- or dose-related changes in any mean inflammatory or immune biomarkers over time during P006 [Ref. 5.3.5.1: P006MK4482: 12.4.2.1.3].

5.2.3.4.3 Phase 1 (P004, P012, P008)

No study intervention-related clinically meaningful changes in other laboratory values were observed as a function of dose or treatment in studies conducted in healthy participants (P004 [Ref. 5.3.3.1: P004MK4482: 12.3], P012 [Ref. 5.3.3.1: P012MK4482: 12.3.2], and P008 [Ref. 5.3.3.3: P008MK4482: 12.5]).

5.2.3.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

5.2.3.5.1 Phase 2/3: P002 (Part 1 and Part 2 Combined)

There were no clinically meaningful findings in vital signs measurements, physical examination findings, or other observations related to safety data from P002 (Part 1 [MOV 800 mg/placebo] and Part 2 combined) [Table 5.3.5.3.3-covid19txallpop: 32]. However, participants in the MOV groups showed a positive mean change in oxygen saturation beginning on Day 5, suggesting an earlier recovery for the MOV group compared with the placebo group (Day 10) [Table 5.3.5.3.3-covid19txallpop: 23].

5.2.3.5.2 Phase 2 (P002 Part 1, P006, and P001 Part 1)

Vital signs and physical examination data from Part 1 of P001 and P002 MOV 200 and 400 mg) were collected, but not analyzed [Ref. 5.3.5.1: P001V01MK4482: 12.4] [Ref. 5.3.5.1: P002V01MK4482: 12.4]. No clinically meaningful changes in vital signs values were observed as a function of dose or treatment in P006 [Ref. 5.3.5.1: P006MK4482: 12.5.1.1.2].

5.2.3.5.3 Phase 1 (P004, P012, and P008)

No study intervention-related clinically meaningful changes in vital signs values, ECGs (including QTc), physical examinations, or other observations related to safety were observed as a function of dose or treatment in studies conducted in healthy participants (P004 [Ref. 5.3.3.1: P004MK4482: 12.4], P012 [Ref. 5.3.3.1: P012MK4482: 12.4], and P008 [Ref. 5.3.3.3: P008MK4482: 12.5]). A concentration-QTc analysis conducted on ECG from dedicated Holter ECGs used in P004 further showed no clinically meaningful effect of NHC on the QT/QTc interval [Sec. 2.7.2-covid19txallpop: 2.4.2] [Ref. 5.3.5.3: 06G3K2].

5.2.4 Safety in Special Groups

5.2.4.1 Intrinsic Factors

The incidence of AEs by intrinsic factors of age, sex, race, and ethnicity for participants in P002 (Part 1 [MOV 800/placebo] and Part 2 combined) are provided in [Sec. 5.3.5.3.3-covid19txallpop: 5.1]. There were no clinically meaningful differences identified in patterns of specific AEs observed between study intervention groups when analyzed by intrinsic factors.

5.2.4.1.1 Age

The percentages of participants with at least 1 AE were generally comparable in the age subgroups ≥65 years and <65 years for both MOV and placebo groups for participants in P002 (Part 1 [MOV 800 mg/placebo] and Part 2 combined) [Table 5.3.5.3.3-covid19txallpop: 32]. Participants ≥65 years had higher rates of SAEs compared with participants <65 years in both intervention groups, which likely reflects the epidemiology of COVID-19 where it has been observed that older patients are at higher risk of severe disease and adverse outcomes.

5.2.4.1.2 Sex

There were no clinically meaningful differences identified in patterns of specific AEs observed between study intervention groups when analyzed by sex for participants in P002 (Part 1 [MOV 800 mg/placebo] and Part 2 combined) [Table 5.3.5.3.3-covid19txallpop: 35].

5.2.4.1.3 Race

There were no clinically meaningful differences identified in patterns of specific AEs observed between study intervention groups when analyzed by race for participants in P002 (Part 1 [MOV 800 mg/placebo] and Part 2 combined) [Table 5.3.5.3.3-covid19txallpop: 36].

5.2.4.1.4 Ethnicity

There were no clinically meaningful differences identified in patterns of specific AEs observed between study intervention groups when analyzed by ethnicity for participants in P002 (Part 1 [MOV 800 mg/placebo] and Part 2 combined) [Table 5.3.5.3.3-covid19txallpop: 37].

5.2.4.2 Extrinsic Factors

5.2.4.2.1 Geographic Region

There were no clinically meaningful differences identified in patterns of specific AEs observed between study intervention groups when analyzed by geographic region for participants in P002 (Part 1 [MOV 800 mg/placebo] and Part 2 combined) [Table 5.3.5.3.3-covid19txallpop: 38].

5.3 Other Safety Topics

5.3.1 Drug Interactions

Based on nonclinical data and the known metabolic pathways of MOV and NHC, no DDIs are anticipated and no clinical DDI studies were conducted [Sec. 2.7.2-covid19txallpop: 1.2].

MOV is unlikely to be a victim or perpetrator of DDIs [Sec. 2.7.2-covid19txallpop: 1.3.1.3]. 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 [Sec. 2.7.2-covid19txallpop: 3.3.1]. Therefore, it is unlikely that other drugs will impact the exposure of NHC-TP in tissues. Additionally, MOV and NHC did not inhibit or induce the activity of xenobiotic metabolic enzymes and inhibit transporters tested in vitro [Sec. 2.7.2-covid19txallpop: 1.4.3]. These data suggest that the potential for DDIs between MOV/NHC and comedications is low. Therefore, no clinical DDI studies were conducted.

No pharmacodynamic interaction is expected between MOV and other commonly administered antivirals based on a lack of synergy or antagonism for antiviral activity in vitro against SARS-CoV-2 for NHC in combination with lamivudine, abacavir, emtricitabine, hydroxychloroquine, nelfinavir, ribavirin, sofosbuvir, or tenofovir. Concomitant remdesivir use did not impact exposures of NHC based on population PK analysis [Sec. 2.7.2-covid19txallpop: 3.3.1].

5.3.2 Use in Pregnancy and Lactation

Animal studies have shown reproductive toxicity after administration of MOV. Administration of MOV to pregnant women is not recommended, and women of childbearing potential should use effective contraception during treatment and for 4 days after the last dose of MOV.

There are no clinical data regarding the use of MOV in pregnancy.

It is unknown if MOV or NHC is secreted in human milk, affects human milk production, or has an effect on the breastfed infant. Breastfeeding is not recommended during treatment and for 4 days after the last dose of MOV.

5.3.3 Overdose

During the Phase 1 clinical development studies presented in the safety evaluation (P004, P012, and P008), no participants met protocol-specified overdose criteria.

In Phase 2/3, 1 participant in the MOV group in P006 had an AE of accidental overdose (no protocol-specified definition). This participant accidentally took an additional dose of MOV 800 mg on Day 2 (for a total of 2400 mg or 3 × MOV 800 mg). No other AEs were reported for this participant during the study [Ref. 5.3.5.1: P006MK4482: 12.3.1.3.4] [Ref. 5.3.5.1: P006MK4482: Table 14.3.1.2.1].

There is no specific information available on the treatment of overdose. Treatment of overdose with MOV should consist of general supportive measures, including the monitoring of clinical status of the patient. Hemodialysis is not expected to result in effective elimination of NHC.

5.3.4 Drug Abuse

There was no indication that MOV/NHC has a pharmacologic profile (including off-target profile) consistent with drug abuse liability potential. Additionally, NHC-TP levels were shown to be much lower in the brain compared with other tissues (eg, lung and spleen) in the tissue distribution studies in rats, dogs, monkeys, and ferrets, and there was no evidence of psychoactive effects (eg, sedative or stimulant effects) in the safety pharmacology or routine repeat-dose toxicity studies. As such, no abuse potential studies were conducted in animals.

5.3.5 Withdrawal and Rebound

Based on the cumulative data in the clinical development program, there is no evidence to suggest a potential for withdrawal or rebound effects after discontinuing MOV.

5.3.6 Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No studies on the effect of MOV on the ability to drive and operate machines have been performed. MOV is expected to have no or negligible influence on the ability to drive and use machines.

5.4 Postauthorization Data

MOV first received conditional marketing authorization in the UK on 04-NOV-2021. The data presented in this section are from postauthorization use in countries where MOV is authorized for use under an Emergency Use Authorization, conditional or provisional marketing authorization or special approval for emergency use as of 31-JAN-2022.

There are no records of any registration being revoked or withdrawn for safety reasons.

5.4.1 Postauthorization Data for Molnupiravir (04-NOV-2021 Through 31-JAN-2022)

As of 31-JAN-2022, the most frequently reported AEs occurred in the SOC of gastrointestinal disorders and skin and subcutaneous tissue disorders: diarrhea, rash, and nausea. The majority of these commonly reported events were nonserious. On review of the cases received in the reporting interval, no AE appears to be reported more commonly in a specific patient age population. Of the events reported as serious, the majority were reported once. Only COVID-19 and pneumonia were reported as serious in >2 reports. There were 20 reports of exposure in pregnancy, none confirmed to be valid with further follow-up.

On 08-FEB-2022, the FDA informed the applicant of 14 cases reported in the FDA Adverse Event Reporting System database (11 were not in the applicant's global safety database) of serious events that may indicate hypersensitivity. An analysis of events in the Company's safety database received as of 31-JAN-2022in the postauthorization period and retrieved using the SMQ "Anaphylactic Reaction" (Narrow), "Hypersensitivity" (Narrow), and "Angioedema" (Narrow) resulted in revision of the Company Core Data Sheet to add hypersensitivity and related terms to the Warnings section and related terms of hypersensitivity, rash, urticaria, erythema, and angioedema to the Postmarketing Experience section (see Module 2.5, Date of Submission 21-MAR-2022, Clinical Overview, Page 3).These events do not alter the conclusion that the overall benefit-risk balance for MOV continues to be positive.

As with all marketing authorization holder products, the safety profile of MOV is closely monitored on a continuing basis.

5.5 Summary of Key Safety Results

MOV (800 mg Q12H for 5 days) is generally well tolerated.

The comparable AE profile between MOV and placebo and lack of clinically meaningful changes in laboratory safety and physical assessments observed in the Phase 1 through Phase 3 clinical studies demonstrate an acceptable safety and tolerability profile of MOV and support this application for the proposed indication. Assessment of the postauthorization data supports the overall safety and tolerability profile of MOV.

6 BENEFITS AND RISKS CONCLUSIONS

6.1 Therapeutic Context

6.1.1 Disease or Condition

As discussed in [Sec. 2.5-covid19txallpop: 1.5.1], COVID-19, a disease resulting from SARS-CoV-2 infection, was declared a global pandemic by the WHO on 11-MAR-2020 [Ref. 5.4: 05LDCR]. Patients with SARS-CoV-2 infection may experience a range of clinical manifestations, from no symptoms to critical illness [Ref. 5.4: 05QYK2]. Available data suggest that 5% to 20% of patients with COVID-19 progress to severe disease, characterized primarily by acute respiratory failure [Ref. 5.4: 05J92M, 05M3T6, 05JSVW] [Ref. 5.4: 05Q368, 05H4S0, 05JQSM]. The burden of COVID-19 extends to extrapulmonary manifestations, including neurologic complications (eg, ischemic and hemorrhagic strokes), thrombotic complications due to hypercoagulable state, gastrointestinal manifestations, dermatologic manifestations, and ocular manifestations [Ref. 5.4: 05JLPX, 05JLPP, 05JM59] [Ref. 5.4: 05JM53]. There is an increased risk of progression to severe COVID-19 in adults ≥60 years of age and individuals with certain underlying medical conditions [Ref. 5.4: 05JSVW, 05Q36T, 05Q5B2] [Ref. 5.4: 06CXMG, 07WF9S].

6.1.2 Current Therapies

Brief background information regarding the current standard-of-care mAbs and antivirals for COVID-19 can be found in [Sec. 2.5-covid19txallpop: 1.4.2], along with associated limitations.

Even with currently available therapeutic options, many challenges remain concerning their use: there are segments of the population for whom these agents may not be appropriate either due to DDIs or the presence of underlying medical conditions (eg, hepatic or renal impairment); all therapeutic options may not be accessible (eg, due to the need to administering IV) to all patients in general or within an appropriate timeframe to ensure optimization of efficacy; and/or some therapeutic options may not be effective due to the emergence of variants with reduced susceptibility.

6.2 Benefits

The treatment benefits of MOV in patients with mild-to-moderate COVID-19 at risk for progressing to severe illness include:

- An approximate 30% reduction in the relative risk of hospitalization or death; the benefit of MOV treatment is consistent across most subgroups.
    - An approximate 89% estimated relative risk reduction in the incidence of death.
- The potential for improvement in patient-reported outcomes for COVID-19 signs and symptoms.

- Oral administration with or without food, a low potential for drug-drug interactions, and no dose adjustments for individuals with renal or hepatic impairment.
- Reduction in SARS-CoV-2 RNA viral load and infectious virus.
- Low risk for of viral resistance.
- A well tolerated and acceptable safety profile.

6.3 Risks

The clinical data from 1468 participants who received any MOV dose in studies where enrollment is completed, including 944 who received at least 800 mg Q12H for 5 days, indicate that MOV was generally well tolerated with no evidence of organ-specific toxicity or major safety concerns.

In the integrated safety analysis of participants with mild-to-moderate COVID-19 who received at least one dose of MOV 800 mg Q12H (P002 Part 1 [MOV 800 mg] and Part 2 combined), the percentages of participants who received MOV and who experienced an AE, study intervention-related AE, or discontinued study intervention due to an AE were comparable to placebo. A lower percentage of participants who received MOV experienced an SAE or discontinued study intervention due to an SAE compared with participants who received placebo. There were no study intervention-related SAEs in participants who received MOV. The proportion of participants with AEs leading to death was lower in the MOV group than in the placebo group.

Safety results from P002 Part 1, from P006 in non-hospitalized participants with COVID-19, and from P004 in healthy participants are supportive of findings from the integrated safety analysis.

Across the clinical development program, there was no evidence of organ toxicities, including hematologic toxicities. Embryo fetal findings (postimplantation loss and teratogenicity) were observed in rats at exposures 7.5-fold higher than the clinical NHC exposure at 800 mg Q12H and fetal growth was noted to be reduced at exposures approximately 3-fold higher than the clinical NHC exposure at 800 mg Q12H. Based on these findings, use in pregnancy is not recommended and WOCBP should use effective contraception for the duration of treatment and 4 days after the last dose.

Overall, all risks are adequately addressed and communicated in the proposed product labeling. Observations indicative of hypersensitivity, occurring mainly in the skin and subcutaneous tissues disorders SOC, do not alter the conclusion that the overall benefit-risk balance for MOV continues to be positive.

6.4 Benefit-Risk Assessment

The benefit/risk profile for MOV is favorable, supporting use of MOV for the proposed indication [Table 2.5-covid19txallpop: 17] and [Table 2.5-covid19txallpop: 18].

In the pivotal clinical study (Part 2 of P002), MOV when administered within 5 days of symptom onset was shown to be superior to placebo in preventing hospitalization or death in patients with mild-to-moderate COVID-19 at risk for progression, with a relative risk reduction of approximately 50% compared with placebo. Benefit was consistently shown across patient risk subgroups and across infection with various viral clades.

The safety analysis demonstrates that MOV is generally well tolerated in patients with COVID-19 and has a favorable safety profile.

There is a tremendous and urgent unmet medical need for safe and effective oral agents for the treatment of COVID-19, especially in the context of an ongoing pandemic. The risk-benefit assessment of MOV to date supports the use of MOV for the treatment of COVID-19.

Table 2.5-covid19txallpop: 17
Summary of Favorable Effects for Molnupiravir

Favorable Effect	Endpoint Description		Results		Uncertainties/ Strength of Evidence	Reference
			MOV	Placebo		
Reduced risk for hospitalization or death[a]	Percentage of participants with all-cause hospitalizations and/or deaths through Day 29	Hospitalization or death Hospitalization Death Unknown survival status	48/709 (6.8%) 48 1 0	68/699 (9.7%) 67 9 1	• 3.0% reduction in risk of hospitalization or death (95% CI: -5.9, -0.1), corresponding to ~30% relative reduction p-value=0.0218	[Sec. 2.5-covid19txallpop: 4.3.1.1] [Table 2.5-covid19txallpop: 6] [Table 2.5-covid19txallpop: 7]
Potential improvement in patient-reported outcome of signs and symptoms of COVID-19	Percentage of participants with sustained resolution or improvement of self-reported COVID-19 signs and symptoms through Day 29		Higher percentages of participants reported sustained improvement or resolution in most self-reported COVID-19 signs and symptoms, as recorded on a daily symptom diary, in the MOV group compared with the placebo group.		• Sign/symptom data were collected daily from a 15-item paper symptom diary completed by the participant. • No formal hypothesis test was conducted and there was no adjustment for multiplicity.	[Sec. 2.5-covid19txallpop: 4.3.1.1.2] [Figure 2.5-covid19txallpop: 2] [Ref. 5.3.5.1: P002V03MK4482: Table 14.2-26] through [Ref. 5.3.5.1: P002V03MK4482: Table 14.2-41]

Favorable Effect	Endpoint Description		Results		Uncertainties/ Strength of Evidence	Reference
			MOV	Placebo		
Reduced SARS-CoV-2 RNA	Change from baseline in SARS-CoV-2 RNA titers in NP swabs relative to placebo Mean reduction in log_{10} copies/mL	Day 3 Day 5 Day 10	-1.17 -2.26 -3.31	-0.96 -1.96 -3.16	• The adjusted mean difference in SARS-CoV-2 RNA (in log_{10} scale; MOV minus placebo) was -0.21 [95% CI: -0.36, -0.05] at Day 3, -0.30 [95% CI: -0.46, -0.14] at Day 5, and -0.16 [95% CI: -0.29, -0.02] at Day 10, which corresponds to a relative reduction in the geometric mean SARS-CoV-2 RNA titer of 38% [95% CI: 11%, 56%], 50% [95% CI: 28%, 65%], and 31% [95% CI: 5%, 49%] for the MOV group compared with the placebo group • Consistent results across study population subgroups based on baseline RNA titer ($\leq 10^6$ copies/mL, $>10^6$ copies/mL)	[Sec. 2.5-covid19txallpop: 4.3.1.1.3] [Ref. 5.3.5.3: 07X2GY: Table 4]

CI confidence interval; COVID 19 coronavirus disease 2019; IA interim analysis; MOV molnupiravir (MK 4482, EIDD 2801); RNA ribonucleic acid; SARS CoV 2 severe acute respiratory syndrome coronavirus 2.

[a] A favorable effect reduced risk for COVID 19 related hospitalization or death was also observed with a 6.8% reduction in risk of COVID related hospitalization or death (95% CI: 11.1, 2.6).

Source: [Ref. 5.3.5.1: P002V03MK4482]

Table 2.5-covid19txallpop: 18
Summary of Unfavorable Effects for Molnupiravir

Unfavorable Effect	Endpoint Description		Results		Uncertainties/ Strength of Evidence	Reference
			MOV	Placebo		
No important unfavorable effects/risks were identified in clinical studies	Proportion of participants with an AE	AE	245/784 (31.3%)	259/775 (33.4%)	Results for the integrated safety from P001 800 mg group and P002 combined: • The percentage of participants who received MOV and had an AE, SAE or who discontinued study intervention due to an AE was comparable to that in the placebo group. • There were no drug-related SAEs in the MOV group. • The percentage of participants who died was lower in participants who received MOV compared to placebo.	[Table 5.3.5.3.3-covid19txallpop: 6]
		Discontinuation of study intervention due to AE	13/784 (1.7%)	21/775 (2.7%)		
		SAE	53/784 (6.8%)	71/775 (9.2%)		
		Death	2/784 (0.3%)	13/775 (1.7%)		
Hypersensitivity identified in postauthorization period	Spontaneous reports of events received from the Company's safety database, and events reported to the FAERS	Rash, urticaria, angioedema, and erythema	N/A	N/A	Postauthorization observational data	[Ref. 5.3.6: 080 D78]

AE adverse event; FAERS Food and Drug Administration Adverse Event Reporting System; IA interim analysis; MOV molnupiravir (MK 4482, EIDD 2801); N/A not applicable; SAE serious adverse event.

6.5 Contraindications

None.

6.6 Use in Specific Populations

6.6.1 Pregnancy

There are no clinical data for the use of MOV in pregnancy. Based on animal studies, MOV may cause fetal harm. Administration of MOV to pregnant women is not recommended, and WOCBP should use effective contraception during treatment and for 4 days after the last dose.

6.6.2 Nursing Mothers

It is unknown if MOV is secreted in human milk. Breastfeeding is not recommended during treatment and for 4 days after the last dose.

6.6.3 Geriatrics

Clinical data do not indicate a difference in the safety profile of MOV in participants ≥65 years of age when compared with participants <65 years. Based on PopPK modeling, PK in patients ≥65 years of age is similar to PK in younger patients. No dose adjustment based on age is recommended.

6.6.4 Pediatrics

Safety and effectiveness of MOV for the treatment of COVID-19 have not been evaluated in patients younger than 18 years of age. Bone and cartilage toxicity was observed in the long bones (femur, tibia) of rapidly growing rats dosed with MOV for 3 months at ≥500 mg/kg/day (5.4 times the NHC exposure in humans at the recommended human dose; see [Ref. 4.2.3.2: TT201014]). The clinical significance of this finding for the pediatric population is unknown.

6.6.5 Hepatic Impairment

Although the effect of hepatic impairment on NHC has not been evaluated clinically, based on preclinical data, hepatic elimination is not expected to be a major route for NHC elimination. Therefore, hepatic impairment is not expected to have a significant effect on NHC elimination. No dose adjustment for any degree of hepatic impairment is recommended.

6.6.6 Renal Impairment

Patients on dialysis or who have eGFR less than 30 mL/min/1.73m^2 were excluded from clinical studies. In a PopPK analysis of those enrolled in clinical studies with eGFR ≥3 mL/min/1.73m^2, there was no difference in NHC PK in patients with mild or moderate renal impairment. Renal elimination does not contribute significantly to elimination of MOV or NHC (<10% of dose was excreted renally) nor is NHC eliminated by metabolic enzyme-mediated pathways that can be impacted by severe renal impairment. Therefore, severe renal impairment and end-stage renal disease are not expected to have a significant effect on NHC elimination. Based on this, no dose adjustment for any degree of renal impairment is recommended.

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