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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ΔΔQTcF	Mean Change from Time Matched Baseline Placebo-Adjusted QTcF
%CV	Percent coefficient of variation
3TC	Lamivudine
ADME	Absorption, distribution, metabolism, excretion
AE	Adverse event
ANOVA	Analysis of variance
AUC	Area under the concentration-time curve
AUC0-12	Area under the concentration-time curve from time 0 to 12 hours
AUC0-inf	Area under the concentration-time curve from time 0 extrapolated to infinity
AUC0-last	Area under the concentration-time curve from time 0 through the last measurable concentration
AUC50	Half maximal effective AUC value
BCRP	Breast Cancer Resistance Protein efflux transporter
BCS	Biopharmaceutics Classification System
BMI	Body mass index
C12	Concentration at 12 hours
CES1	Carboxylesterase 1
CES2	Carboxylesterase 2
CI	Confidence interval
CL/F	Apparent clearance
Cmax	Maximum concentration
CNT1	Concentrative nucleoside transporter 1
CNT2	Concentrative nucleoside transporter 2
CNT3	Concentrative nucleoside transporter 2
COVID-19	Coronavirus disease 2019
CTD	Common technical document
CV	Coefficient of variation
CYP	Cytochrome P450

Abbreviation	Definition
DDI	Drug-drug interaction
DFC	Dry-filled capsule
DDI	Drug-drug interaction
ECG	Electrocardiograms
EDTA	ethylenediaminetetraacetic acid
eGFR	Estimated glomerular filtration rate
EIDD	Emory Institute for Drug Development
ENT1	Equilibrative nucleoside transporter 1
ENT2	Equilibrative nucleoside transporter 2
EOT	End of treatment
E-R	Exposure-response
F	Absolute bioavailability
Fa	Fraction absorbed
FaSSIF	Fasted state simulated intestinal fluid
FeSSIF	Fed state simulated intestinal fluid
Fe0-12	Percentage of the dose administered recovered in urine over the time interval 0 to 12 hours postdose
Fe0-24	Percentage of the dose administered recovered in urine over the time interval 0 to 24 hours postdose
FIH	First in human
FMI	Final market image
FSS	Formal stability study
FTC	Emtricitabine
GI	Gastrointestinal
GLP	Good Laboratory Practice
GLSM	Geometric least squares mean
GM	Geometric mean
GMR	Geometric mean ratio
hERG	Human ether-à-go-go-related gene
HR	Heart rate
IC50	Half-maximal inhibitory concentration

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Abbreviation	Definition
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INR	International normalized ratio
IV	Intravenous
IVDM	Integrated viral dynamics model
JAK	Janus kinase
LLC-PK1	Epithelial cells derived from porcine kidneys
LLOQ	Lower limit of quantitation
LNS	Low frequency nucleotide substitutions
LSM	Least squares mean
mAbs	Monoclonal antibodies
mARC1	Mitochondrial amidoxime reducing component 1
mARC2	Mitochondrial amidoxime reducing component 2
MATE1	Multidrug and toxin extrusion protein 1
MATE2K	Multidrug and toxin extrusion protein 2K
MDR1	Multidrug resistance 1 (p-glycoprotein)
MDRD	Modification of Diet in Renal Disease study
MERS	Middle east respiratory syndrome
MOV	Molnupiravir, MK-4482, EIDD-2801
MTT	Mean transit time
NGS	Next generation sequencing
NHC	N-hydroxycytidine, EIDD-1931
NHC-TP	N-hydroxycytidine-5′-triphosphate, EIDD-2601
NP	Nasopharyngeal
OAT1B1	Organic anion transporter 1B1
OAT1B3	Organic anion transporter 1B3
OATP1B1	Organic anion transporting peptide 1B1
OATP1B3	Organic anion transporting peptide 1B3
OCT1	Organic cation transporter 1
OCT2	Organic cation transporter 2
OP	Oropharyngeal

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Abbreviation	Definition
P	Protocol (number)
PBMC	Peripheral blood mononuclear cells
PBS	Phosphate-buffered saline
PCR	Polymerase chain reaction
Peff	Effective permeability
P-gp	P-glycoprotein
PIB	Powder-in-bottle
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetics
Q12H	Every 12 hours
QC	Quality control
QT	Q-T interval
QTc	Q-T interval corrected for heart rate
QTcF	Q-T interval corrected for heart rate using Fridericia's formula
RH	Relative humidity
RNA	Ribonucleic acid
SAD	Single-ascending dose
SAE	Serious adverse event
SARS-CoV-1	Severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SGF	Simulated gastric fluid
SIF	Simulated intestinal fluid
t1/2	Half-life
TESNV	Treatment-Emergent Single Nucleotide Variants
Tmax	Time of maximum concentration
TSSO	Time since symptom onset
ULOQ	Upper limit of quantitation
US	United States
USP	United States Pharmacopeia
VAF	Variant allele frequencies

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Abbreviation	Definition
Vc/F	Apparent central volume of distribution
VDM	Viral dynamics model
Vp/F	Apparent peripheral volume of distribution

1 BACKGROUND AND OVERVIEW

Molnupiravir (also known as MK-4482 and EIDD-2801; hereafter referred to as MOV) is an orally administered prodrug of the small molecule ribonucleoside analog, NHC (also known as EIDD-1931). Rapid hydrolysis of MOV occurs during absorption/first pass to deliver NHC to systemic circulation. Once taken up by cells, NHC is anabolized to NHC-TP (also known as EIDD-2061), which inhibits the replication of multiple RNA viruses, including SARS-CoV-2, the virus responsible for COVID-19.

MOV has been developed for use as an immediate release, 200-mg strength DFC formulation intended for Q12H administration for the treatment of COVID-19.

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: 1.1]. No changes to the DFC formulation composition were made after the initial selection of the formulation used to support the Phase 1 FIH study (MK-4482-004, 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.

Following oral administration, MOV was generally not detectable in plasma [Sec. 2.7.1: 2.2]. Plasma concentrations of the nucleoside metabolite NHC were detectable. NHC has a rapid Tmax, approximately 1.75-hours postdose following administration of the MOV DFC. NHC Cmax and AUC increased in an approximately dose-proportional manner across the range of doses and formulations tested. There was no meaningful food effect on NHC PK with a DFC formulation, as administration in the fed state delayed the rate, but not the extent, of NHC absorption [Sec. 2.7.1: 2.3].

The absolute human bioavailability of MOV, the prodrug, has not been determined but is considered to be negligible, given that little or no intact MOV was detected systemically [Sec. 2.7.1: 2.1, 2.2]. As the prodrug is designed to deliver NHC systemically, NHC bioavailability after oral prodrug dosing was determined in animals. In non-clinical species, MOV delivers NHC with moderate to high oral bioavailability with 52% in rat (range 14% to 87%) and ≥77% (range 77% to 100%) in the dog [Sec. 2.6.4: 3]. The absolute oral bioavailability of NHC following prodrug dosing has also not been determined in humans, as no IV formulation has been developed.

MOV is a BCS Class I drug. High intestinal permeability is corroborated by the observation that food did not alter the extent of absorption. MOV/NHC are not substrates of human efflux transporters, MDR1 P-gp or BCRP [Sec. 2.6.4: 7.1]. Human absorption is expected to be high with Fa >95% for MOV and NHC based on data from the rat intestinal perfusion model, along with MOV stability in intestinal milieu and physiologically based biopharmaceutics modeling [Sec. 2.7.1: 1.2.1]. High absorption of MOV or NHC can also be expected based on PK studies in rat and dog where the oral bioavailability of NHC after oral dosing of MOV ranged from 52% to 100% (relative to IV administered NHC).

Given the totality of the absorption and bioavailability data, MOV and NHC are classified as highly permeable compounds according to the BCS. Combined with the high aqueous solubility values in buffer preparations from pH 1.2 to pH 8, MOV meets BCS Class I drug substance requirements, formulated as a DFC [Sec. 2.7.1: 1.2].

Key biopharmaceutic properties of MOV include the following:

- MOV is a BCS Class I drug, and both MOV and NHC have demonstrated high solubility and high intestinal permeability/absorption.
- MOV is rapidly hydrolyzed to NHC in vivo with rapid absorption (NHC Tmax of 1 to 1.75 hours) and overall linear NHC PK with the PIB solution and DFC formulations over a dose range of 50 to 1600 mg.
- There are no relevant differences in the extent of MOV and/or NHC absorption between the PIB solution and DFC formulation based on similar NHC exposures in the plasma. The FMI is the same as the 200-mg DFC formulation used in the clinical development program, with the exception of a printed marking to the outer surface of the capsule shell for product differentiation.
- MOV may be administered without regard to food.
- Given the high aqueous solubility for MOV/NHC, no pH-mediated drug interactions with acid reducing agents are expected.

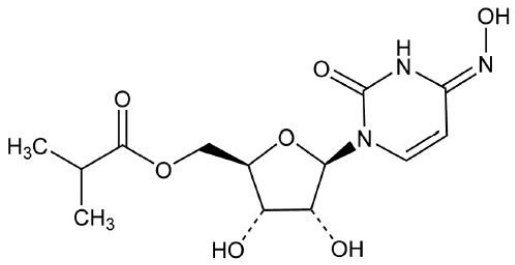
This summary document of biopharmaceutics studies focuses on MOV as a DFC. An overview of the Phase 1 studies conducted as part of the MOV clinical development program is presented in [Table 2.7.2-covid19txallpop: 1]. Studies that assessed both biopharmaceutics and other aspects of MOV clinical pharmacology, such as initial safety, tolerability and PK, are also described in [Sec. 2.7.2-covid19txallpop: 2].

1.1 Overview of Formulation Development

MOV is a BCS Class I compound and has been formulated for commercial use as an immediate-release, 200-mg strength DFC intended for Q12H administration. 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.

The chemical structure of MOV is shown in [Figure 2.7.1: 1]. 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.

Figure 2.7.1: 1
Chemical Structure of MOV



MOV=molnupiravir, MK-4482

Data Source: [Sec. 3.2.S.1.2-4482]

MOV has 3 ionizable groups with pKa's of 2.2 ([redacted]), 10.2 ([redacted]) and 12.0 ([redacted]) and is largely in the unionized state over the pH range of [redacted] to [redacted]. The partition (distribution) coefficient, logD (pH 7), was determined to be 0.46 [Sec. 3.2.S.1.2-4482].

A 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, three DFC formulations, [redacted], [redacted] and 200-mg strengths, were developed to support the clinical development program [Sec. 3.2.P.2.1-4482-capsule]. A summary of MOV DFC formulations of various drug loads, along with the function of each excipient, used in the clinical development program are presented in [Table 2.7.1: 1]. No changes in capsule fill excipients or their levels were made after the initial selection of the formulation used to support the FIH 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. The formulations used in each clinical study are provided in [Table 2.7.1: 2].

Table 2.7.1: 1
Composition of MOV DFC Formulations Used in the Clinical Development Program

Component	Function	Unit Strength		
		[redacted] mg	[redacted] mg	200 mg
		mg/capsule	mg/capsule	mg/capsule
Molnupiravir	Active	[redacted]	[redacted]	200.0
Hydroxypropyl cellulose	[redacted]	[redacted]	[redacted]	[redacted]
Microcrystalline cellulose	[redacted]	[redacted]	[redacted]	[redacted]
Croscarmellose sodium	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Magnesium stearate	[redacted]	[redacted]	[redacted]	[redacted]
Total capsule fill weight		[redacted]	[redacted]	285.7
Swedish orange opaque, hypromellose size "0" capsules	Capsule	-	-	-
DFC=dry-filled capsule; MOV=molnupiravir, MK-4482, EIDD-2801 [redacted]				

Data Source: [Sec. 3.2.P.2.2-4482-capsule]

Table 2.7.1: 2
MOV Formulations Used in the Clinical Development Program

Formulation Type	Dosage Strength	Protocols
PIB[a]	[redacted] mg/mL	P004
DFC	[redacted] mg	P004
	[redacted] mg	P004, P006
	200 mg	P001, P002, P004, P006, P008, P012
DFC=dry-filled capsule; MOV=molnupiravir, MK-4482, EIDD-2801; P=protocol (number); PIB=powder-in-bottle [a] PIB was reconstituted in water to achieve the dosage strength		

Note: More details are in [Appendix 2.7.1: 1]

1.2 Overview of Solubility and Dissolution

1.2.1 MOV Solubility and Permeability

MOV is classified as a high solubility and high permeability compound, and is therefore classified as BCS Class I. According to the BCS definition [Ref. 5.4: 07Y69X], a drug is considered highly soluble when the highest dose strength is soluble in ≤250 mL of aqueous media over the pH range of 1 to 6.8. MOV does not show significant pH-dependent solubility over gastrointestinal pH values. Solubility of MOV was determined in buffer systems across a pH range of 1.2 to 8. The solubility of [redacted] is 46 mg/mL in water and ranges from [redacted] to [redacted] mg/mL in pH 1.2 to 8 buffer at 37ºC. The equilibrium solubility of MOV [redacted] in aqueous buffers across the physiologically relevant pH range and select biorelevant media are compiled in [Table 2.7.1: 3]. NHC is also highly soluble in biorelevant media. The solubility of NHC is [redacted] mg/mL in SGF, [redacted] mg/mL in FaSSIF and [redacted] mg/mL in FeSSIF [Sec. 3.2.P.2.2-4482-capsule].

The intestinal permeability values of MOV and NHC were evaluated in the rat intestinal perfusion model. MOV stability in intestinal milieu was confirmed; MOV was stable in SGF and SIF [Sec. 2.6.4: 5.2]. MOV and NHC were estimated to have a higher human Peff than metoprolol (highly permeable reference standard). MOV, NHC and metoprolol Peff values were calculated to be 2.16 x 10^{-4} cm/s, 4.72 x 10^{-4} cm/s and 1.50 x 10^{-4} cm/s, respectively, from rat Peff data. As metoprolol has a known human Fa of 95%, both MOV and NHC have estimated projected human Fa values of >95%. Based on the high permeability in the in situ rat intestinal perfusion model, MOV and NHC are classified as highly permeable compounds according to the BCS [Ref. 5.3.1.3: 06G53Q]. Consistent with BCS Class I drug biopharmaceutic behavior, MOV/NHC did not show a significant food effect. AUC values were similar in the fasted and fed state with the DFC [Ref. 5.3.3.1: P004MK4482] [Ref. 5.3.3.3: P008MK4482] indicating high intestinal permeability. MOV and NHC are not substrates of human efflux transporters, MDR1 P-gp or BCRP, in membrane vesicles isolated from baculovirus infected Sf9 cells containing human MDR1 P-gp or human BCRP [Sec. 2.6.4: 7.1].

Table 2.7.1: 3
Equilibrium Solubility of MOV ([redacted])

Media [Final pH]	Solubility (mg/mL)
Water [5.7]	46
pH 1.2 buffer [2.3]	[redacted]
pH 2 buffer [3.1]	
pH 3 buffer [3.2]	
pH 4 buffer [4.0]	
pH 5 buffer [4.9]	
pH 6 buffer [5.9]	
pH 7 buffer [6.8]	
pH 8 buffer [7.2]	
SGF, pH 1.8 [3.0]	
FaSSIF, pH 6.4 [6.4]	[redacted]
FeSSIF, pH 5.0 [5.0]	[redacted]
FaSSIF=fasted simulated intestinal fluid; FeSSIF=fed simulated intestinal fluid; MOV=molnupiravir, MK-4482, EIDD-2801; SGF=simulated gastric fluid Crystal form of remaining solids after solubility was determined to be [redacted] by X-ray powder diffraction at all conditions.	

Data Source: [Sec. 3.2.P.2.1-4482-capsule]

1.2.2 MOV DFC Dissolution

A summary of the proposed dissolution method for MOV DFC is provided in [Table 2.7.1: 4]. Further details of the dissolution method and proposed specifications are provided in [Sec. 3.2.P.2.2-4482-capsule] and [Sec. 3.2.P.5.6-4482-capsule].

The dissolution performance of the MOV DFC was monitored using USP Dissolution Apparatus II at a rotational speed of [redacted] RPM in [redacted]. Additional dissolution method details can be found in [Sec. 3.2.P.5.2-4482-capsule: 2].

Determination of appropriate dissolution acceptance criteria was based on [redacted]. The proposed specification for MOV DFC is single-point dissolution specification as Q = [redacted] % in [redacted] minutes. Details are provided in [Sec. 3.2.P.5.6-4482-capsule].

Dissolution data for clinical and formal stability batches are depicted in [Figure 2.7.1: 2]. The hypromellose capsule shell is known to have variability in capsule rupture time and is a rate-limiting step which results in variability in earlier timepoints up to [redacted] minutes [Sec. 3.2.P.2.2-4482-capsule]. Notwithstanding, rapid dissolution was observed after capsule rupture which leads to a complete dissolution of the capsules from the different batches. The percent dissolved at [redacted] minutes meets the intended dissolution specification criteria.

Table 2.7.1: 4
Dissolution Method and Specifications for MOV Capsules

Dissolution Apparatus	USP Apparatus II at [redacted] rpm
Dissolution Medium	[redacted]
Medium Volume	[redacted] mL
Medium Temperature	37°C ± 0.5°C
Sampling Times	[redacted] minutes
Proposed Specification	Q = [redacted]% in [redacted] minutes

[redacted]; MOV=molnupiravir, MK-4482, EIDD-2801; USP=United States Pharmacopeia

Data Source: [Sec. 3.2.P.2.2-4482-capsule]

Figure 2.7.1: 2
Dissolution Profiles of MOV Clinical and Formal Stability Batches in the Proposed Dissolution Method



FSS=formal stability studies; [redacted]; MOV=molnupiravir, MK-4482

Note: The dotted lines in the plot represent the proposed dissolution specification of Q = [redacted]% at [redacted] minutes. The error bars represent standard deviation.

Data Source: [Sec. 3.2.P.5.6-4482-capsule]

1.3 Overview of Dosage Form In Vivo Performance

A FIH MOV study (P004) in healthy adult participants consisted of 3 main parts which evaluated a PIB solution formulation, as well as a DFC formulation. The effect of food was also evaluated following administration of the DFC formulation. No human mass balance or IV PK data have been generated to date. The 3 main parts for P004 were as follows:

- Part 1: single dose 50-, 100-, 200-, 400-, 600-, or 800-mg MOV (PIB solution formulation) or 1200- or 1600-mg MOV (DFC formulation).
- Part 2: single dose 200-mg MOV (DFC formulation) in the fasted and fed state.
- Part 3: multiple dose (Q12H dosing for 5.5 days) 50-, 100-, 200-, 300-, 400-, 600-, or 800-mg MOV (DFC formulation).

DFCs were provided as [redacted] (batch/lot number [redacted]), [redacted] (batch/lot number [redacted]), and 200-mg (batch/lot number [redacted]) strengths. PIB was provided from batch/lot number [redacted].

Key findings were as follows:

- MOV was only quantifiable in plasma following administration of MOV at higher single doses of at least 600 mg and multiple doses of at least 100 mg; however, plasma concentrations were close to the LLOQ. Therefore, the bioavailability of MOV (the prodrug) is considered to be negligible. The NHC:MOV geometric mean Cmax ratio ranged from 329 to 610 (where measurable).
- NHC was observed at early timepoints in plasma following MOV dosing, with a median Tmax of 1 hour for the PIB formulation and 1 to 1.75 hours for the DFC formulation across all dose levels.
- MOV DFC formulation administration provided similar systemic exposure to NHC (based on AUC0-inf and AUC0-last) as the PIB formulation administered as an oral solution at the same dose. However, Cmax was up to 24% lower and Tmax was up to 0.75 hours later following administration of the DFC formulation, indicating that the rate of absorption for the DFC formulation was slightly lower, but the extent of absorption was similar. The difference in Cmax and Tmax is likely due to rapid gastric emptying with the solution formulation.
- NHC AUC0-inf and AUC0-last were similar (within 5%) when the MOV DFC formulation was administered in the fed and fasted states. Administration in the fed state delayed median Tmax for NHC by 2 hours and reduced Cmax by 35.6% when compared to administration in the fasted state. These results indicate that the rate, but not the extent, of absorption was lower in the fed state.
- Plasma NHC Cmax and AUC increased in an approximately dose-proportional manner following administration of single doses of MOV as a PIB solution formulation up to 800 mg and following single or multiple doses up to 1600 mg and 800 mg, respectively, as a DFC formulation.

1.4 Overview of Bioanalytical Methods

1.4.1 Bioanalytical Methods for MOV, NHC, and NHC-TP

Quantitative LC-MS/MS methods were established for the determination of NHC in human plasma [Appendix 2.7.1: 2] and NHC and NHC-TP in lysed human PBMCs [Appendix 2.7.1: 3]. Methods were also established for the simultaneous determination of MOV and NHC in human urine [Appendix 2.7.1: 4] and plasma. In the case of the simultaneous MOV/NHC plasma assay, the matrix was treated at the clinical or bioanalysis site to prevent the ex-vivo hydrolysis of MOV [Appendix 2.7.1: 2].

The plasma methods utilized protein precipitation followed by LC-MS/MS and quantitation was achieved by weighted linear regression using stable isotope-labelled internal standards. The urine and lysed PBMC method utilized sample dilution as sample preparation method followed by LC-MS/MS.

All method validation and study sample analysis were performed in accordance with applicable regulatory guidelines to support the clinical development program [Ref. 5.3.1.4: 04ZYLV]. Summary validation data for the MOV and/or NHC plasma or urine assays, as well as NHC and NHC-TP assay in PBMCs, are presented in [Appendix 2.7.1: 5, 6, 7, 8, 9, 10, 11, 12].

Although the NHC methods for human plasma (ED28HPP and NHC9HPP) were not cross validated, both methods utilized similar methodology and were independently validated in accordance with current guidance. Similar precision and accuracy results were obtained during the validation of these 2 assays.

References to comprehensive validation reports for all assays are included in [Appendix 2.7.1: 5, 6, 7, 8, 9, 10, 11, 12]. In-study assay performance metrics for the MOV and/or NHC plasma assays and NHC-TP PBMC assay are tabulated in [Appendix 2.7.1: 11, 12, 13, 14, 15, 16, 17]. The bioanalytical reports for all studies as well as validation reports are included either as appendices in the respective clinical study reports or as standalone documents [Ref. 5.3.1.4: 07Y6BJ, 06G3JR, 07YFGY, 05PL3C, 06G3JB, 05PL2T, 05Q2TM, 07X6DZ, 07Y56R, 06FFKH, 07X537, 07WN87, 07XNXQ, 07Y0W6, 07Y9PH], [Ref. 5.3.3.1: P004MK4482: 16.2.9.1].

The determined analyte concentrations in study samples were verified by assaying quality control samples of blank matrix spiked with known concentrations of the respective analytes. Concentrations above the LLOQ were determined within a precision of 15% and an accuracy within 85% to 115%, with concentrations at the LLOQ being determined within a precision of 20% and accuracy within 80% to 120%.

Long-term frozen matrix stability at -60°C to -80°C was established for NHC in human plasma (420 and 504 days for methods NHC9HPP and EDD2HPP, respectively), and treated plasma (202 days). Long-term frozen matrix stability at ≤-70°C was established for MOV in human treated plasma (202 days) and urine (204 days). For NHC-TP, long-term frozen

matrix stability at ≤-70°C was established (148 days). All samples were analyzed within the established analyte stability.

1.4.2 Other Bioanalytical Methods Used During the Clinical Program

An assay for the simultaneous determination of NHC monophosphate, diphosphate, and triphosphate levels in PBMCs resuspended in PBS was developed. Validation parameters assessed for this assay included linearity of standard curves as well as precision and accuracy of fresh quality control samples of NHC-phosphates. This assay was utilized to support analysis of PBMC samples from study protocol P004. In this method, human PBMCs were spiked with stable label isotopes of the phosphates and diluted with methanol. After mixing and centrifugation, the supernatant was injected for LC-MS/MS analysis. A LC-MS/MS method similarly validated was utilized to determine the total NHC concentration levels after conversion of the phosphates to NHC by hydrolysis using acid phosphatase. The exploratory study report is included in [Ref. 5.3.1.4: 05R9QF].

2 SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

2.1 Absolute Bioavailability Studies

There have been no clinical studies to date dedicated to evaluating the absolute bioavailability of NHC following oral MOV administration.

2.2 Relative Bioavailability Studies

2.2.1 A Randomized, Double-blind, Placebo-controlled, First-in-human Study Designed to Evaluate the Safety, Tolerability, and Pharmacokinetics of EIDD-2801 Following Oral Administration to Healthy Volunteers (P004)

The full design of P004 is described in [Sec. 2.7.2-covid19txallpop: 2.1.1]. This 3-part study included both oral DFC and PIB formulations. Part 1 included single-dose administration of 50-, 100-, 200-, 400-, 600-, or 800-mg MOV or placebo as a PIB formulation reconstituted in water at the site to an oral solution, and 1200- or 1600-mg MOV or placebo as a DFC formulation. Part 3 included multiple-dose administration of 50-, 100-, 200-, 300-, 400-, 600-, or 800-mg MOV or placebo Q12H for 5.5 days as a DFC formulation. The results related to the relative bioavailability study parts (Part 1 and Part 3) are shown below.

Results (Part 1 and Part 3)

Following administration of the 2 oral formulations (PIB solution and DFC), MOV was largely not detectable in plasma due to rapid conversion to NHC, therefore NHC PK were used as a means to compare formulations.

Single-Dose Administration in Part 1: Following single-dose administration up to 800-mg MOV with the PIB solution formulation, NHC was observed in plasma at early timepoints, with a median Tmax of 1-hour postdose across all cohorts. Following single-dose administration of 1200- and 1600-mg MOV as a DFC formulation, median Tmax was

delayed relative to the lower doses (PIB solution formulation) and occurred at 1.75 and 1.50 hours, respectively.

Comparison of Single-Dose Administration in Part 1 and Part 3: The PK of NHC were compared following administration of a single-dose administration as PIB in Part 1 and administration of the first dose in Part 3 as DFC formulation, up to 800 mg. GMRs (reported as DFC/PIB) ranged from 0.91 to 1.07 for AUC0-last and 0.76 to 1.00 for Cmax across the dose range. At the clinical dose of 800 mg, the GMR was 0.94 for AUC0-last and 0.76 for Cmax. Compared to administration of the PIB formulation, the median Tmax for the DFC formulation was delayed by 0.75 hours at the 600- and 800-mg dose levels (1.75 versus 1.00 hours) and delayed 0.5 hours at the 200- and 400-mg dose levels (1.50 versus 1.00 hours).

A summary of PK parameter values is provided in [Appendix 2.7.1: 18]. For additional details, see the Clinical Study Report [Ref. 5.3.3.1: P004MK4482]. For further discussion and interpretation of results, see [Sec. 2.7.1: 3.2].

2.3 Food Effect Studies

2.3.1 A Randomized, Double-blind, Placebo-controlled, First-in-human Study Designed to Evaluate the Safety, Tolerability, and Pharmacokinetics of EIDD-2801 Following Oral Administration to Healthy Volunteers (P004)

The full design of this study is described in [Sec. 2.7.2-covid19txallpop: 2.1.1]. Part 2 of this 3-part study was an open-label, single-dose, randomized, 2-period, 2-treatment crossover study in 10 healthy participants. In one period, participants received MOV 200-mg DFC under fasted conditions. In the other period, participants received MOV 200-mg DFC under high-fat, fed conditions. There was a 14-day washout between treatment periods. The results related to the food effect component (Part 2) are shown below.

Results (Part 2)

The effect of a high-fat meal on the PK of NHC was evaluated. The ratio (reported as fed/fasted) of the geometric least squares mean (90% CI) was 0.955 (0.881, 1.03) for AUC0-inf and 0.644 (0.535, 0.775) for Cmax. The median plasma Tmax of NHC following administration of 200-mg MOV in the fasted and fed states was 1.00 hour and 3.00 hours, respectively. Based on these findings, a high-fat meal did not impact the extent of absorption of NHC following administration of a single 200-mg dose of MOV in healthy participants.

A summary of PK parameter values is provided in [Appendix 2.7.1: 18]. For additional details, see the Clinical Study Report [Ref. 5.3.3.1: P004MK4482]. For further discussion and interpretation of results, see [Sec. 2.7.1: 3.3].

2.3.2 A Single and Multiple Dose Clinical Study to Evaluate the Safety, Tolerability and Pharmacokinetics of MK-4482 in Healthy Japanese Adult Participants (P008)

The full design of this study is described in [Sec. 2.7.2-covid19txallpop: 2.2.1]. Part 1 of this 2-part study was a double-blind, randomized, placebo-controlled, single ascending dose, 3-panel study, including a 2-period food effect panel (Panel C). Participants in Panel C received 800-mg MOV DFC formulation or placebo under fasted conditions in Period 1 and under fed conditions following a high fat meal in Period 2. The assigned intervention for Period 1 (fasted) and Period 2 (fed) were the same, such that the same participants received MOV or placebo in both treatment periods. There was a 10-day washout between treatment periods. The results related to the food effect components (Part 1 Panel C) are shown below.

Results (Part 1 Panel C)

Administration of MOV in the fed state delayed median Tmax for NHC by 1.50 hours (3.00 hours versus 1.50 hours) and reduced Cmax by 24% (3610 ng/mL versus 4750 ng/mL) when compared to administration in the fasted state. AUC0-inf was comparable between the fed and fasted states (13700 hour*ng/mL versus 12400 hour*ng/mL), which indicates that the rate, but not the extent, of absorption is slightly lower in the fed state.

A summary of PK parameter values is provided in [Appendix 2.7.1: 18]. For additional details, see the Clinical Study Report [Ref. 5.3.3.3: P008MK4482]. For further discussion and interpretation of results, see [Sec. 2.7.1: 3.3].

3 COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

3.1 Bioavailability

MOV was observed in plasma only at low concentrations and at higher doses [Sec. 2.7.2-covid19txallpop: 2.1.1], suggesting the bioavailability of MOV (the prodrug) is negligible. There have been no clinical studies to date dedicated to evaluating the absolute bioavailability of NHC following administration of MOV.

3.2 Relative Bioavailability

Comparison of the PIB and DFC formulations following either single-dose or multiple-dose administration, indicated that NHC AUC were similar, but Cmax was up to 24% lower for the DFC formulation, with greater differences at the higher doses (600- and 800-mg MOV) [Sec. 2.7.1: 2.2.1]. The median Tmax for NHC was also up to 0.75 hours later following DFC administration at similar dose levels. Combined across the PK parameters, this indicates that the rate, but not the extent, of absorption was slightly lower for the DFC formulation; this is likely due to more rapid gastric emptying with the solution.

PopPK modeling was used to characterize the PK of NHC after dosing MOV using data from Part 1 (Phase 2) of MK-4482-001 (P001), both Part 1 (Phase 2) and Part 2 (Phase 3) of MK-4482-002 (P002), the Phase 2a study MK-4482-006 (P006), and the Phase 1 study P004 [Sec. 2.7.2-covid19txallpop: 2.5.2.2]. The PK of NHC in plasma were described by a linear 2

compartment model with absorption captured by a series of transit compartments and with first order elimination. Formulation was evaluated as a covariate on relative bioavailability and absorption parameters. Administration of MOV as PIB was shown to decrease the mean transit time by 61.6%, compared to administration as DFC or DFC contents as a suspension [Ref. 5.3.5.3: 07ZRF9]. Formulation was not found to be a significant covariate on relative bioavailability. These findings from the PopPK model are consistent with clinical observations from P004 that administration of the PIB formulation of MOV has a faster absorption than the DFC; however, the extent of absorption is similar between the 2 formulations, indicating that MOV/NHC demonstrate high permeability in the gastrointestinal tract.

3.3 Food Effect

Administration of MOV with food did not meaningfully affect the exposure (AUC) of NHC which is the parameter most closely associated with efficacy. At the 200-mg dose in P004, the GMR and 90% CI (fed vs fasted) for AUC0-inf was 0.955 (0.881, 1.03) [Sec. 2.7.1: 2.3.1] [Appendix 2.7.1: 18] and at the 800-mg dose in P008, it was 1.11 (1.02, 1.20) [Sec. 2.7.1: 2.3.2] [Appendix 2.7.1: 18]. Administration of MOV with food appeared to slow the rate of absorption as evidenced by a 2-hour delay in NHC Tmax and a 35.6% reduction in geometric mean Cmax at the 200-mg dose (P004). Similarly, a 1.50-hour delay in NHC Tmax and a 24% reduction in geometric mean Cmax was observed at the 800-mg dose (P008) [Sec. 2.7.1: 2.3.2]. The effect of food on NHC appears to be similar across Japanese and non-Japanese and is consistent with its physicochemical properties. MOV is considered to be a BCS Class I compound, wherein the lower Cmax and later Tmax for NHC observed under fed conditions are likely related to the delayed gastric emptying. This effect on rate of absorption would not be expected to alter either the efficacy or the safety profile of MOV since AUC is the primary PK parameter associated with safety and efficacy.

Based on a cross-study population PK analysis [Sec. 2.7.2-covid19txallpop: 2.5.2.2], dietary state (fed versus fasted) was evaluated as a covariate on relative NHC bioavailability and absorption parameters. This analysis determined that a high-fat meal prior to dosing would increase the mean transit time by 5.22-fold, suggesting that high-fat food has a substantial effect on MOV/NHC absorption kinetics; however, dietary state was not a significant covariate on relative NHC bioavailability [Ref. 5.3.5.3: 07ZRF9]. These findings are consistent with the comparison of NHC PK in Part 2 of P004 [Sec. 2.7.1: 2.3.1] and Part 1 Panel C of P008 [Sec. 2.7.1: 2.3.2]. In those studies, of Japanese and non-Japanese participants, respectively, a meal delayed the rate of absorption but did not alter the extent of absorption from the gut, consistent with MOV/NHC high intestinal permeability. Together, these findings suggest that MOV can be taken without regard to food, with no meaningful clinical impact.

4 CONCLUSIONS

The in vitro and in vivo studies summarized in this section support the following conclusions regarding the biopharmaceutic properties of MOV and NHC:

- MOV is a BCS Class I drug, and both MOV and NHC have demonstrated high solubility and high intestinal permeability/absorption.

- MOV is rapidly hydrolyzed to NHC in vivo with rapid absorption (NHC Tmax of 1 to 1.75 hours). NHC PK increases approximately dose-proportionally with the PIB solution and DFC formulations over a dose range of 50 to 1600 mg.

- Bioanalytical methods were validated and found to deliver comparable precision and accuracy results, supporting the integration of data across studies and stages of development.

- There are no relevant differences in the extent of MOV and/or NHC absorption between the PIB solution and DFC formulations based on similar NHC exposures in the plasma. The FMI is the same as the 200-mg DFC formulation used in the clinical development program, with the exception of a printed marking to the outer surface of the capsule shell for product differentiation.

- MOV may be administered without regard to food.

- Given the high aqueous solubility for MOV/NHC no pH-mediated drug interactions with acid reducing agents are expected.

5 APPENDIX

5.1 Formulations Used in Clinical Studies

Appendix 2.7.1: 1
Tabular Summary of Formulations Used in Clinical Studies

Protocol Number	Protocol Description	Formulation	Drug Product Lot Number
MK-4482-004 (EIDD-2801-1001)	A Randomized, Double-Blind, Placebo-Controlled, First-in-Human Study Designed to Evaluate the Safety, Tolerability, and Pharmacokinetics of EIDD-2801 Following Oral Administration to Healthy Volunteers	[redacted] mg/mL PIB	[redacted]
		[redacted] mg DFC	
		[redacted] mg DFC	
		200 mg DFC	
MK-4482-006 (EIDD-2801-2003)	A Phase IIa Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Safety, Tolerability and Efficacy of EIDD-2801 to Eliminate Infectious Virus Detection in Persons With COVID-19	[redacted] mg DFC	
		200 mg DFC	
MK-4482-008	A Single and Multiple Dose Clinical Study to Evaluate the Safety, Tolerability and Pharmacokinetics of MK-4482 in Healthy Japanese Adult Participants	200 mg DFC	
MK-4482-012	A Multiple Ascending Dose Clinical Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Molnupiravir in Healthy Participants	200 mg DFC	
MK-4482-001	A Phase 2/3, Randomized, Placebo-Controlled, Double-Blind Clinical Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MK-4482 in Hospitalized Adults With COVID-19	200 mg DFC	
MK-4482-002[b]	A Phase 2/3, Randomized, Placebo-Controlled, Double-Blind Clinical Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MK-4482 in Non-Hospitalized Adults With COVID-19	200 mg DFC	

COVID-19=coronavirus disease 2019; DFC=dry-filled capsule; PIB-powder-in-bottle

[a] Drug product lots [redacted] and [redacted] are equivalent
[b] Ongoing clinical study

Data Source: [Sec. 3.2.P.2.2-4482-capsule] [Ref. 5.3.3.1: P004MK4482] [Ref. 5.3.3.3: P008MK4482]

5.2 Bioanalytical Methods Used to Support the MOV Clinical Development Program

Methods for the determination of NHC in plasma, MOV and NHC in treated plasma and urine, and NHC-TP in PBMCs that were utilized to support the clinical program are listed in the following tables.

Appendix 2.7.1: 2
Methods for the Determination of NHC in Plasma or MOV and NHC in Treated Plasma

Analyte	NHC	MOV, NHC	MOV (Exploratory), NHC (Validated)	MOV, NHC
Validation Type	Full	Full	Partial (based on ED28HPP)	Partial
eCTD reference number	NA	NA	NA	NA
Method ID	NHC9HPP	ED28HPP	EDD2HPP	ED28HPP
Duration of time method is in use	[redacted]	[redacted]	[redacted]	[redacted]
Bioanalytical Site	[redacted] USA	[redacted] England	[redacted] USA	[redacted] USA
Matrix	K_2EDTA Plasma	Plasma, K_2EDTA as anticoagulant (precipitated with acetonitrile at point of sample collection, Plasma: Acetonitrile 1:3 v/v)	Plasma, K_2EDTA as anticoagulant (precipitated with acetonitrile at the bioanalysis site, Plasma: Acetonitrile 1:3 v/v)	Plasma, K_2EDTA as anticoagulant (precipitated with acetonitrile at point of sample collection, Plasma: Acetonitrile 1:3 v/v)

Platform	LC-MS/MS			
Format	Protein precipitation, addition of stable label internal standard, with analysis via LC-MS/MS			
Stock reference, lot number, expiration date	NHC: [redacted] 20[redacted]	MOV: [redacted] 20[redacted]; NHC: [redacted] 20[redacted]	MOV: [redacted] 20[redacted], 20[redacted]; NHC: [redacted] 20[redacted], 20[redacted]	MOV: [redacted] 20[redacted]; NHC: [redacted] 20[redacted]
Calibration range from the LLOQ to the ULOQ	1.0 to 1000 ng/mL	5 to 5000 ng/mL	5 to 5000 ng/mL	5 to 5000 ng/mL
Matrix Study Population	Normal	Normal	Normal	Normal
Links to reports and applicable amendments	[Ref. 5.3.1.4: 07Y6BJ]	[Ref. 5.3.1.4: 06G3JR]	[Ref. 5.3.1.4: 07YFGY]	[Ref. 5.3.1.4: 05PL3C]
Synopsis of amendment history	Appended Addendum No. 1 (additional freeze/thaw cycles and long term matrix stability of NHC in plasma)	NA	Partial Validation to determine short and long term matrix stability of MOV and NHC in whole blood and plasma	Partial validation to cross-validate between 2 bioanalytical laboratories

LC-MS/MS= liquid chromatography/tandem mass spectrometry; LLOQ=lower limit of quantitation; ID=identification; K_2EDTA=dipotassium ethylenediaminetetraacetic acid; MOV=molnupiravir, MK-4482, EIDD-2801; NA=not applicable; NHC=N-hydroxycytidine, EIDD-1931; ULOQ=upper limit of quantitation; v/v=volume per volume

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Appendix 2.7.1: 3
Method for the Determination of NHC and NHC-TP in PBMC Lysate

Analyte	NHC-TP, NHC	NHC-TP
Validation Type	Full	Full
eCTD reference number	NA	NA
Method ID	NA	TM.3160.04
Duration of time method is in use	[redacted]	[redacted]
Bioanalytical Site	[redacted]	[redacted] Canada,
Matrix	PBMCs lysed in 70% methanol	Human PBMCs (sodium heparin) lysed in 70% methanol
Platform	LC-MS/MS	LC-MS/MS
Format	Sample dilution, addition of label internal standard, followed by LC-MS/MS	Automated protein precipitation
Stock reference, lot number, expiration date	NHC: [redacted] NHC-TP: [redacted]	NHC-TP [redacted] Merck & Co., [redacted]
Calibration range from the LLOQ to the ULOQ	NHC: 2 to 1500 pmol/sample; NHC-TP: 1 pmol/sample to 1500 pmol/sample	NHC-TP: 5 to 2000 ng/mL
Matrix Study Population	Normal	Normal
Links to reports and applicable amendments	[Ref. 5.3.1.4: 05Q2TM]	[Ref. 5.3.1.4: 07X6DZ]
Synopsis of amendment history	NA	NA

LC-MS/MS= liquid chromatography/tandem mass spectrometry; LLOQ=lower limit of quantitation; ID=identification; NA=not applicable; NHC=N-hydroxycytidine, EIDD-1931; NHC-TP=N-hydroxycytidine triphosphate, EIDD-2061; PBMC=peripheral blood mononuclear cells; ULOQ=upper limit of quantitation

Appendix 2.7.1: 4
Method for the Determination of MOV and NHC in Urine

Analyte	MOV, NHC	MOV, NHC
Validation Type	Full	Partial
eCTD reference number	NA	NA
Method ID	ED28HUP	ED28HUP
Duration of time method is in use	[redacted] 20[redacted] 20	[redacted] 20[redacted] 20
Bioanalytical Site	[redacted] England	[redacted] USA
Matrix	Urine	Urine
Platform	LC-MS/MS	
Format	Sample dilution, addition of label internal standard, followed by LC-MS/MS	
Stock reference, lot number, expiration date	MOV: [redacted] 20 NHC: [redacted] 20	MOV: [redacted] 20 NHC: [redacted] 20
Calibration range from the LLOQ to the ULOQ	25 to 25000 ng/mL	25 to 25000 ng/mL
Matrix Study Population	Normal	Normal
Links to reports and applicable amendments	[Ref. 5.3.1.4: 06G3JB]	[Ref. 5.3.1.4: 05PL2T
Synopsis of amendment history	NA	Partial validation to cross-validate between 2 bioanalytical laboratories

LC-MS/MS= liquid chromatography/tandem mass spectrometry; LLOQ=lower limit of quantitation; ID=identification; MOV=molnupiravir, MK-4482, EIDD-2801; NA=not applicable; NHC=N-hydroxycytidine, EIDD-1931; ULOQ=upper limit of quantitation

5.3 NHC in Plasma, NHC and MOV in Treated Plasma and Urine, and NHC and NHC-TP In Lysed PBMC Assay Validation Data

Validation data for methods for the determination of NHC in untreated plasma; NHC and/or MOV in treated plasma and urine; NHC-TP and/or NHC in lysed PBMC that were utilized to support the clinical program are listed in the following tables.

Appendix 2.7.1: 5
Validation Data – Method NHC9HPP

Bioanalytical method validation report name, amendments, and hyperlinks	Validation of a Method for the Determination of NHC in Human Plasma by HPLC with MS/MS Detection. [redacted]: 8451017 [Ref. 5.3.1.4: 07Y6BJ]		
Method description	LC-MS/MS method for the determination of NHC in human plasma		
Materials used for standard calibration curve and concentration	Control human plasma and NHC reference standard. Calibrator Concentrations: 1.00, 2.00, 8.00, 30.0, 120, 450, 900, and 1000 ng/mL		
Validated assay range	1.00 to 1000 ng/mL		
Material used for QCs and concentration	Control human plasma and NHC reference standard. QC concentrations at 1.00, 3.00, 40.0, 500, 800, and 8000 ng/mL.		
Matrix/Sample Volume	Plasma/100 µL		
Source and lot of reagents	Control human plasma. NHC reference standard from [redacted]		
Regression model and weighting	Linear $1/x^2$		
Validation parameters	**Method validation summary**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	Table 7.2 of Report 07Y6BJ
	Cumulative accuracy (%bias) from LLOQ to ULOQ NHC	-2.3% to 2.0%	Table 7.2 of Report 07Y6BJ
	Cumulative precision (%CV) from LLOQ to ULOQ NHC	≤5.2%	Table 7.2 of Report 07Y6BJ

Performance of QCs during accuracy and precision runs	**Cumulative accuracy (%bias) in 5 QCs** QCs for NHC	0.3% to 2.4%	Table 7.4 of Report 07Y6BJ
	Inter-batch %CV QCs for NHC	≤7.8%	Table 7.4 of Report 07Y6BJ
	Total Error	Not calculated	
Selectivity & matrix effect	Analysis of LLOQ samples prepared in 6 different lots of control matrix. Mean %Bias 4.0% and %CV ≤3.6%		Table 7.8 of Report 07Y6BJ
Interference & specificity	Six lots of control matrix tested. No interference was observed in any of the lots tested.		Figures 8.8 to 8.13 of Report 07Y6BJ
Hemolysis effect	Low and High QC samples prepared in hemolyzed plasma (n=6) Mean bias was -2.7% to 1.3% with CV≤1.6%		Table 7.11 of Report 07Y6BJ
Lipemic effect	Low and High QC samples prepared in lipemic plasma (n=6) Mean bias was -4.0% to -0.5% with CV≤3.4%		Table 7.12 of Report 07Y6BJ
Dilution linearity & hook effect	8,000 ng/mL tested (n=6) with a 100-fold dilution factor. Mean bias was –3.6%, CV 3.7%		Table 7.4 of Report 07Y6BJ
Bench-top/process stability	25 hours at RT for Low and High QC samples was established. Mean % bias was 0.0% to 9.4% with a CV ≤8.7% 24 hours at wet ice spiked with 1.00 ng/mL of MK-4482 (LQC) and 267 ng/mL of MOV (HQC) was established. Mean % bias was 4.30% to 10.6% with a CV ≤4.0% 52 hours processed sample stability (~ 2℃-8℃) for Low and High QC samples was established. Mean % bias was -3.3% to 2.3% with a CV ≤3.3%		Tables 7.16, 7.17, and 7.22 of Report 07Y6BJ
Freeze-Thaw stability	Low and high QC samples with or without MOV were prepared, stored at -10℃ to -80°C and subjected to three F/T cycles. Mean % bias was determined to be -7.7% to 12.0% with a CV ≤12.1%.		Tables 7.18 to 7.19 of Report 07Y6BJ
4 and 5 Freeze-Thaw stability	Low and high QC samples with or without MOV were prepared, stored at -60°C to -80°C and subjected to 4 or 5 F/T cycles. NHC Only; 4 F/T Cycles: Mean % bias was determined to be -7.3% to 1.6% with a CV ≤2.6% NHC Only; 5 F/T Cycles: Mean % bias was determined to be 0% to 0.4% with a CV ≤14.9% (statistics excluding outlier) NHC + MOV; 4 F/T Cycles: Mean % bias was determined to be -5.4% to 3.0% with a CV ≤4.5% NHC + MOV; 5 F/T Cycles: Mean % bias was determined to be -4.8% to 5.3% with a CV ≤5.2%		Tables 6.6 to 6.9 of Addendum No.1 of Report 07Y6BJ
Long-term storage	Low and high QC samples with or without MOV were prepared, stored at –10°C to -80°C. Stability was established for 46 days. Mean % bias was determined to be -10.0% to 12.0% with a CV ≤7.5%		Tables 7.20 to 7.21 of Report 07Y6BJ

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Extended Long-term storage	Low and high QC samples with or without MOV were prepared, stored at –60°C to -80°C. Stability was established for 171 and 420 days. NHC Only stored for 171 days: Mean % bias was determined to be 2.6% to 8.0% with a CV ≤2.9% NHC Only stored for 420 days: Mean % bias was determined to be 1.0% to 5.0% with a CV ≤3.4% NHC + MOV stored for 171 days: Mean % bias was determined to be 5.0% to 6.0% with a CV ≤1.5% NHC + MOV stored for 420 days: Mean % bias was determined to be 1.7% to 7.1% with a CV ≤3.7%	Tables 6.10 to 6.11 of Report 07Y6BJ
Parallelism	Not applicable.	
Carryover	Carryover within the bioanalytical method was evaluated in the validation by injecting 2 blank matrix samples analyzed immediately following the highest calibration standard. There was no evidence of carry over at the retention times of analyte and internal standard.	Figure 8.7 of Report 07Y6BJ
Stability in Blood	Mid QC of NHC with or without MOV was prepared in blood, and plasma harvested at 0, and after 2 hours storage in wet ice. Percent difference from 0 hour ranged from 2.8% to 4.8%	Tables 7.24 to 7.25 of Report 07Y6BJ
Solution Stability	Stability established for NHC intermediate solution (40 ng/mL in 50/50 MeOH/water) when stored for 14 days at -10°C to -30°C, and when stored for 6 hours at room temperature or wet ice	Table 7.13 to 7.15 of 07Y6BJ

CV=coefficient of variation; F/T=freeze-thaw; HPLC=high performance liquid chromatography; HQC=high quality control sample; LC-MS/MS= liquid chromatography/tandem mass spectrometry; LLOQ=lower limit of quantitation; LQC=low quality control sample; MeOH=methanol; MOV=molnupiravir, MK-4482, EIDD-2801; MS/MS=tandem mass spectrometry; NHC=N-hydroxycytidine, EIDD-1931; QC=quality control; RT=room temperature; ULOQ=upper limit of quantitation

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Appendix 2.7.1: 6
Validation Data – Method ED28HPP

Bioanalytical method validation report name, amendments, and hyperlinks	Validation for the Determination of EIDD-2801 and EIDD-1931 in Human Plasma using Liquid Chromatography with Tandem Mass Spectrometric Detection, [redacted]: 8427435 [Ref. 5.3.1.4: 06G3JR]		
Method description	LC-MS/MS method for the determination of MOV and NHC in human plasma		
Materials used for standard calibration curve and concentration	Control human plasma, MOV and NHC reference standards. Calibrator concentrations: 5.00, 10.0, 40.0, 200, 800, 2500, 4500, and 5000 ng/mL		
Validated assay range	5.00 to 5000 ng/mL for both analytes		
Material used for QCs and concentration	Control human plasma, MOV and NHC reference standards. QC Concentrations: 5.00, 15.0, 175, 2000, 4000, and 25,000 ng/mL		
Matrix/Sample Volume	Precipitated plasma/100 µL supernatant		
Source and lot of reagents	Control human plasma MOV and NHC reference standards from [redacted]		
Regression model and weighting	Linear $1/x^2$		
Validation parameters	**Method validation summary**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	Tables 7.2 to 7.3 of Report 06G3JR
	Cumulative accuracy (%bias) from LLOQ to ULOQ	MOV: -1.3% to 1.2% NHC: -2.4% to 1.4%	Tables 7.2 to 7.3 of Report 06G3JR
	Cumulative precision (%CV) from LLOQ to ULOQ	MOV: ≤6.3% NHC: ≤5.3	Tables 7.2 to 7.3 of Report 06G3JR
Performance of QCs during accuracy and precision runs	**Cumulative accuracy (%bias) in 5 QCs**	MOV: -2.9% to 0.5% NHC: -5.5% to -2.3%	Tables 7.6 to 7.7 of Report 06G3JR
	Inter-batch %CV	MOV: ≤10.6% NHC: ≤8.6	Tables 7.6 to 7.7 of Report 06G3JR
	Total Error	Not calculated	
Selectivity & matrix effect	Analysis of LLOQ samples prepared in 6 different lots of control matrix. MOV Mean % Bias -7.8% and %CV ≤8.4%; NHC Mean % Bias 0.2% and %CV ≤7.2%		Tables 7.12 to 7.13 of Report 06G3JR
Interference & specificity	Six lots of control matrix tested. No interference was observed in any of the lots tested		Figures 8.9 to 8.14 of Report 06G3JR

Hemolysis effect	Low and High QC samples prepared in hemolyzed plasma (n=6). MOV Mean % Bias -3.3% to -0.5% and %CV ≤2.7%; NHC Mean % Bias -5.5% to -4.0% and %CV ≤3.2%	Tables 7.20 to 7.21 of Report 06G3JR
Lipemic effect	Low and High QC samples prepared in hemolyzed plasma (n=6). MOV Mean % Bias -1.3% to -0.8% and %CV ≤6.1%; NHC Mean % Bias -3.8% to -2.7% and %CV ≤3.2%	Tables 7.22 to 7.23 of Report 06G3JR
Dilution linearity & hook effect	25,000 ng/mL tested (n=6) with a 10-fold dilution factor. MOV Mean bias was 7.6%, CV 4.5%; NHC Mean bias was 4.0%, CV 2.7%.	Tables 7.6 to 7.7 of Report 06G3JR
Bench-top/process stability	24 hours at room temperature for Low and High QC samples was established. MOV Mean % bias was -2.0% to 0.3% with a CV ≤3.5%. NHC Mean % bias was -6.7% to -5.0% with CV≤4.0% 94 hours processed sample stability (~ 2°C to 8 °C) for Low and High QC samples was established. MOV Mean % bias was -2.7% to 2.0% with a CV ≤5.7%. NHC Mean % bias was -5.3% to 0.3% with CV≤6.2%	Tables 7.34 to 7.35 and Tables 7.46 to 7.47 of Report 06G3JR
Freeze-Thaw stability	Low and high QC samples were prepared, stored at -10°C to -30ºC, and -50°C to -90ºC and subjected to 4 freeze-thaw cycles. MOV Mean % bias was determined to be -2.7% to 0.7% with a CV ≤7.5%; NHC Mean % bias was determined to be -9.0% to -3.3% with a CV ≤8.7%	Tables 7.36 to 7.41 of Report 06G3JR
Long-term storage	Low and high QC samples (precipitated plasma) were prepared, stored at –10°C to -30ºC and -50°C to -90ºC Stability was established for 7 days when stored at -10°C to -30ºC. MOV Mean % bias was determined to be -4.0% to -1.5% with a CV ≤4.5%; NHC Mean % bias was determined to be -9.3 to -2.5% with a CV ≤3.6% Stability was established for 202 days when stored at –50°C to -90ºC. MOV Mean % bias was determined to be -6.0% to 1.5% with a CV ≤3.6%; NHC Mean % bias was determined to be -11.3% to -1.5% with a CV ≤13.8%	Tables 7.42 to 7.45 of Report 06G3JR Tables 7.8 to 7.9 of Addendum#2 of Report 06G3JR
Parallelism	Not applicable.	
Carryover	Carryover within the bioanalytical method was evaluated in the validation by injecting 2 blank matrix samples analyzed immediately following the highest calibration standard. There was no evidence of carry over around the retention times of analyte and internal standard.	Figure 8.8 of Report 06G3JR
Stability in Blood/Plasma (Prior to Precipitation)	Mid QC was prepared in blood, and plasma harvested at 0, 0.5, and after 1 hour storage in wet ice. Percent difference from 0 hour ranged from -10.4% to 1.2%. Prior to precipitation, aliquots of Low and High QC samples were stored on wet ice at 0, 0.25, and 0.5 hour. Percent difference from 0 hour ranged from -4.0% to 2.7%.	Tables 7.48 to 7.49 and Tables 7.50 to 7.51 of Report 06G3JR
Solution Stability	Primary Solution (1.0 mg/mL) prepared in 50/50 MeOH/water stored frozen (-10°C to -30°C) MOV: 24 days NHC: 24 days	Tables 6.10 to 6.11 of Addendum No.1 of Report 06G3JR
CV=coefficient of variation; LC-MS/MS= liquid chromatography/tandem mass spectrometry; LLOQ=lower limit of quantitation; MeOH=methanol; MOV=molnupiravir, MK-4482, EIDD-2801; NHC=N-hydroxycytidine, EIDD-1931; QC=quality control; ULOQ=upper limit of quantitation		

Appendix 2.7.1: 7
Partial Validation Data – Method EDD2HPP

Bioanalytical method validation report name, amendments, and hyperlinks	Evaluation of Short Term and Long Term Matrix Stability of EIDD-2801 and EIDD-1931 in Human Whole Blood and Human Plasma using Liquid Chromatography with Tandem Mass Spectrometric Detection, [redacted] 8444055 [Ref. 5.3.1.4: 07YFGY]		
Method description	LC-MS/MS method for the determination of MOV and NHC in human plasma		
Materials used for standard calibration curve and concentration	Control human plasma, MOV and NHC reference standards. Calibrator Concentrations: 5.00, 10.0, 40.0, 200, 800, 2500, 4500, and 5000 ng/mL		
Validated assay range	5.00 to 5000 ng/mL for both analytes		
Material used for QCs and concentration	Control human plasma, MOV and NHC reference standards. QC Concentrations: 15.0, 175, 2000, 4000 ng/mL; Stability QC levels: Molnupiravir (Spiked Alone): 15.0 and 4000 ng/mL; NHC (Spiked Alone): 15.0 and 4000 ng/mL; MOV/NHC (Spiked Combined): 15/45 ng/mL		
Matrix/Sample Volume	Plasma/100 µL supernatant		
Source and lot of reagents	Control human plasma MOV and NHC reference standards from [redacted]		
Regression model and weighting	Linear $1/x^2$		
Validation parameters	**Method validation summary**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	Tables 7.2 to 7.3 of Report 07YFGY
	Cumulative accuracy (%bias) from LLOQ to ULOQ	MOV: -4.2% to 3.3% NHC: -3.8% to 2.7%	Tables 7.2 to 7.3 of Report 07YFGY
	Cumulative precision (%CV) from LLOQ to ULOQ	MOV: ≤4.2% NHC: ≤8.8	Tables 7.2 to 7.3 of Report 07YFGY
Performance of QCs during accuracy and precision runs	**Cumulative accuracy (%bias) in 4 QCs** (Precipitated Human Plasma)	MOV: -2.0% to 4.5% NHC: -4.0% to 2.3%	Tables 7.6 and 7.8 of Report 07YFGY
	Inter-batch %CV	MOV: ≤3.6% NHC: ≤6.6	Tables 7.6 and 7.8 of Report 07YFGY
	Cumulative accuracy (%bias) in 3 QCs (Non-Precipitated Human Plasma)	MOV: -6.0% to -4.5% NHC: -10.0% to -5.3%	Tables 7.7 and 7.9 of Report 07YFGY
	Inter-batch %CV	MOV: ≤3.4% NHC: ≤4.1	Tables 7.7 and 7.9 of Report 07YFGY
Interference & specificity	Interference peak was observed in the NHC channel in 1 lot of plasma tested – did not affect integrity of data.		Figure 8.3 of Report 07YFGY

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Matrix Freeze-Thaw stability (non-precipitated plasma)	Low (individual or combined) and high QC samples were prepared, stored at -10°C to -30ºC, and -60°C to -80ºC and subjected to one freeze-thaw cycle. MOV: Not stable at -10°C to -30°C or -60°C to -80°C NHC: Stable at -10°C to -30°C or -60°C to -80°C, Mean % bias was determined to be -11.3% to -3.1% with a CV ≤7.7%	Tables 7.11 to 7.12 of Report 07YFGY
Matrix Frozen Stability Long-term storage (non-precipitated plasma)	Low (individual or combined) and high QC samples were prepared, stored at -10°C to -30ºC, and -60°C to -80ºC MOV: Not stable at -10°C to -30ºC or -60°C to -80ºC after storage for 19, 43, and 206 days NHC: Stability was established for 19 days when stored at –10°C to -30ºC. Mean % bias was determined to be -2.0% to 10.4% with a CV ≤4.3%; Stability was established for 206 days when stored at –60°C to -80ºC. Mean % bias was determined to be -12.7% to -5.1% with a CV ≤9.2% NHC: Stability was established for 504 days when stored at -60°C to -80°C. Mean % bias was determined to be 2.0% to 14.0% with a CV ≤1.8% MOV: Not stable at -60°C to -80ºC after storage for 504 days	Tables 7.14 to 7.15 of Main; and Tables 7.8 to 7.9 of Addendum No. 1 Report 07YFGY
Stability in Blood (prior to refrigerated centrifugation)	Mid QCs (individual analytes or combined) prepared in blood, and plasma harvested and precipitated at 0, 1, 2, and after 4-hour storage in wet ice. Percent MOV difference from 0 hour ranged from -20.7% to -0.3%. NHC: Percent difference from 0 hour ranged from -7.7% to 0.7%	Tables 7.17 to 7.18 of Report 07YFGY
CV=coefficient of variation; LC-MS/MS= liquid chromatography/tandem mass spectrometry; LLOQ=lower limit of quantitation; MOV=molnupiravir, MK-4482, EIDD-2801; NHC=N-hydroxycytidine, EIDD-1931; QC=quality control; ULOQ=upper limit of quantitation		

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Appendix 2.7.1: 8
Cross Validation Data – Method ED28HPP

Bioanalytical method cross validation report name, amendments, and hyperlinks	Cross Validation between [redacted] of a Bioanalytical Method for the Determination of EIDD-2801 and EIDD-1931 in Human Plasma using Liquid Chromatography with Tandem Mass Spectrometric Detection 8440169 [Ref. 5.3.1.4: 05PL3C]		
Method description	Cross Validation between [redacted] of an LC-MS/MS method for the determination of MOV and NHC in human plasma		
Materials used for standard calibration curve and concentration	Control human plasma, MOV and NHC reference standards. Calibrator Concentrations: 5.00, 10.0, 40.0, 200, 800, 2500, 4500, and 5000 ng/mL		
Validated assay range	5.00 to 5000 ng/mL for both analytes		
Material used for QCs and concentration	Control human plasma, MOV and NHC reference standards. QC Concentrations: 15.0, 175, 2000, and 4000 ng/mL		
Matrix/Sample Volume	Precipitated Plasma/100 µL supernatant		
Source and lot of reagents	Control human plasma. Molnupiravir and NHC reference standards from [redacted]		
Regression model and weighting	Linear $1/x^2$		
Cross-Validation parameters		**Method cross validation summary**	**Source location**
Standard calibration curve performance during cross-validation runs	Number of standard calibrators from LLOQ to ULOQ	8	Tables 7.2 to 7.3 of Main and Contributing Report 05PL3C
	Cumulative accuracy (%bias) from LLOQ to ULOQ	[redacted]: MOV: -3.5 to 4.4%; NHC: -5.0 to 3.6%; [redacted]: MOV: -7.0 to 3.6%; NHC: -5.9 to 4.4%;	Tables 7.2 to 7.3 of Main and Contributing Report 05PL3C
	Cumulative precision (%CV) from LLOQ to ULOQ	[redacted]: MOV: CV≤ 9.0; NHC:CV≤ 9.5 [redacted]: MOV: n/a; NHC: CV≤ 5.5	Tables 7.2 to 7.3 of Main and Contributing Report 05PL3C
Performance of QCs during cross validation runs	**Cumulative accuracy (%bias) in 4 QCs**	[redacted]: MOV: -1.5 to 2.0%; NHC: -1.1 to 1.8%; [redacted]: MOV: -4.7 to 1.5%; NHC: -3.3 to 3.3%;	Tables 7.6 to 7.7 of Main and Contributing Report 05PL3C
	Inter-batch %CV	[redacted]: MOV: CV≤ 15.1; NHC:CV≤ 11.3 [redacted]: Molnupiravir: n/a; NHC: CV≤ 4.9	Tables 7.6 to 7.7 of Main and Contributing Report 05PL3C

Cross Validation of QC Samples (4 concentration levels)	Cross validation QC samples at LQC, LMQC, MQC, and HQC were prepared at [redacted] and analyzed at both sites. Comparison of the Mean Accuracy Values of the calculated QC Concentrations showed a range of Relative % Difference of -8.4% to -4.8% for MOV; and -10.4 to 4.9% for NHC.	Tables 7.18 to 7.19 of Main Report 05PL3C
Cross Validation Pooled Incurred Sample	Incurred sample pools (3 pools, 6 replicates, n=18) were prepared and analyzed at both sites. Comparison of calculated NHC concentrations between the 2 sites had 15 out of 18 within ± 20% Relative difference	Table 7.12 of the Main Report of 05PL3C
Selectivity & specificity	Matrix blank and Blank matrix with internal standard demonstrated lack of significant interference.	Figures 8.3 to 8.4 of Main Figures 9.3 to 9.4 of Contributing Report 05PL3C
Carryover	Carryover was evaluated in the cross validation by injecting 2 blank matrix samples analyzed immediately following the highest calibration standard. There was no evidence of carry over around the retention times of analyte and internal standard	Figures 8.6 of Main and Figure 9.6 of Contributing Report 05PL3C

CV=coefficient of variation; HQC=high quality control; LC-MS/MS= liquid chromatography/tandem mass spectrometry; LLOQ=lower limit of quantitation; LMQC= low-middle quality control; LQC=low quality control; MOV=molnupiravir, MK-4482, EIDD-2801; MQC=middle quality control; NHC=N-hydroxycytidine, EIDD-1931; QC=quality control; ULOQ=upper limit of quantitation

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Appendix 2.7.1: 9
Validation Data – Method ED28HUP

Bioanalytical method validation report name, amendments, and hyperlinks	Validation for the Determination of EIDD-2801 and EIDD-1931 in Human Urine using Liquid Chromatography with Tandem Mass Spectrometric Detection, [redacted]: 8440118 [Ref. 5.3.1.4: 06G3JB]		
Method description	LC-MS/MS method for the determination of MOV and NHC in human urine		
Materials used for standard calibration curve and concentration	Control human urine, MOV and NHC reference standards. Calibrator Concentrations: 25.0, 50.0, 200, 800, 4000, 12500, 22500, and 25000 ng/mL		
Validated assay range	25.0 to 25,000 ng/mL for both analytes		
Material used for QCs and concentration	Control human urine, MOV and NHC reference standards. QC Concentrations: 25.0, 75.0, 875, 10000, 20000, and 200000 ng/mL		
Matrix/Sample Volume	Urine, 50 µL		
Source and lot of reagents	Control human urine. MOV and NHC reference standards from [redacted]		
Regression model and weighting	Linear $1/x^2$		
Validation parameters	**Method validation summary**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	Tables 7.2 to 7.3 of Report 06G3JB
	Cumulative accuracy (%bias) from LLOQ to ULOQ	MOV: -4.4% to 3.1% NHC: -2.2% to 1.6%	Tables 7.2 to 7.3 of Report 06G3JB
	Cumulative precision (%CV) from LLOQ to ULOQ	MOV: ≤3.8% NHC: ≤4.6	Tables 7.2 to 7.3 of Report 06G3JB
Performance of QCs during accuracy and precision runs	**Cumulative accuracy (%bias) in 5 QCs**	MOV: -2.0% to 3.9% NHC: -0.8% to 0.5%	Tables 7.6 to 7.7 of Report 06G3JB
	Inter-batch %CV	MOV: ≤9.5% NHC: ≤8.3	Tables 7.6 to 7.7 of Report 06G3JB
	Total Error	Not calculated	
Selectivity & matrix effect	Analysis of LLOQ samples prepared in 6 different lots of control matrix. MOV Mean % Bias 10.0% and %CV ≤11.1%; NHC Mean % Bias -5.2% and %CV ≤4.6%		Tables 7.12 to 7.13 of Report 06G3JB
Interference & specificity	Six lots of control matrix tested. No interference was observed in any of the lots tested		Figures 8.9 to 8.14 of Report 06G3JB

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Dilution linearity & hook effect	200,000 ng/mL tested (n=6) with a 10-fold dilution factor. MOV Mean bias was -2.5%, CV 0.5%; NHC Mean bias was 2.0%, CV 0.6%.	Tables 7.6 to 7.7 of Report 06G3JB
Bench-top/process stability	25 hours at room temperature for Low and High QC samples was established. Molnupiravir Mean % bias was -4.1% to -3.5% with a CV ≤9.2%. NHC Mean % bias was -9.9% to 0.5% with CV≤ 9.2% 92 hours processed sample stability (~ 2°C to 8 °C) for Low and High QC samples was established. MOV Mean % bias was -1.0% to 5.1% with a CV ≤4.9%. NHC Mean % bias was 1.6% to 2.5% with CV≤4.0%	Tables 7.26 to 7.27 and Tables 7.38 to 7.39 of Report 06G3JB
Freeze-Thaw stability	Low and high QC samples were prepared, stored at -10°C to -30ºC, and -50°C to -90ºC and subjected to 4 freeze-thaw cycles. MOV Mean % bias was determined to be –5.0% to -0.3% with a CV ≤4.7%; NHC Mean % bias was determined to be -2.9% to 1.5% with a CV ≤4.6%	Tables 7.30 to 7.33 of Report 06G3JB
Long-term storage	Low and high QC samples (precipitated plasma) were prepared, stored at –10°C to -30ºC and -50°C to -90ºC Stability was established for 20 days when stored at –10°C to -30ºC. MOV Mean % bias was determined to be -4.0% to -1.1% with a CV ≤3.7%; NHC Mean % bias was determined to be -4.3% to 2.0% with a CV ≤4.0% Stability was established for 204 days when stored at –50°C to -90ºC. MOV Mean % bias was determined to be 0.5% to 1.5% with a CV ≤2.2%; NHC Mean % bias was determined to be 0.5% to 2.4% with a CV ≤3.3%	Tables 7.34 to 7.37 of Report 06G3JB Tables 6.8 to 6.9 of Addendum#2 of Report 06G3JB
Parallelism	NA	
Carryover	Carryover within the bioanalytical method was evaluated in the validation by injecting 2 blank matrix samples analyzed immediately following the highest calibration standard. There was no evidence of carry over around the retention times of analyte and internal standard.	Figure 8.8 of Report 06G3JB

CV=coefficient of variation; LC-MS/MS= liquid chromatography/tandem mass spectrometry; LLOQ=lower limit of quantitation; MOV=molnupiravir, MK-4482, EIDD-2801; NA=not applicable; NHC=N-hydroxycytidine, EIDD-1931; QC=quality control; ULOQ=upper limit of quantitation

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Appendix 2.7.1: 10
Cross Validation Data – Method ED28HUP

Bioanalytical method cross validation report name, amendments, and hyperlinks	Cross Validation between [redacted] of a Bioanalytical Method for the Determination of EIDD-2801 and EIDD-1931 in Human Urine using Liquid Chromatography with Tandem Mass Spectrometric Detection, 8440170 [Ref. 5.3.1.4: 05PL2T]		
Method description	Cross Validation between [redacted] of an LC-MS/MS method for the determination of MOV and NHC in human urine		
Materials used for standard calibration curve and concentration	Control human urine, MOV and NHC reference standards. Calibrator Concentrations: 25.0, 50.0, 200, 800, 4000, 12500, 22500, and 25000 ng/mL		
Validated assay range	25.0 to 25,000 ng/mL for both analytes		
Material used for QCs and concentration	Control human urine, MOV and NHC reference standards. QC Concentrations: 75.0, 875, 10000, and 20000 ng/mL		
Matrix/Sample Volume	Urine, 50 µL		
Source and lot of reagents	Control human urine. MOV and NHC reference standards from [redacted]		
Regression model and weighting	Linear $1/x^2$		
Cross-Validation parameters		**Method cross validation summary**	**Source location**
Standard calibration curve performance during cross-validation runs	Number of standard calibrators from LLOQ to ULOQ	8	Tables 7.2 to 7.3 of Main and Contributing Report 05PL2T
	Cumulative accuracy (%bias) from LLOQ to ULOQ	[redacted]: MOV: -2.4% to 1.6%; NHC: -6.8% to 3.6%; [redacted]: MOV: -9.8% to 4.4%; NHC: -6.2% to 3.2%	Tables 7.2 to 7.3 of Main and Contributing Report 05PL2T
	Cumulative precision (%CV) from LLOQ to ULOQ	[redacted]: NA [redacted]: NA	NA
Performance of QCs during cross validation runs	**<u>Cumulative accuracy (%bias) in 4 QCs</u>**	[redacted]: MOV: -0.5% to 3.1%; NHC: -4.4% to 2.0% [redacted]: MOV: -1.0% to 6.8%; NHC: 0.3 to 2.0%	Tables 7.6 to 7.7 of Main and Contributing Report 05PL2T
	<u>Inter-batch %CV</u>	[redacted]: NA [redacted]: NA	NA
Cross Validation of QC Samples (4 concentration levels)	Cross validation QC samples at LQC, LMQC, MQC, and HQC were prepared at [redacted] and analyzed at both sites. Comparison of the Mean Accuracy Values of the calculated QC Concentrations showed a range of Relative % Difference of -10.9% to 5.1% for MOV; and -5.4% to -2.1% for NHC.		Tables 7.13 to 7.14 of Main Report 05PL2T

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Cross Validation Pooled Incurred Sample	Incurred sample pools (3 pools, 6 replicates, n=18) were prepared and analyzed at both sites. Comparison of calculated NHC concentrations between the 2 sites had 18 out of 18 within ± 20% Relative difference	Table 7.10 of the Main Report of 05PL2T
Selectivity & specificity	Matrix blank and blank matrix with internal standard demonstrated lack of significant interference.	Figures 8.3 to 8.4 of Main and Figures 9.3 to 9.4 of Contributing Report 05PL2T
Carryover	Carryover was evaluated in the cross validation by injecting 2 blank matrix samples analyzed immediately following the highest calibration standard. There was no evidence of carry over around the retention times of analyte and internal standard	Figures 8.6 of Main and Figure 9.6 of Contributing Report 05PL2T
CV=coefficient of variation; HQC=high quality control; LC-MS/MS= liquid chromatography/tandem mass spectrometry; LLOQ=lower limit of quantitation; LMQC= low-middle quality control; LQC=low quality control; MOV=molnupiravir, MK-4482, EIDD-2801; MQC= middle quality control; NA=not applicable; NHC=N-hydroxycytidine, EIDD-1931; QC=quality control; ULOQ=upper limit of quantitation		

Appendix 2.7.1: 11
Validation Data – Method for NHC-TP

Bioanalytical method validation report name, amendments, and hyperlinks	Quantitation of ß-D-N4-hydroxycytidine (NHC or EIDD-1931) and ß-D-N4-hydroxycytidine-triphosphate (NHC-TP or EIDD-2061) in Human Peripheral Blood Mononuclear Cell Lysate via Combined Liquid Chromatography-Tandem Mass Spectrometric (LC-MS/MS) Analysis , [redacted]: [Ref. 5.3.1.4: 05Q2TM]		
Method description	LC-MS/MS method for the determination of NHC and NHC-TP in PBMC		
Materials used for standard calibration curve and concentration	Control human PBMC, NHC and NHC-TP reference standards. Calibrator Concentrations: NHC: 2.00, 5.00, 25.0, 100, 500, 1000, 1500 pmol/sample; NHC-TP: 1.00, 5.00, 25.0, 100, 500, 1000, 1500 pmol/sample		
Validated assay range	2.00 to 1500 pmol/sample for both NHC; 1.00 to 1500 pmol/sample for NHC-TP		
Material used for (QCs and concentration	Control human PBMC, NHC, and NHC-TP reference standards. QC Concentrations: NHC: 2.00, 6.00, 250, 1200, and 6,000 pmol/sample; NHC-TP: 1.00, 3.00, 250, 1200, and 6,000 pmol/sample		
Matrix/Sample Volume	PBMC lysate in 70% methanol/100 µL		
Source and lot of reagents	Control human PBMC. NHC and NHC-TP reference standards from [redacted]		
Regression model and weighting	Linear $1/x^2$		
Validation parameters	**Method validation summary**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	7	Tables 2 to 3 of Report 05Q2TM
	Cumulative accuracy (%bias) from LLOQ to ULOQ	NHC: -3.94% to 4.28% NHC-TP: -2.87% to 3.81%	Tables 2 to 3 of Report 05Q2TM
	Cumulative precision (%CV) from LLOQ to ULOQ	NHC: ≤3.81% NHC-TP: ≤12.7%	Tables 2 to 3 of Report 05Q2TM
Performance of QCs during accuracy and precision runs	**Cumulative accuracy (%bias) in 4 QCs**	NHC: -1.77% to 6.96% NHC-TP: -11.2% to 8.77%	Tables 4 to 5 of Report 05Q2TM
	Inter-batch %CV	NHC: ≤4.32% NHC-TP: ≤11.8%	Tables 4 to 5 of Report 05Q2TM
	Total Error	Not calculated	
Selectivity & Specificity	Six lots of control matrix tested. No interference was observed in any of the lots tested		Figures 8 and 11 of Report 05Q2TM
Matrix Effect	Analysis of Low, Mid, High QC NHC Mean Relative Matrix Effect: 102%; CV≤3.1% NHC-TP: Mean Relative Matrix Effect: 94.8%; CV≤7.25%		Tables 34 to 35 of Report 05Q2TM

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Recovery	Defined as the average of the mean concentration for interday concentrations of QCs divided by the theoretical concentrations Mean Recovery for NHC: 101% Mean Recovery for NHC-TP: 101%	Tables 4 to 5 of Report 05Q2TM
Dilution linearity & hook effect	6000 pmol/sample tested (n=6) with 5, 10, 50-fold dilution factor. NHC Mean bias ranged -4.27% to -4.20%, CV ≤4.67%; NHC-TP Mean bias ranged from -5.60% to -3.16%, CV≤4.15%.	Tables 6 to 7 of Report 05Q2TM
Bench-top/process stability	77 hours at room temperature for Low, Mid, and High QC samples was established. NHC Mean % bias was -1.55% to 1.81% with a CV ≤4.62%. NHC-TP Mean % bias was -7.28% to 9.36% with CV≤8.89% 137 hours processed sample stability (~ 2°C to 8°C) for Low, Mid, and High QC samples was established. NHC Mean % bias was -2.91% to 1.13% with a CV ≤4.16%. NHC-TP Mean % bias was -0.667% to 10.2% with CV≤7.13%	Tables 12 to 13 and Tables 14 to 15 of Report 05Q2TM
Freeze-Thaw stability	Low, Mid, and high QC samples were prepared, stored at ≤-70ºC and subjected to 3 freeze-thaw cycles. NHC Mean % bias was determined to be -1.64% to 2.24% with a CV ≤4.81%; NHC-TP Mean % bias was determined to be -8.56% to 2.93% with a CV ≤5.87%	Tables 10 to 11 of Report 05Q2TM
Long-term storage	Low, Mid, and high QC samples in PBMC lysate were prepared, stored at ≤-70ºC Stability was established for 49 days when stored at ≤-70ºC. NHC Mean % bias was determined to be -2.03% to 3.67% with a CV ≤3.02%; NHC-TP Mean % bias was determined to be -1.79% to 4.80% with a CV ≤8.6%	Tables 20 to 21 of Report 05Q2TM
Extended Long-term Stability	Stability of quality control samples was established for 148 days when stored at ≤-70ºC. NHC: Mean Bias was -0.97% to 1.65% with CV ≤2.1% NHC-TP: Mean bias was -6.21% to 5.79% with CV≤8.3%	Appendix VI of the Bioanalytical Report 07X537
Parallelism	NA	
Carryover	Carryover within the bioanalytical method was evaluated in the validation by injecting blank matrix samples analyzed immediately following the highest calibration standard. Carryover was not significant (≤20% of LLOQ)	Tables 38 to 39 of Report 05Q2TM
Cell Concentration Effect	Low, Mid, and high QC samples in PBMC lysate at 0.2 x 10^6 , 2.0 x 10^6, 10 x 10^6, and 20 x 10^6 cells/mL were prepared and analyzed. There was no difference in the quantitation of NHC and NHC-TP based on the cell concentration.	Tables 44 to 45 of Report 05Q2TM
Solution Stability	Stock solution of NHC-TP (0.5 or 1.0 mg/mL) prepared in 70/30 acetonitrile/water stored at -20°C was stable for 20 days	Table 23 of Report 05Q2TM

CV=coefficient of variation; LC-MS/MS= liquid chromatography/tandem mass spectrometry; LLOQ=lower limit of quantitation; NA=not applicable; NHC=N-hydroxycytidine, EIDD-1931; NHC-TP=N-hydroxycytidine triphosphate, EIDD-2061; PBMC=peripheral blood mononuclear cells; QC=quality control; ULOQ=upper limit of quantitation

Appendix 2.7.1: 12
Validation Data – Method for NHC-TP (TM.3160.04)

Bioanalytical method validation report name, amendments, and hyperlinks	Validation of a Liquid Chromatographic Method Using Tandem Mass Spectrometry Detection and Automated Extraction for the Determination of N-hydroxy cytidine Triphosphate (5 to 2000 ng/mL) in Human Peripheral Blood Mononuclear Cells (PBMC) (Sodium Heparin), [redacted] Canada [redacted]: [Ref. 5.3.1.4: 07X6DZ]		
Method description	LC-MS/MS method for the determination of NHC-TP in human PBMC (sodium heparin)		
Materials used for standard calibration curve and concentration	Control human PBMC, NHC-TP and [$^{13}C_5$] NHC-TP reference standards. Calibrator Concentrations: NHC-TP: 5.00, 10.00, 40.00, 200.00, 400.00, 800.00, 1600.00, 2000.00 ng/mL		
Validated assay range	5.00 to 2000.00 ng/mL		
Material used for QCs and concentration	Control human PBMCs in 30/70 water/methanol, NHC-TP reference standard. QC Concentrations: NHC-TP: 5.00, 15.00, 1000.00, 1500.00, and 20,000 ng/mL		
Matrix/Sample Volume	PBMC lysate in 70% methanol/50 µL		
Source and lot of reagents	Control human PBMC. NHC-TP and [$^{13}C_5$] NHC-TP reference standards from Merck & Co.		
Regression model and weighting	Linear 1/conc^2		
Validation parameters	**Method validation summary**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	Table 3A of Report 07X6DZ
	Cumulative accuracy (%bias) from LLOQ to ULOQ	NHC-TP: -5.04% to 3.13%	Table 3A of Report 07X6DZ
	Cumulative precision (%CV) from LLOQ to ULOQ	NHC-TP: ≤8.0	Table 3A of Report 07X6DZ
Performance of QCs during accuracy and precision runs	**Cumulative accuracy (%bias) in 4 QCs**	NHC-TP: -2.69% to 0.65%	Table 4A of Report 07X6DZ
	Inter-batch %CV	NHC-TP: ≤11.15%	Table 4A of Report 07X6DZ
	Total Error	Not calculated	Not calculated
Dilution linearity (Frozen Sample)	20,000 ng/mL tested (n=6) with 20-fold dilution factor. NHC-TP Mean bias -1.45%, CV ≤4.45%		Table 8A of Report 07X6DZ
Selectivity	Eight lots of control matrix tested. No interference was observed in any of the lots tested		Table 9A of Report 07X6DZ

Potentially Interfering and Commonly Used Drugs	No effect on the quantitation of the analyte	Table 10A of Report 07X6DZ
Matrix Effect	QC1: Mean IS-Normalized matrix factor of 1.001188 and CV%=2.08; ULOQ: Mean IS-Normalized matrix factor of 0.997720 and CV%=2.48	Tables 11A to 12A of Report 07X6DZ
Matrix Effect (Higher Cells Concentration)	Analysis of QC1 samples at 50 to 75 x 10^6 cells/mL; Mean Bias -14.13% to -10.47% and CV% ≤1.88%	Table 13A of Report 07X6DZ
Carry over	No Significant carryover observed	Tables 14.1A to 14.2A of Report 07X6DZ
Reinjection Reproducibility	Analysis of QCs (Low, Mid, High): Mean Bias was -1.41% to 1.86%; CV% ≤ 2.8%	Table 15A of Report 07X6DZ
Freeze and Thaw Stability in the Matrix	4 cycles for Low and High QC samples were established for samples stored at -20°C: Mean bias -4.86% to 1.1%; CV% ≤4.61; Stored at -80°C: Mean bias -4.30% to 1.66%; CV% ≤ 3.83	Tables 16A to 17A of Report 07X6DZ
Short-Term Stability of Analyte in Matrix	Low and high QC samples were prepared, stability established when kept for 24hr, 39 min at room temperature with Mean Bias range of -8.80% to -4.73% and CV% ≤ 8.99; Kept for 24 hr, 07 min at 4°C with Mean Bias range of -7.13% to -2.11% and CV% ≤5.44	Tables 18A to 19A of Report 07X6DZ
Long-term storage	In progress	
Pre-Automated Extraction Stability	Low and high QC samples were analyzed, stability established when kept for 24 hr, 10 min at 4°C with Mean Bias range of -3.41% to -0.64% and CV% ≤ 2.40;	Table 20A of Report 07X6DZ
Post-Preparative Stability	Low and high QC samples were extracted and kept for 118 hr, 32 min at 4°C before being analyzed. Mean Bias range of -5.41% to -3.40% and CV% ≤ 2.80;	Table 21A of Report 07X6DZ
Short-Term Stability of Analyte and IS in Solution (High Concentration)	23 hr 31 min at room temperature	Tables 22A to 23A of Report 07X6DZ
Short-Term Stability of Analyte in Solution (Low Concentration)	21 hr 25 min at room temperature	Tables 24A of Report 07X6DZ
Short-Term Stability of IS in Solution (Low Concentration)	23 hr 31 min at room temperature	Tables 25A of Report 07X6DZ

CV=coefficient of variation; hr=hour(s); LC-MS/MS= liquid chromatography/tandem mass spectrometry; LLOQ=lower limit of quantitation; min=minute(s); NHC=N-hydroxycytidine, EIDD-1931; NHC-TP=N-hydroxycytidine triphosphate, EIDD-2061; PBMC=peripheral blood mononuclear cells; QC=quality control; ULOQ=upper limit of quantitation

5.4 NHC in Plasma, NHC and MOV in Treated Plasma and Urine, and NHC and NHC-TP in Lysed PBMC In-Study Performance

Appendix 2.7.1: 13
In-study Performance of Method NHC9HPP

Study #	Run Acceptance Rate	Std. Curve Performance		QC Performance		ISR Passing Rate (%)
		Bias (%)	CV (%)	Bias (%)	CV (%)	
P001	92.3% (24 out of 26)	NHC: -2.3% to 2.0%	≤8%	-4.7% to 0.5%	≤10.4%	93.9% (93 out of 99)
P002	87.0% (40 out of 46)	NHC: -2.9% to 1.7%	≤7.3%	-4.7% to 1.4%	≤10.8%	77.0% (114 out of 148)
P008	87.8% (43 out of 49)	NHC: -1.5% to 1.3%	≤6.3%	-2.0% to 0.0%	≤11.4%	96.8% (149 out of 154)
P012	91.7% (11 out of 12)	NHC: -1.1% to 1.7%	≤5.6%	-1.7% to 0.4%	≤3.5%	86.8% (46 out of 53)

CV=coefficient of variation; ISR=incurred sample reanalysis; NHC=N-hydroxycytidine, EIDD-1931; P=protocol (number); QC=quality control

Appendix 2.7.1: 14
In-study Performance of Method ED28HPP and EDD2HPP

Study #	Run Acceptance Rate	Std. Curve Performance		QC Performance		ISR Passing Rate (%)
		Bias (%)	CV (%)	Bias (%)	CV (%)	
P004	100% (31 out of 31)	NHC: -1.0% to 1.0% MOV: -0.8 to 0.4%	NHC: ≤5.1% MOV: ≤3.7%	NHC: 0.5% to 0.8% MOV: 0.0% to 0.7%	NHC: ≤4.2 MOV: ≤3.3	NHC: 100% (156 out of 156)
P006	NHC: 69% (9 out of 13) MOV: 75% (6 out of 8)	NHC: -3.0% to 3.2% MOV: -1.8% to 2.4%	NHC: ≤6.8% MOV: ≤4.3%	NHC: -2.9% to 2.3% MOV: 0.0% to 7.0%	NHC: ≤4.8 MOV: ≤3.2	NHC: 83.3% (25 out of 30)

CV=coefficient of variation; ISR=incurred sample reanalysis; MOV=molnupiravir, MK-4482, EIDD-2801; NHC=N-hydroxycytidine, EIDD-1931; P=protocol (number); QC=quality control

Appendix 2.7.1: 15
In-study Performance of Method ED28HUP

Study #	Run Acceptance Rate	Std. Curve Performance		QC Performance		ISR Passing Rate (%)
		Bias (%)	CV (%)	Bias (%)	CV (%)	
P004	100% (17 out of 17	NHC: -1.6% to 2.0% MOV: -1.3% to 1.0%	NHC: ≤6.1 MOV: ≤4.8	NHC: -0.7% to 2.0% MOV: 0.0% to 2.1%	NHC: ≤4.2 MOV: ≤3.5	NHC: 100% (78 out of 78)

CV=coefficient of variation; ISR=incurred sample reanalysis; MOV=molnupiravir, MK-4482, EIDD-2801; NHC=N-hydroxycytidine, EIDD-1931; P=protocol (number); QC=quality control

Appendix 2.7.1: 16
In-study Performance of Method for NHC-TP ([redacted])

Study #	Run Acceptance Rate	Std. Curve Performance		QC Performance		ISR Passing Rate (%)
		Bias (%)	CV (%)	Bias (%)	CV (%)	
P001 and P002	100% (11 out of 11)	-4.91% to 3.50%	≤6.77	2.15% to 10.8%	≤10.5	85% (17 out of 20)
P008	94% (17 out of 18)	-2.55% to 2.99%	≤13.1	-2.39% to 1.83% (outliers excluded); -2.39% to 7.39% (outliers included)	≤8.15 (outliers excluded); ≤25.6 (outliers included)	77.5% (55 out of 71)

CV=coefficient of variation; ISR=incurred sample reanalysis; [redacted]; NHC-TP=N-hydroxycytidine triphosphate, EIDD-2061; P=protocol (number); QC=quality control

Appendix 2.7.1: 17
In-study Performance of Method for NHC-TP (TM.3160.04)

Study #	Run Acceptance Rate	Std. Curve Performance		QC Performance		ISR Passing Rate (%)
		Bias (%)	CV (%)	Bias (%)	CV (%)	
P012	80% (4 out of 5)	-2.90% to 2.24%	≤5.69%	-1.79% to 61.73% (statistics including outside accepted range of bias); -1.64% to 4.44% (statistics excluding outside accepted range of bias)	≤112.04% (statistics including outside accepted range of bias); ≤4.23% (statistics excluding outside accepted range of bias)	96% (48 out of 50)

CV=coefficient of variation; ISR=incurred sample reanalysis; NHC-TP=N-hydroxycytidine triphosphate, EIDD-2061; P=protocol (number); QC=quality control

5.5 Tabular Summary of Bioavailability and Food Effect PK Parameters by Study

Appendix 2.7.1: 18
Tabular Summary of NHC PK Parameter Values by Study

PN	Short Title/ Design	MOV Dose/ Treatment	Day	N	GM (GCV%)					GMR (90% CI)		
					Cmax (ng/mL)	Tmax[a] (hr)	AUC0-inf (ng/mL*hr)	AUC0-last (ng/mL*hr)	t1/2 (hr)	AUC0-inf	Cmax	Ref
P004	A Randomized, Double-blind, Placebo-controlled, First-in-human Study Designed to Evaluate the Safety, Tolerability, and Pharmacokinetics of EIDD-2801 Following Oral Administration to Healthy Volunteers/ Part 1: SAD Part 2: Food effect Part 3: MAD	50 mg PIB	1	6	223 (46.2)	1.00 (0.517-1.00)	432 (26.5)	415 (27.4)	0.945 (12.1)	-	-	-
		100 mg PIB	1	6	454 (42.2)	1.00 (0.500-1.50)	932 (27.0)	917 (27.5)	0.907 (10.1)	-	-	-
		200 mg PIB	1	6	926 (12.6)	1.00 (0.500-1.00)	1830 (19.6)	1810 (20.0)	1.02 (16.4)	-	-	-
		400 mg PIB	1	6	1850 (22.7)	1.00 (0.500-1.00)	4010 (20.2)	4000 (20.2)	1.03 (8.86)	-	-	-
		600 mg PIB	1	6	2720 (27.0)	1.00 (1.00-1.00)	6130 (21.4)	6120 (21.6)	1.06 (10.3)	-	-	-
		800 mg PIB	1	6	3640 (13.4)	1.00 (0.500-1.00)	8740 (10.4)	8720 (10.4)	1.29 (7.10)	-	-	-
		1200 mg DFC	1	6	4500 (17.9)	1.75 (1.00-2.50)	13800 (11.8)	13800 (11.7)	1.81 (73.5)	-	-	-
		1600 mg DFC	1	6	6350 (20.6)	1.50 (1.00-2.00)	20700 (31.4)	20700 (31.4)	4.59 (71.6)	-	-	-
		200 mg DFC (fasted)	1	10[b]	893 (36.8)	1.00 (1.00-2.50)	1980 (29.3)	1950 (29.9)	0.977 (13.0)	0.955 (0.881, 1.03)	0.644 (0.535, 0.775)	Fed versus Fasted
		200 mg DFC (fed)	1	10[b]	575.0 (27.7)	3.00 (2.00-4.00)	1890 (28.8)	1950 (29.0)	1.09 (16.3)	-	-	-

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PN	Short Title/ Design	MOV Dose/ Treatment	Day	N	GM (GCV%)					GMR (90% CI)		
					Cmax (ng/mL)	Tmax[a] (hr)	AUC0-inf (ng/mL*hr)	AUC0-last (ng/mL*hr)	t1/2 (hr)	AUC0-inf	Cmax	Ref
		50 mg DFC Q12H x 5.5d	1	6	223 (19.4)	1.00 (1.00-1.00)	461 (15.7)	444 (17.3)	0.937 (14.0)	-	-	-
		100 mg DFC Q12H x 5.5d	1	6	395 (18.5)	1.25 (1.00-2.03)	855 (19.8)	835 (19.9)	0.918 (9.08)	-	-	-
		200 mg DFC Q12H x 5.5d	1	6	766 (16.3)	1.50 (1.00-1.50)	1660 (15.3)	1640 (15.5)	0.960 (10.4)	-	-	-
		300 mg DFC Q12H x 5.5d	1	6	1280 (15.2)	1.50 (1.00-1.50)	3090 (17.4)	3080 (17.4)	1.09 (17.7)	-	-	-
		400 mg DFC Q12H x 5.5d	1	6	1530 (23.2)	1.50 (1.00-2.00)	3800 (19.5)	3790 (19.5)	1.05 (13.1)	-	-	-
		600 mg DFC Q12H x 5.5d	1	6	2160 (31.4)	1.75 (1.00-6.00)	6680 (17.6) [d]	6110 (26.9)	1.16 (3.50)[d]	-	-	-
		800 mg DFC Q12H x 5.5d	1	6	2770 (13.3)	1.75 (1.50-2.50)	8200 (21.6)	8180 (21.5)	1.18 (7.28)	-	-	-

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PN	Short Title/ Design	MOV Dose/ Treatment	Day	N	GM (GCV%)					GMR (90% CI)		
					Cmax (ng/mL)	Tmax[a] (hr)	AUC0-inf (ng/mL*hr)	AUC0-last (ng/mL*hr)	t1/2 (hr)	AUC0-inf	Cmax	Ref
P008	A Randomized, Double-blind, Placebo-Controlled Clinical Study to Evaluate the Safety, Tolerability and Pharmacokinetics of MK-4482 in Healthy Japanese Adult Participants Part 1: Single dose and food effect Part 2: MAD	200 mg DFC	1	6	1210 (58.8)	1.00 (0.50-5.00)	2310 (21.7)	2310 (21.7)	1.28 (13.9)	-	-	-
		400 mg DFC	1	6	3160 (11.6)	1.00 (1.00-1.50)	6410 (18.0)	6390 (18.0)	8.37 (15.1)	-	-	-
		800 mg DFC (fasted)	1	7[c]	4750 (20.0)	1.50 (0.52-2.50)	12400 (15.4)	12400 (15.5)	3.95 (113.3)	1.11 (1.02, 1.20)	0.76 (0.67, 0.86)	Fed versus Fasted
		800 mg DFC (fed)	1	6[c]	3760 (17.0)	3.00 (2.00-3.00)	13800 (17.7)	13700 (17.8)	3.74 (78.5)	-	-	-
		1600 mg DFC	1	6	8910 (21.5)	2.00 (1.00-2.00)	26300 (13.5)	26300 (13.5)	5.50 (57.1)	-	-	-
		400 mg DFC Q12H x 5.5d	1	15	2340 (24.1)	1.50 (1.00-2.00)	NC	5240 (17.1)[e]	NC	-	-	-
		800 mg DFC Q12H x 5.5d	1	15	5000 (15.5)	1.50 (1.00-2.00)	NC	12100 (15.6)[e]	NC	-	-	-

AUC0-inf =area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC0-last=area under the plasma concentration-time curve from time 0 to the last measurable non-zero concentration (tlast); CI=confidence interval; Cmax=maximum observed concentration; DFC=dry-filled capsule; GCV%=percent coefficient of variation based on geometric mean; GM=geometric mean; MAD=multiple ascending dose; MOV=molnupiravir, MK-4482, EIDD-2801; N = number of subjects with valid observations; NC=not calculated; NHC=N-hydroxycytidine; PIB=powder-in-bottle; PK=pharmacokinetic; P=protocol (number); Q12H=every 12 hours; SAD=single ascending dose; t1/2=apparent terminal elimination half-life; Tmax=time of the maximum observed concentration

[a] Median (minimum- maximum) values are presented for Tmax
[b] n=10 received 2 single oral 200-mg DFC doses in fasted and fed state separated by a 14-day washout
[c] n=6 received 2 single oral 800-mg DFC doses in the fasted and fed state separated by a 10-day washout
[d] n=5
[e] AUC0-12

Data source: [Ref. 5.3.3.1: P004MK4482], [Ref. 5.3.3.3: P008MK4482]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ΔΔQTcF	Mean Change from Time Matched Baseline Placebo-Adjusted QTcF
^{14}C	Radioactive isotope of carbon
%CV	Percent coefficient of variation
3TC	Lamivudine
ADME	Absorption, distribution, metabolism, excretion
AE	Adverse event
AIC	Akaike information criteria
ANOVA	Analysis of variance
AUC	Area under the concentration-time curve
AUC0-12	Area under the concentration-time curve from time 0 to 12 hours
AUC0-inf	Area under the concentration-time curve from time 0 extrapolated to infinity
AUC0-last	Area under the concentration-time curve from time 0 through the last measurable concentration
AUC50	Half maximal effective AUC value
BCRP	Breast Cancer Resistance Protein efflux transporter
BCS	Biopharmaceutics Classification System
BIC	Bayesian information criteria
BLOQ	Below limit of quantification
BMI	Body mass index
C12	Concentration at 12 hours
CES1	Carboxylesterase 1
CES2	Carboxylesterase 2
CFB	Change from baseline
CI	Confidence interval
CL/F	Apparent clearance
Cmax	Maximum concentration
CNT1	Concentrative nucleoside transporter 1
CNT2	Concentrative nucleoside transporter 2

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Abbreviation	Definition
CNT3	Concentrative nucleoside transporter 2
COVID-19	Coronavirus disease 2019
C-QTC	Concentration-corrected QT interval
CSR	Clinical Study Report
CTD	Common technical document
Ctrough	Trough concentration
CV	Coefficient of variation
CYP	Cytochrome P450
DDI	Drug-drug interaction
DFC	Dry-filled capsule
DDI	Drug-drug interaction
E0	Placebo effect
EC50	Exposure at 50% of maximal response
ECG	Electrocardiograms
EDTA	Ethylenediaminetetraacetic acid
eGFR	Estimated glomerular filtration rate
EIDD	Emory Institute for Drug Development
Emax	Maximum drug effect
ENT1	Equilibrative nucleoside transporter 1
ENT2	Equilibrative nucleoside transporter 2
EOT	End of treatment
E-R	Exposure-response
F	Absolute bioavailability
Fa	Fraction absorbed
FaSSIF	Fasted state simulated intestinal fluid
FeSSIF	Fed state simulated intestinal fluid
Fe0-12	Percentage of the dose administered recovered in urine over the time interval 0 to 12 hours postdose
Fe0-24	Percentage of the dose administered recovered in urine over the time interval 0 to 24 hours postdose
FIH	First in human

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Abbreviation	Definition
FMI	Final market image
FSS	Formal stability study
FTC	Emtricitabine
GI	Gastrointestinal
GLP	Good Laboratory Practice
GLSM	Geometric least squares mean
GM	Geometric mean
GMR	Geometric mean ratio
HBV	Hepatitis B virus
HCV	Hepatitis C virus
hERG	Human ether-à-go-go-related gene
HIV	Human immunodeficiency virus
HR	Heart rate
IC50	Half-maximal inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INR	International normalized ratio
IV	Intravenous
IVDM	Integrated viral dynamics model
LLC-PK1	Epithelial cells derived from porcine kidneys
LLOQ	Lower limit of quantitation
LNS	Low frequency nucleotide substitutions
LSM	Least squares mean
mAbs	Monoclonal antibodies
mARC1	Mitochondrial amidoxime reducing component 1
mARC2	Mitochondrial amidoxime reducing component 2
MATE1	Multidrug and toxin extrusion protein 1
MATE2K	Multidrug and toxin extrusion protein 2K
MDR1	Multidrug resistance 1 (P-glycoprotein)
MDRD	Modification of Diet in Renal Disease study
MERS	Middle east respiratory syndrome

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Abbreviation	Definition
MOV	Molnupiravir, MK-4482, EIDD-2801
MRP2	Multidrug resistance protein-2 efflux transporter
MTT	Mean transit time
NGS	Next generation sequencing
NHC	N-hydroxycytidine, EIDD-1931
NHC-TP	N-hydroxycytidine-5′-triphosphate, EIDD-2601
NP	Nasopharyngeal
OAT1B1	Organic anion transporter 1B1
OAT1B3	Organic anion transporter 1B3
OATP1B1	Organic anion transporting peptide 1B1
OATP1B3	Organic anion transporting peptide 1B3
OCT1	Organic cation transporter 1
OCT2	Organic cation transporter 2
OP	Oropharyngeal
P	Protocol (number)
PBMC	Peripheral blood mononuclear cells
PBS	Phosphate-buffered saline
PCR	Polymerase chain reaction
Peff	Effective permeability
P-gp	P-glycoprotein
PIB	Powder-in-bottle
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetics
Q12H	Every 12 hours
QC	Quality control
QT	Q-T interval
QTc	Q-T interval corrected for heart rate
QTcF	Q-T interval corrected for heart rate using Fridericia's formula
RH	Relative humidity
RNA	Ribonucleic acid

Abbreviation	Definition
SAD	Single-ascending dose
SAE	Serious adverse event
SARS-CoV-1	Severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SGF	Simulated gastric fluid
SIF	Simulated intestinal fluid
t1/2	Half-life
TESNV	Treatment-Emergent Single Nucleotide Variants
Tmax	Time of maximum concentration
TQT	Thorough QT
TSSO	Time since symptom onset
ULOQ	Upper limit of quantitation
US	United States
USP	United States Pharmacopeia
VAF	Variant allele frequencies
Vc	Central volume
Vc/F	Apparent central volume of distribution
VDM	Viral dynamics model
Vp/F	Apparent peripheral volume of distribution

1 BACKGROUND AND OVERVIEW

1.1 General Background

Coronaviruses are a family of enveloped positive-strand RNA viruses, which include SARS-CoV-1 and MERS-CoV, that primarily target the respiratory system in humans and animals [Ref. 5.4: 05JRQN]. COVID-19, the disease caused by the novel SARS-CoV-2 virus, can produce a range of clinical manifestations, from an asymptomatic carrier state to critical illness, characterized primarily by acute respiratory failure [Ref. 5.4: 05J92M, 05Q368, 05H4S0]. Increased risk for hospitalization with COVID-19 as well as increased mortality rates are associated with known risk factors, and mortality rates rise significantly (>50%) for patients requiring admission to the intensive care unit [Ref. 5.4: 05Q339, 05Q3GB, 05JQSM, 05H4S0, 05Q59Q, 05Q59S]. There remains a need for direct-acting antiviral agents active against SARS-CoV-2, particularly orally administered agents that reduce the risk of disease progression.

Molnupiravir (also known as MK-4482 and EIDD-2801; hereafter referred to as MOV) is an oral 5′-isobutyrate prodrug of the broadly active, antiviral ribonucleoside analog NHC (also known as EIDD-1931), which has activity against SARS-COV-2. MOV is hydrolyzed by esterases during absorption/first-pass to deliver NHC into systemic circulation. Once distributed inside cells, NHC is phosphorylated to its triphosphate anabolite (NHC-TP, also known as EIDD-2061). NHC-TP inhibits viral replication by increasing the viral mutation rate beyond a biologically tolerable threshold, introducing errors in the viral RNA that result in impairment of viral fitness leading to viral extinction. In vitro, MOV inhibits replication of viral pathogens from multiple RNA virus families, including pathogenic coronaviruses (eg, MERS-CoV, SARS-CoV-1, and SARS-CoV-2).

Proposed Dose Regimen:

MOV has been developed for the treatment of mild and moderate COVID-19 in adults who are at high risk for progressing to severe COVID-19 and/or hospitalization. The proposed dosage of MOV for adults is 800 mg (four 200-mg capsules) taken orally Q12H for 5 days, with or without food.

1.2 Overview of Clinical Pharmacology Program

This Summary of Clinical Pharmacology provides an overview of the clinical pharmacology of MOV, including characterization of the PK of MOV, NHC, and NHC-TP. Clinical Pharmacology assessments include 3 Phase 1 studies in healthy participants (MK-4482-004 [P004], MK-4482-012 [P012] and MK-4482-008 [P008]) [Table 2.7.2-covid19txallpop: 1] [Appendix 2.7.2-covid19txallpop: 1]. A total of 227 participants were enrolled in the Phase 1 program (P004, P008, P012); 175 received at least 1 dose of MOV, while 56 received at least 1 dose of placebo. Some participants received both MOV and placebo due to the cross-over design in certain studies. Safety and tolerability data from these studies are summarized in [Sec. 2.7.4-covid19txallpop: 2.3]. Based on nonclinical data and the known metabolic pathways of MOV and NHC, no DDIs are anticipated and no DDI studies were conducted [Sec. 2.7.2-covid19txallpop: 1.3]. Concentration-QTc assessment to evaluate the relationship

of plasma NHC concentration and QTcF was conducted using data collected in the initial safety, tolerability and PK study (P004); therefore, no dedicated TQT study was conducted [Sec. 2.7.2-covid19txallpop: 1.3.2.2].

Table 2.7.2-covid19txallpop: 1
Completed Phase 1 Clinical Pharmacology Studies

Study Type	Protocol Number
PK and Initial Tolerability Studies in Healthy Participants	
Single and Multiple Ascending Dose Study (Q12H for 5.5 days) with Food Effect Assessment in Healthy Participants	P004
Multiple Ascending Dose Study (Q12H for 10.5 days) in Healthy Participants	P012
Intrinsic Factor PK Studies	
Single and Multiple Ascending Dose Study (Q12H for 5.5 days) with Food Effect Assessment in Healthy Japanese Participants	P008
P=protocol (number); PK=pharmacokinetic(s); Q12H=every 12 hours	

Two formulations of MOV have been evaluated. The initial single ascending dose levels (50 to 800 mg) in P004 were administered as a PIB formulation that was extemporaneously compounded as a [redacted] mg/mL oral solution. Subsequent single doses (1200 and 1600 mg), food effect (200 mg), and multiple ascending doses (50 to 800 mg Q12H for 5.5 days) were administered using [redacted] or 200-mg strength DFCs [Sec. 2.7.1: 1]. The DFC formulation was used in all other studies in the clinical development program and the 200-mg strength DFC is the final market formulation. Details on the biopharmaceutics of MOV can be found in [Sec. 2.7.1: 1].

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. A total of 1207 participants were included in the PopPK analyses [Ref. 5.3.5.3: 07ZXLB] [Ref. 5.3.5.3: 07ZRF9] including data obtained from the following studies:

- Phase 1 study in healthy participants (P004)
- Phase 2 study in hospitalized participants with COVID-19 (P001)
- Phase 2 study in nonhospitalized participants with COVID-19 (P006)
- Phase 2/3 study in nonhospitalized participants with COVID-19 (P002)

The PopPK analyses included covariate evaluation to inform on the effects of intrinsic and extrinsic factors.

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] [Ref. 5.3.5.3: 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]. This CTD section provides an integrated discussion of the key findings and characteristics and how they informed both development decisions and recommendations proposed for MOV use.

PK Parameters Used in the Evaluation of MOV:

MOV is converted almost entirely to NHC during absorption/first pass. NHC is taken up into cells where it is phosphorylated to the active triphosphate metabolite, NHC-TP. NHC is the primary circulating analyte and was evaluated across Phase 1, Phase 2, and Phase 2/3 studies. The concentration of NHC-TP was evaluated in PBMCs as a surrogate for NHC-TP concentrations at the site of action. Due to the complexity of PBMC collection and isolation in the clinical setting, it was not practical to implement sufficient PBMC collection in Phase 2 and 2/3 studies [Sec. 2.7.2-covid19txallpop: 2.5.1]. The PK of NHC-TP in PBMCs was, however, evaluated following multiple Q12H doses of up to 800 mg in healthy participants in P012 [Sec. 2.7.2-covid19txallpop: 2.1.2] and in healthy Japanese participants in P008 [Sec. 2.7.2-covid19txallpop: 2.2.1]. NHC exposures in plasma were shown to be well correlated with NHC-TP exposures in PBMCs, with plasma NHC AUC being a consistent strong correlate of NHC-TP exposures [Ref. 5.3.5.3: 07ZL42]. Additionally, the t1/2 of NHC-TP in PBMCs was consistent with the terminal t1/2 of NHC in plasma. Based on this, the more readily available NHC exposures were considered an appropriate surrogate for NHC-TP for the evaluation of intrinsic/extrinsic factors and E-R analyses.

Rationale for Dose Selection:

A dose of 800 mg Q12H administered without regard to food is proposed for the treatment of mild and moderate COVID-19 in nonhospitalized adult patients. This dose is based on E-R analyses described in [Sec. 2.7.2-covid19txallpop: 2.5] and dose/E-R relationships as described in [Sec. 2.7.3-covid19txallpop: 4]. These analyses support the selection of the clinical dose of MOV, bounds defining a clinically relevant change in MOV exposure, and the effect of intrinsic and extrinsic factors on the exposure and response of MOV.

1.3 MOV Clinical Pharmacology Profile

1.3.1 Pharmacokinetics

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 postdose, followed by a biphasic decline with an effective t1/2 of 3.3 hours. The GM mean terminal t1/2 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]. Administration of MOV with a high-fat meal delayed absorption (based on delayed Tmax of

3 hours and reduction in Cmax of 35.6%) with minimal impact on the extent of absorption, with values for NHC AUC0-inf similar for the fed and fasted states. Thus, no clinically meaningful food effect was observed following single MOV doses of either 200 or 800 mg [Sec. 2.7.1: 3.3].

Following uptake of NHC into cells, NHC is phosphorylated to the active triphosphate metabolite, NHC-TP. The t1/2 of NHC-TP in PBMCs was consistent with the terminal t1/2 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 AUC0-12 exposures of NHC in the plasma and AUC0-12 exposures of NHC-TP in PBMCs.

1.3.1.1 Absorption, Distribution, Metabolism, Excretion

Following oral administration, MOV is rapidly converted to NHC, the primary circulating metabolite. NHC reaches maximum concentrations approximately 1.5 hours following administration of MOV under fasted conditions [Sec. 2.7.2-covid19txallpop: 2.1]. A high-fat meal delayed the Tmax and reduced the maximum concentration of NHC, but did not impact the extent of absorption [Sec. 2.7.2-covid19txallpop: 2.1.1, 2.2.1]. Based on PopPK analysis, the apparent volume of distribution of NHC was estimated to be 131.9 L, indicating that NHC distributes in peripheral tissues [Ref. 5.3.5.3: 07ZRF9]. NHC does not bind to human plasma proteins [Sec. 2.7.2-covid19txallpop: 1.4.1]. High capacity and widely distributed CES1 and CES2 carboxylesterases are likely responsible for the conversion of MOV to NHC [Sec. 2.7.2-covid19txallpop: 1.4.2]. Following uptake into cells, NHC is anabolized to the active moiety NHC-TP via endogenous pyrimidine metabolism pathways. PopPK analysis indicates that the CL/F of NHC is 70.6 L/h [Ref. 5.3.5.3: 07ZRF9]. In healthy adults, only a small amount (3%) of an 800-mg dose was excreted in urine as NHC from 0 to 12 hours after administration, suggesting that renal excretion is not a meaningful route of elimination of NHC [Sec. 2.7.2-covid19txallpop: 2.1.1].

1.3.1.2 Intrinsic Factors and Special Populations

The 800 mg dose of MOV can be administered to patients with mild or moderate COVID-19 regardless of intrinsic factors. No dose adjustment is required based on age, sex, body weight, race, or ethnicity [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 nonclinical and clinical data [Sec. 2.7.2-covid19txallpop: 3.2.5]. 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 nonclinical 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) [Ref. 5.3.5.3: 07ZRF9]. Hepatic impairment is not expected to result in a clinically meaningful change in NHC exposure [Sec. 2.7.2-covid19txallpop: 3.2.6]. No dose adjustment is recommended in patients with any degree of hepatic impairment.

1.3.1.3 Extrinsic Factors: Drug-Drug Interactions

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]. 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. 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 dose adjustment is recommended for MOV when coadministered with other medications.

1.3.2 Pharmacodynamics and Special Safety

1.3.2.1 Antiviral Activity

Virological endpoints, including 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]. Briefly, treatment with MOV was associated with a greater reduction in the mean CFB 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 [Sec. 2.7.3-covid19txallpop: 2.2.1.2]. 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 [Ref. 5.3.5.3: 07X2GY].

1.3.2.2 Safety-Effect on QTc Interval

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) following a single dose of 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].

1.4 Overview of In Vitro Human Biomaterial Studies

An extensive nonclinical evaluation of the PK and metabolism of MOV and the nucleoside NHC, as well as the distribution and exposure of NHC-TP in tissues, was completed to support administration of MOV in clinical studies and to support the overall clinical pharmacology evaluation [Sec. 2.6.4: 1].

1.4.1 Plasma Protein Binding

NHC has low protein binding in vitro in human plasma, and in the presence of human alpha-1-acid glycoprotein and human serum albumin with an unbound fraction of approximately 1 in all matrices and at all concentrations tested (2 to 200 µM) [Sec. 2.6.4: 4]. The plasma protein binding of MOV was not assessed as MOV is not stable in plasma; however, plasma protein binding is expected to be very low.

1.4.2 In Vitro Metabolism

When incubated in human plasma and liver microsomes, MOV was relatively unstable with t1/2 of 1 and 1.2 hours, respectively [Sec. 2.6.4: 5.2]. In contrast, NHC was relatively stable in human plasma and liver microsomes with t1/2 of 10 and >24 hours, respectively [Sec. 2.6.4: 5.2]. In vitro, MOV is a substrate of the broadly distributed CES1 and CES2 carboxylesterases [Sec. 2.6.4: 7.1] which, given their expression in the intestine and liver, are likely involved in the typically complete presystemic conversion of MOV to NHC during absorption and/or first pass. NHC and NHC-TP were formed in all human cell lines tested with MOV in vitro [Sec. 2.6.4: 5.2]. NHC was also the major early metabolite formed from MOV in vitro in human hepatocytes, along with cytidine, uridine, and/or their phosphorylated anabolites [Sec. 2.6.4: 5.2]. In vitro, cytidine deaminase converts NHC to uridine, while mARC1 and mARC2 convert NHC to cytidine [Sec. 2.6.4: 7.1]. Each of these widely distributed cellular proteins likely play a role in the conversion of MOV-related drug material to endogenous anabolites of the pyrimidine pathway in vivo.

1.4.3 In Vitro Inhibition and Induction of Human Cytochromes P450 and Other Relevant Enzymes

MOV and NHC had IC50 values >1000 µM for CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 enzyme activity when evaluated in vitro [Sec. 2.6.4: 7.2]. Neither MOV nor NHC demonstrated time-dependent inhibition of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 enzyme activity when evaluated in vitro at concentrations of 10 and 50 µM [Sec. 2.6.4: 7.2].

At concentrations up to and including the highest concentration tested, neither MOV (50 µM) nor NHC (20 µM) produced an induction response in CYP1A2, 2B6, and 3A4 mRNA or enzyme activity in cultured cryopreserved human hepatocytes from 3 human donors. [Sec. 2.6.4: 7.2]. The maximum concentration (GM) of NHC in participants with COVID-19 was 10 µM [Ref. 5.3.5.3: 07ZRF9]. These data indicate both MOV and NHC are unlikely to cause DDIs due to the inhibition or induction of CYPs.

1.4.4 In Vitro Permeability and Transporter Studies

In vitro studies conducted with LLC-PK1 cell monolayers showed that MOV and NHC had low passive permeability (2.7×10^{-6} cm/s and 2.9×10^{-6} cm/s) [Sec. 2.6.4: 3]. Due to the potential for intracellular metabolism of both MOV and NHC during these assays, the in vitro assessment of permeability may be an underestimation.

MOV and NHC were evaluated as substrates of a series of human nucleoside transporters, BCRP and MDR1 P-gp in vitro [Sec. 2.6.4: 7.2]. MOV was a comparatively weak substrate of human CNT1 and was not a substrate of CNT2, CNT3, ENT1 or ENT2. In contrast, NHC was a substrate of CNT1, CNT2, CNT3 and ENT2, and it could not be excluded as a substrate of ENT1. Based on the high transport capacity and functional redundancy of nucleoside transporters, coupled with the lack of evidence of CNT- or ENT-mediated DDIs reported in the literature, clinically meaningful DDIs mediated by these transporters are not anticipated [Ref. 5.4: 05R0PD, 05R0PT, 05R0PK]. Neither MOV nor NHC were substrates of human MDR1 P-gp or BCRP.

The potential for MOV or NHC to inhibit human transporters was evaluated in vitro [Sec. 2.6.4: 7.2]. MOV and NHC did not inhibit OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2K, and MRP2 with IC50 values greater than the highest concentration tested of 100 µM, and they did not inhibit MDR1 P-gp and BCRP with IC50 values greater than the highest concentration tested of 1000 µM. Taken together, the overall risk for MOV and NHC to be a perpetrator of transporter-mediated DDIs is low.

1.5 Overview of Comparability Bounds Defining a Clinically Important Change in Pharmacokinetics

The proposed dose of MOV is 800 mg administered orally Q12H for 5 days, with or without food. The selected dose is based on a benefit-risk assessment, which is supported by efficacy and safety data from individual studies and integrated analyses.

The rationale and data that support the recommended dose for MOV are discussed in [Sec. 2.7.3-covid19txallpop: 4] as well as in this section. In this section, the basis for the choice of 800 mg Q12H for the Phase 3 dose is discussed first, followed by the totality of evidence in support of 800 mg Q12H (including from the Phase 3 study, P002 Part 2) for the proposed marketed dose.

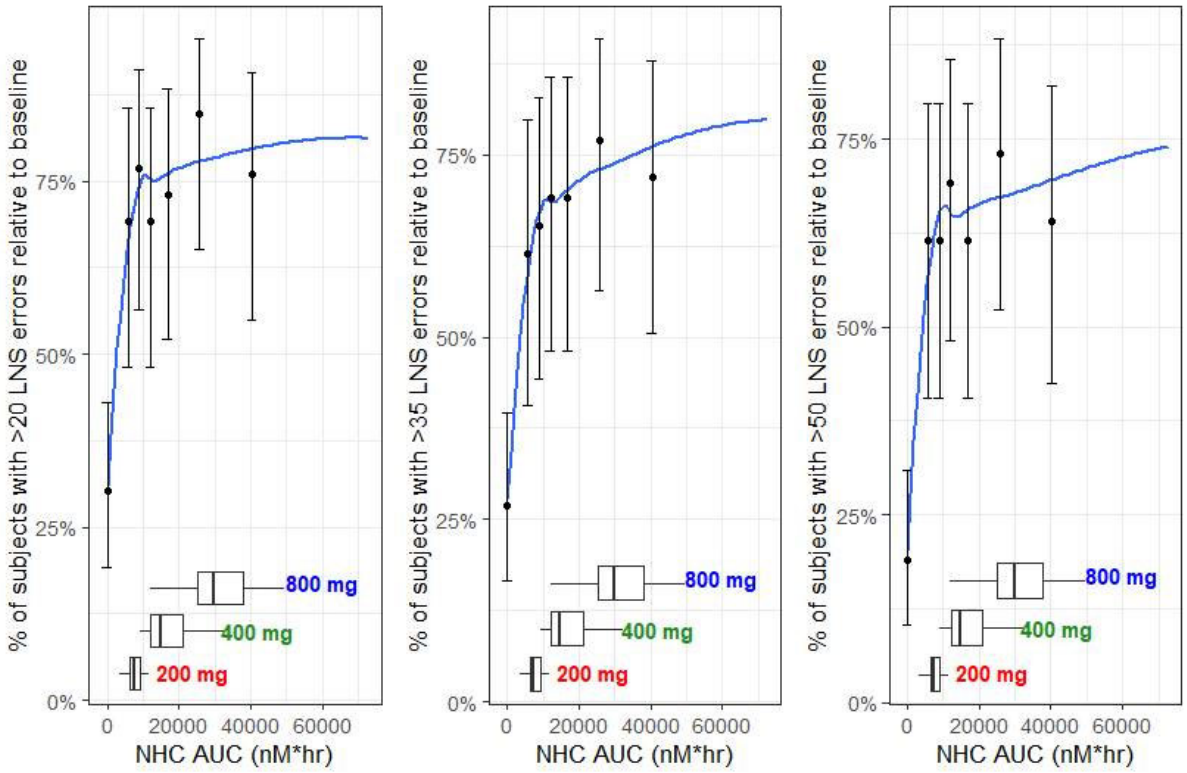
1.5.1 Dose Selection for Phase 3

The Phase 3 dose, 800 mg Q12H for 5 days, was chosen at the time of the Phase 2 interim analysis based on: the virologic data from P001, P002 and P006; trends in the clinical efficacy in P002 Part 1; safety data from all clinical studies (P004, P001, P002, and P006); and E-R modeling. E-R results from the Phase 2 studies [Sec. 2.7.2-covid19txallpop: 2.5.3.1] for viral load and NGS error rate showed that the highest dose evaluated (800 mg) provides a larger drug effect than lower doses (200 mg and 400 mg).

Analysis of the SARS-CoV-2 LNS error rate (a marker consistent with MOV's mechanism of action of viral error catastrophe) in P001 and P002 identified a highly significant E-R relationship [Figure 2.7.2-covid19txallpop: 1]. The thresholds shown in [Figure 2.7.2-covid19txallpop: 1] are in the range of an estimated 10 to 30 mutations per genome, which results in robust viral inhibition [Ref. 5.4: 05K8L0]. Simulations utilizing these E-R models indicate that 80% of participants receiving 800-mg MOV achieve the >20 mutations per genome threshold and 75% achieve the >35 threshold, suggestive of substantial reduction in infectivity. This was confirmed in the Phase 2a study (P006), where participants treated with MOV had lower percentages of positive viral cultures than participants receiving placebo. In P006, 16.7% (9/54) 18.2% (4/22), 11.6% (5/43), and 1.9% (1/53) of participants on Day 3 and 11.1% (6/54), 4.5% (1/22), 0.0% (0/42), and 0.0% (0/53) on Day 5 had positive viral cultures in the placebo, 200-, 400-, and 800-mg arms, respectively [Ref. 5.3.5.1: P006MK4482: Table 6]. While small numbers in this study precluded E-R analysis, the overall dose trend suggests 800 mg reduced infectivity faster, or to a greater extent, than the lower doses.

E-R relationships for SARS-CoV-2 viral load CFB at Days 5 and 10, and slope of viral load decline were all highly significant (p-values ≤0.005) for both evidence of drug effect and exposure-dependency [Ref. 5.3.5.3: 08074R]. In nonhospitalized patients with a TSSO ≤5 days, mean (95% CI) viral load reductions (measured in terms of log10 copies/mL) relative to placebo were -0.12 (-0.32, -0.02), -0.254 (-0.59, -0.039), and -0.46 (-1.06, -0.10) on Day 5 for the 200-, 400-, and 800-mg arms, respectively, based on the E-R model. In general, the MOV effect size at 800 mg is comparable to that previously seen with mAbs that have been shown to be effective and have been previously authorized for use for treatment of COVID-19 [Ref. 5.4: 05Q5RY, 05Q5X8] Finally, E-R analyses of the clinical efficacy data (Part 1 of P002) suggested a non-significant trend of reduced hospitalizations or death at higher doses. The similar size of 800-mg drug effect on viral load to authorized mAbs and the more rapid and substantial drop in infectivity with 800 mg both suggested this dose was likely to provide meaningful benefit to patients. On this basis, the 800-mg dose was chosen for study in Phase 3.

Figure 2.7.2-covid19txallpop: 1
Model-predicted probability of >20, >35 and >50 LNS errors relative to baseline in P001/P002



Note: The solid lines show the mean of the model-prediction. The vertical bars show the mean and 95% C.I. of the observed rates in placebo and MOV arms (binned by sextiles of AUC exposures when administered). For the exposure boxplots, the solid line within the box represents the median exposure at that dose. The lower and upper hinges represent the 25th and 75th percentiles, respectively. The whiskers extend to the most extreme values within 1.5 times the interquartile range.

AUC=area under the concentration-time curve; LNS= low frequency nucleotide substitutions; NHC=N-hydroxycytidine, EIDD-1931.

Source: [Ref. 5.3.5.3: 08074R]

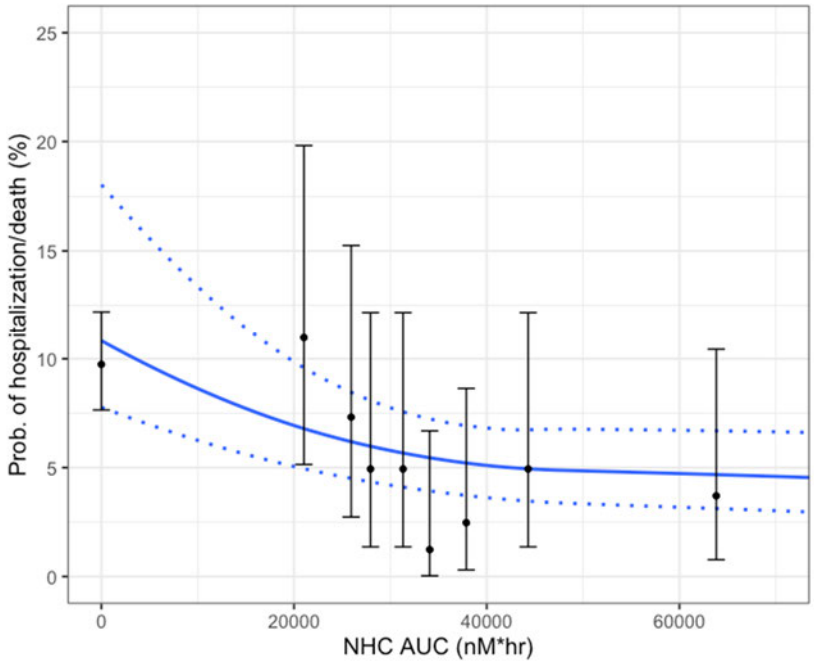
1.5.2 Dose Confirmation Including Phase 3 Data

Results from the PopPK and E-R analyses of the Phase 3 data supported the characterization of E-R for MOV and further informed the appropriateness of the 800-mg dose choice based on totality of evidence from exposure- and dose-response.

The primary clinical endpoint in Part 2 (Phase 3) of P002 of occurrence of hospitalization or death during the 29-day study period was evaluated for E-R [Ref. 5.3.5.3: 08074R]. As shown in [Figure 2.7.2-covid19txallpop: 2], the hospitalization rate (all deaths were preceded by hospitalization prior to death) observed in the lowest octile of AUC exposures was similar to the rate in placebo and the observed data are suggestive of exposure-dependency. However,

several risk factors (including obesity and diabetes) are more prevalent in the lower PK octiles, indicating a potential for confounding in the observed hospitalization rates. In development of the E-R models, careful accounting for the influence of risk factors and other covariates on hospitalization rates was conducted to accurately characterize potential exposure dependencies during the E-R model development. The logistic regression E-R relationship was best described by an Emax term with AUC50 of 19900 nM*hr, in a model which also included the effect of other baseline factors (age, cancer, diabetes, body weight, disease severity, viral clade [groups of viral strains which are similar based on their genetic sequence], baseline viral load) on the risk or hospitalization and/or death. The results are consistent with some exposure-dependency in the drug effect from 800 mg Q12H at exposures below ~ 30000 nM*hr, but support that even at the lowest exposures from Phase 3 there remains a drug effect of reduced event rate relative to PBO. This suggests that the comparable hospitalization rate observed in the lowest PK octile and PBO arm is obtained due to both some reduction in drug effect, but also a contribution of the distribution of other influential factors in this octile.

Figure 2.7.2-covid19txallpop: 2
Probability of Hospitalization as a Function of MOV Exposure in Part 2 of P002



AUC=area under the concentration-time curve; CI=confidence interval; E-R=exposure-response; MOV=molnupiravir, MK-4482, EIDD-2801; NHC=N-hydroxycytidine, EIDD-1931; PK=pharmacokinetic(s); SE=standard error

The solid and dotted blue lines show the mean and 95% C.I of the model-predicted probabilities, respectively. The vertical bars show the mean and 95% C.I. of the observed hospitalization/death rates in placebo (n=683) and MOV 800 mg (n=630) arms (binned by octiles of AUC exposures when administered). This plot excludes data for 8 participants with outlying exposures (AUC>120000 nM*hr) The model predicted probabilities are averaged over all other covariates.

Source [Ref. 5.3.5.3: 07YDDS]

MOV was generally well-tolerated across the clinical program [Sec. 2.7.4-covid19txallpop: 7]. 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. No clinically meaningful hematological or liver function laboratory test result abnormalities were observed. Single doses of MOV up to 1600 mg were evaluated in Phase 1 studies with no dose-limiting safety findings [Sec. 2.7.4-covid19txallpop: 2.3]. The 800-mg Q12H dose has also been evaluated out to an extended duration of 10.5 days, without dose-limiting safety findings [Sec. 2.7.4-covid19txallpop: 2.3.2]. An E-R analysis was conducted wherein AE rates were compared across quartiles at the 800 mg dose using data from Parts 1 and 2 of P002 [Sec. 5.3.5.3.3-covid19txallpop: 1] and Part 2 of P002 only [Table 2.7.2-covid19txallpop: 2]. In both assessments, the AE rates in the highest quartile of AUC were similar to those seen in the second and third quartiles at the 800-mg dose level. Further, the rates of AEs and SAEs in the highest quartile of AUC were no higher than those rates which were observed in placebo participants [Ref. 5.3.5.1: P002V03MK4482: Table 12-1], indicating no evidence for worsening tolerability at the highest exposures. Higher incidence of AEs in the lowest quartile was observed, which was due to COVID-19/COVID-19 symptoms-based AEs. This finding is consistent with the reduced efficacy and higher prevalence of risk factors in the patients represented in the lowest quartile of exposures [Ref. 5.3.5.3: 07YDDS] [Sec. 5.3.5.3.3-covid19txallpop: 1].

Table 2.7.2-covid19txallpop: 2
Adverse Event Summary by MOV AUC Quartile During Treatment and 14-Day Follow-Up Period All Participants as Treated Population MK-4482-002 Part 2 Day 29 DBL

	MK-4482 800 mg							
	[10335, 27032)[b]		[27032, 32816)[b]		[32816, 40673)[b]		[40673, 210590][b]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	163		162		163		163	
with one or more adverse events	71	(43.6)	42	(25.9)	31	(19.0)	46	(28.2)
with no adverse event	92	(56.4)	120	(74.1)	132	(81.0)	117	(71.8)
with drug-related[a] adverse events	13	(8.0)	16	(9.9)	10	(6.1)	11	(6.7)
with non-serious adverse events	66	(40.5)	38	(23.5)	28	(17.2)	42	(25.8)
with serious adverse events	15	(9.2)	7	(4.3)	4	(2.5)	8	(4.9)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.6)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)
discontinued drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the drug.
[b]AUC bin: NHC plasma exposure (AUC12 at steady state, nmol*h/L) binned into 4 exposure quartiles for MK-4482 (Molnupiravir) treated participants.

AUC = area under the concentration-time curve, MOV = molnupiravir, DBL = database lock

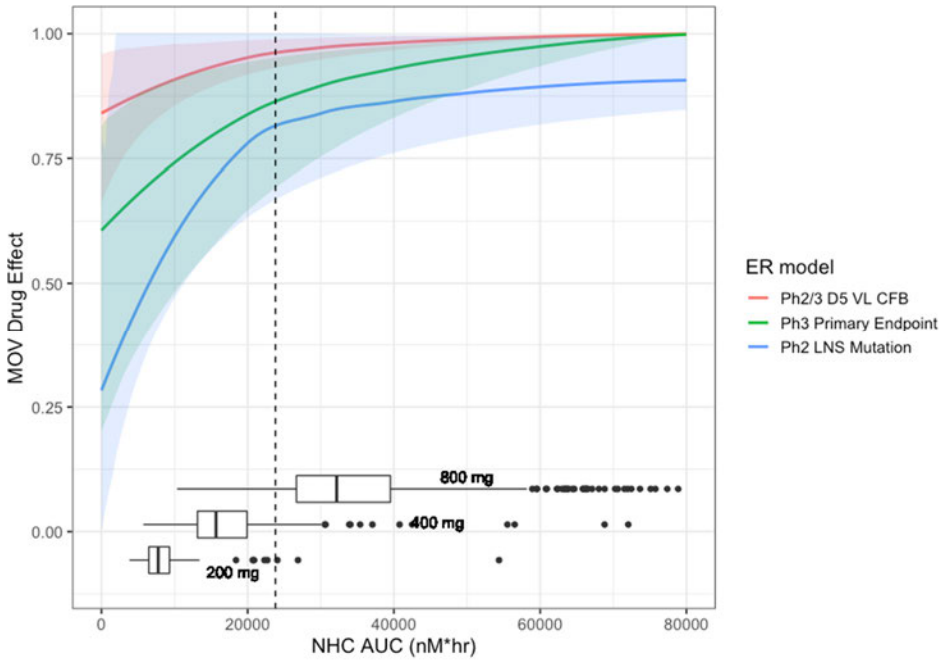
Source: [P002V03MK4482: adam-adsl; adae; adpp]

Confidential

E-R relationships for drug effect on SARS-CoV-2 viral load were assessed using pooled Phase 2 (P002 and P006, subset with TSSO ≤5 days) and Phase 3 data (P002 Part 2). The E-R relationship for viral load CFB on Day 5 is consistent with an Emax relationship with AUC50 of 10260 nM*hr, in a model which also included other influential factors (baseline viral load and disease severity on E0 and diabetes on Emax). The model-simulated dose-response relationship for the virology endpoint of Day 5 viral load change from baseline indicates an initial steep increase in viral load drug effect (relative to placebo) up to 400-mg dose, and then it appears to plateau at 800 mg with little benefit gained at higher doses. The predicted viral load CFB (relative to placebo) at 800 mg is ~ 0.35 log 10.

Overall, the E-R data confirm the choice of the 800-mg dose for the treatment of mild or moderate COVID-19 with MOV. Importantly, the 800-mg dose of MOV was shown to reduce the incidence of hospitalization or death in a Phase 3 study of nonhospitalized participants with mild or moderate COVID-19, compared to placebo. The 800-mg dose of MOV demonstrates effects across several virology endpoints, including a reduction in viral load on Day 5 and a reduction in infectious viral titer relative to placebo. The E-R results support a consistent interpretation of dose- and exposure-dependency for MOV across clinical outcome and pharmacodynamic markers as illustrated in [Figure 2.7.2-covid19txallpop: 3], with exposures at 800 mg falling near the top of the E-R curves. The exposure distributions of the 200- or 400-mg doses fall on the exposure-dependent portions of the E-R curves and, therefore, can be expected to be associated with reduced drug effects relative to 800 mg, supporting the choice of 800 mg over lower doses. All E-R models suggest that gains above 800 mg would be small with the steepest portions of the exposure- or dose-dependency falling at exposures obtained at doses <800 mg. The viral load E-R and LNS error models indicate that maximal response is essentially obtained at 800 mg, while the hospitalization E-R model suggests that small gains in drug benefit may be seen if doses are increased over 800 mg. However, the available results suggest that additional clinical benefit from increased doses above 800 mg would at best be modest in magnitude and overall the results support the appropriateness of the 800-mg dose choice for MOV.

Figure 2.7.2-covid19txallpop: 3
Normalized Emax E-R Relationships Established for Day 5 Viral Load CFB (Phase 2 and Phase 3), Hospitalization or Death (Phase 3), and LNS Error count (Phase 2) Compared to AUC Distribution at 200, 400, and 800 mg Q12H from PopPK Results



Top curve: Ph2/3 D5 VL CFB

Middle curve: Ph3 Primary Endpoint

Lower curve: Ph2 LNS Mutation

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

Y-axis is a relative scale (0 to 1) and reflects the predicted drug effect relative to the model estimated Emax value for each E-R model. Three different efficacy responses were simulated for a range of exposures using their corresponding E-R models. The efficacy was normalized to a [0, 1] scale using a min-max normalization method where the corresponding emax value is considered as maximum efficacy. The red, green, and blue lines and shaded regions show the mean and 90% C.I. of the drug effect for various efficacy measures. The shaded uncertainty bands are created by accounting for the uncertainty in the drug effect model parameter estimates (Emax and EC50). The dashed vertical line represents the AUC value (23800 nM*hr) that corresponds to the 0.7 lower clinical bound. All other covariates were fixed to the mean values for continuous covariates and to the most prevalent category for the categorical covariates. The solid line within the box represents the median. The lower and upper hinges represent the 25th and 75th percentiles, respectively. The whiskers extend to the most extreme values within 1.5 times the interquartile range.

Source: [Ref. 5.3.5.3: 07YDDS]

1.5.3 Rationale for Comparability Bounds

The term 'comparability bounds' refers to a range of plasma NHC exposures, relative to typical MOV 800-mg Q12H exposure, that have been demonstrated to have clinical comparability with respect to the efficacy and safety of MOV. When changes in the GM exposure of MOV for a subpopulation (defined by intrinsic or extrinsic factors) fall within these prespecified comparability bounds, safety and efficacy in that subpopulation are expected to be comparable to that of the standard clinical dose of MOV in the overall population.

The totality of data support plasma NHC AUC exposures as the primary PK measure from which to judge the clinical relevance of PK effects on both efficacy and safety. The E-R results strongly support plasma NHC AUC0-12 as the preferred PK parameter for driving efficacy response [Ref. 5.3.5.3: 08074R, 07YDDS]. Statistically significant exposure-dependency with AUC became less significant or non-significant when trough concentration (C12) was used instead as the exposure parameter in the models when tested. The active moiety (NHC-TP) in tissue cells, as reflected in data from PBMCs, has a longer effective t1/2 compared to plasma NHC and accumulates with Q12H dosing such that the active levels at the site of action would be expected to reflect a cumulative process of cellular uptake and phosphorylation. As such, AUC as a cumulative measure of exposure is consistent with that mechanism. Additionally, the mechanism of action of introducing errors into the viral RNA is also a cumulative process of accumulation of substitutions which render the new virus produced to be noninfectious [Ref. 5.4: 06G338]. Phase 1 PK data from P012 (10-day dosing) and P008 (with Japanese participants), during which full NHC-TP profiles in PBMCs were obtained, is consistent with this interpretation [Sec. 2.7.2-covid19txallpop: 2.1.2, 2.2.1]. Plasma NHC AUC was a stronger predictor of PBMC NHC-TP exposures than plasma NHC Ctrough values [Sec. 2.7.2-covid19txallpop: 2.5.1].

Comparability bounds (0.7 to 2.0) for MOV based on NHC AUC are proposed based on the totality of the E-R results. The lower bound of 0.7 corresponds to plasma NHC AUC0-12 of approximately 23,800 nM*hr (that is, 70% of the GM of model-predicted AUC0-12 for patients with COVID-19). This represents the lower threshold for which subpopulations can be expected to derive meaningful clinical benefit from dosing with 800 mg Q12H without the need for dose adjustment. This bound would maintain subpopulation exposures above the AUC50 from the hospitalization E-R model, thus maintaining drug benefit. As discussed earlier in this section, the increased observed hospitalization rate in the lowest AUC octile is likely due to increased prevalence of other risk factors, as well as some reduction in drug effect. The median (95% CI) exposure observed in the lowest AUC octile was 21020 (15650, 23780) nM*hr. A lower comparability bound of 0.7 (23,800 nM*hr) would ensure that subpopulations maintain exposures which are above this lowest exposure octile. The upper bound of 2.0 corresponds to plasma NHC AUC0-12 of approximately 68,000 nM*hr (that is, 2 times the GM of model-predicted AUC0-12 for patients with COVID-19 at 800 mg). This ensures that subpopulations are maintained within the range of clinical experience at 800 mg, as 48 participants have achieved plasma NHC AUC0-12 greater than this threshold in the MOV clinical studies without notable alteration in the safety and tolerability profile seen in subgroup analyses of higher exposures [Ref. 5.3.5.3: 07ZRF9].

2 SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

This section briefly summarizes the study designs and key results of the clinical pharmacology studies. The Phase 1 program (P004, P008, and P012) evaluated the PK of MOV, NHC and NHC-TP in healthy adult male and female participants [Sec. 2.7.2-covid19txallpop: 2.1, 2.2]. The PK of MOV, NHC, and NHC-TP were also evaluated in 1 intrinsic factor study in healthy male Japanese participants (P008) [Sec. 2.7.2-covid19txallpop: 2.2]. No other dedicated intrinsic factor studies were conducted due to the lack of anticipated effect of hepatic or renal impairment.

No dedicated extrinsic factor studies were conducted in the clinical pharmacology program due to the lack of anticipated DDI potential for MOV [Sec. 2.7.2-covid19txallpop: 2.3]. Additionally, no dedicated pharmacodynamic or other safety endpoint studies were conducted [Sec. 2.7.2-covid19txallpop: 2.4]; however, antiviral activity in participants with COVID-19 was evaluated in Phase 2 and Phase 3 studies and is reported [Sec. 2.7.3-covid19txallpop: 2]. An NHC concentration/QTc analysis was also conducted using ECG Holter data collected in the initial safety, tolerability and PK study (P004) [Sec. 2.7.2-covid19txallpop: 2.4.1].

A tabular summary of clinical pharmacology studies in the development of MOV is provided in [Appendix 2.7.2-covid19txallpop: 1]. A tabular summary of PK parameter values from the clinical pharmacology studies is presented in [Appendix 2.7.1: 1] and [Appendix 2.7.2-covid19txallpop: 2]. The conclusions and interpretations of the individual study data are provided collectively in the cross-study comparison in [Sec. 2.7.2-covid19txallpop: 3] rather than in the summaries of each individual study to reflect conclusions based on integrated data from relevant studies.

2.1 Healthy Participant Pharmacokinetics and Initial Tolerability Studies

2.1.1 A Randomized, Double-blind, Placebo-controlled, First-in-human Study Designed to Evaluate the Safety, Tolerability, and Pharmacokinetics of MOV Following Oral Administration to Healthy Volunteers (P004)

This was a 3-part, randomized, double-blind, placebo-controlled single- and multiple-ascending dose study with an open-label, food effect assessment in 130 healthy participants (100 receiving at least 1 dose of MOV, 30 receiving at least 1 dose of placebo) [Ref. 5.3.3.1: P004MK4482: 2].

In Part 1, single doses of MOV up to 1600 mg (50 to 800 mg administered as PIB solution and 1200 mg and 1600 mg as a DFC) or matching placebo (n=8, 3:1 ratio in each panel) were administered. In Part 2, single doses of 200-mg MOV with and without a high-fat meal were administered as a DFC (n=10, 1:1 fasted/fed:fed/fasted). In Part 3, 11 dose administrations given Q12H of MOV from 50 to 800 mg or matching placebo (n=8, 3:1 ratio in each panel) over a duration of 5.5 days (last dose administered in the morning of Day 6) were administered as a DFC. Blood and urine samples for plasma and urine MOV and NHC were collected.

RESULTS:

Part 1: Plasma NHC PK parameter values following single doses of MOV 50 to 800 mg (PIB) and plasma NHC PK parameter values following single doses of MOV 1200 and 1600 mg (DFC) are summarized in [Appendix 2.7.2-covid19txallpop: 2]. The following key results were observed:

- MOV was generally only detected in the plasma at levels near the LLOQ and only around Tmax.
- Median NHC Tmax was 1.00 hour for doses up to 800 mg (PIB) and 1.75 and 1.50 hours for the 1200-mg and 1600-mg doses (DFC), respectively.
- NHC concentrations declined in an essentially monophasic manner in most participants with a t1/2 of approximately 1 hour. In some participants at higher doses, a second terminal phase was apparent, although data were inadequate to reliably estimate the t1/2.
- Increases in NHC AUC0-inf and Cmax were approximately dose proportional across the range of doses evaluated.
- MOV was detected in urine at doses ≥800 mg at approximately 0.002% of the dose administered; the fraction of the dose excreted in urine as NHC over 24 h following the 800-mg dose was 2.86%.

Part 2: Plasma NHC PK parameter values following single doses of MOV 200 mg (DFC) in both the fasted and fed states are summarized in [Appendix 2.7.2-covid19txallpop: 2]. MOV was generally not detected in plasma following dosing with or without food. Dosing following a high-fat meal did not meaningfully affect AUC0-inf but delayed Tmax by 2 hours and reduced geometric mean Cmax by 35.6% relative to fasted administration.

Part 3: Plasma NHC PK parameter values following multiple Q12H doses of MOV 50 and 800 mg (DFC) for 5.5 days are summarized in [Appendix 2.7.2-covid19txallpop: 2]. The following key results were observed:

- MOV was generally not detected in the plasma. MOV Cmax on Day 6 was 8.52 ng/mL (or 0.026 µM, based on a molecular weight of 329.3 g/mol) following administration of 800 mg Q12H. This is <0.5% of the NHC Cmax.
- No accumulation of NHC was observed.
- NHC concentrations declined in a bi-exponential manner. The t1/2 of the alpha-phase was ~ 1 hour; the t1/2 of the terminal phase (only observed at higher doses following multiple doses) was up to approximately 19 hours.
- NHC AUC0-12 and Cmax were approximately dose proportional across the range of doses tested.

Further discussion and interpretation of study results can be found in [Sec. 2.7.2-covid19txallpop: 3.1.1].

2.1.2 A Multiple Ascending Dose Clinical Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MOV in Healthy Participants (P012)

This was a randomized, placebo-controlled, multiple-ascending dose, double-blind study of MOV in 32 healthy participants (24 receiving MOV, 8 receiving placebo) [Ref. 5.3.3.1: P012MK4482: 2].

MOV (400, 600 or 800 mg) or matching placebo (n=8, 3:1 ratio in each panel) was given Q12H over a duration of 10.5 days (last dose in the morning of Day 11) in 3 sequential ascending-dose panels (Panels A to C). A fourth panel (Panel D) was additionally conducted at a dose of 800-mg MOV or matching placebo administered Q12H for 10.5 days, effectively expanding the number of participants receiving 800 mg. Blood samples for plasma NHC and PBMC NHC-TP were collected predose and at select timepoints postdose up to 24 hours (PBMC) or 72 hours (plasma) following the last dose on Day 11.

RESULTS:

Plasma NHC and PBMC NHC-TP PK parameter values following multiple Q12H doses of MOV 400 to 800 mg (DFC) for 10.5 days in healthy participants are summarized in [Appendix 2.7.2-covid19txallpop: 2]. The following key results were observed:

NHC in Plasma

- Following multiple-dose administration of MOV, plasma NHC concentrations appeared rapidly in plasma, with a median Tmax ranging from 1.50 to 1.98 hours.

- NHC concentrations were detectable up to 72 hours (the last measured plasma concentration) following the last dose on Day 11. Biphasic elimination of NHC was apparent after the last dose, where it exhibited a rapid distributional phase followed by an extended terminal elimination phase. The GM terminal t1/2 on Day 11 ranged from 16.41 to 20.65 hours.

- Minimal to no accumulation of NHC exposure, in terms of AUC0-12 and Cmax, was observed.

- AUC0-12 and Cmax increased in a dose-proportional fashion over the dose range studied.

NHC-TP in PBMCs

- NHC-TP concentrations measured in PBMCs were detectable at the first measured timepoint, 4 hours, with a median Tmax ranging from 4.00 to 8.06 hours.

- NHC-TP concentrations were detectable up to 24 hours (the last measured PBMC concentration) following the last dose on Day 11. The GM terminal elimination t1/2 was 13.60 to 18.04 hours.

- The LSM accumulation ratio of AUC0-12 and Cmax ranged from 2.10 to 2.65 and 1.92 to 2.49, respectively.

- AUC0-12 and Cmax increased in a less than dose-proportional fashion over the dose range studied.

- Overall exposures, in terms of AUC0-12 of NHC-TP in PBMCs, correlated well with NHC exposure in plasma.

Further discussion and interpretation of study results can be found in [Sec. 2.7.2-covid19txallpop: 3.1.1].

2.2 Intrinsic Factor Studies

2.2.1 A Single and Multiple Dose Clinical Study to Evaluate the Safety, Tolerability and Pharmacokinetics of MOV in Healthy Japanese Adult Participants (P008)

This was a 2-part, randomized, placebo-controlled, double-blind study in 65 healthy Japanese males (51 receiving at least 1 dose of MOV; 18 receiving at least 1 dose of placebo) [Ref. 5.3.3.3: P008MK4482: 2].

In Part 1, participants received single oral doses of MOV (200, 400, 800 [with and without food] and 1600 mg) or placebo (n=8 per panel, 3:1 ratio) as a DFC in each panel. In Part 2, 11 dose administrations given Q12H of 400 mg (Panel E) or 800 mg (Panel F) MOV or matching placebo (n=8, 3:1 ratio in each panel) over a duration of 5.5 days (last dose administered in the morning of Day 6) were administered as a DFC. Blood samples for assessment of plasma NHC and PBMC NHC-TP concentrations were collected.

RESULTS:

Plasma NHC PK parameter values following single doses of MOV 200 to 1600 mg (DFC) fasted and 800 mg with a high-fat meal and multiple Q12H dosing of MOV 400 and 800 mg (DFC) for 5.5 days in healthy Japanese males are summarized in [Appendix 2.7.2-covid19txallpop: 2]. The following key results were observed:

<u>NHC in Plasma</u>

- Median Tmax of NHC following administration of MOV in the fasted state was between 1.00 and 2.00 hours.

- NHC concentrations declined in an approximately bi-exponential manner following Tmax, with a shorter distribution phase followed by a longer terminal phase. The terminal phase was not apparent for all participants due to the LLOQ of the assay, which is reflected in the terminal t1/2 estimates. The GM terminal t1/2 was 11.5 hours and 10.2 hours after the last dose of 400 mg and 800 mg Q12H, respectively.

- AUC0-inf for NHC increased in a slightly greater than dose proportional manner with the slope estimate (95% CI) of 1.152 (1.092, 1.213). This may be due to inadequately capturing the terminal phase at the lowest dose of 200 mg. Cmax increased in a slightly less than dose proportional manner with the slope estimate (95% CI) of 0.866 (0.755, 0.978).

- Administration of MOV in the fed state delayed median Tmax for NHC by 1.50 hours and reduced Cmax by 24% when compared to administration in the fasted state. However, AUC0-inf was comparable, which indicates that the rate, but not the extent, of absorption is slightly lower in the fed state.

- No meaningful accumulation of NHC was observed following administration of multiple oral doses of MOV Q12H for 5.5 days.

- Exposures from Japanese participants in P008 were similar to those in non-Japanese participants with similar weight.

NHC-TP in PBMCs

- Following single oral dose administration of MOV DFC in the fasted state to healthy Japanese males, NHC-TP PBMC concentrations reached Cmax with a median Tmax between 3.00 and 8.00 hours, and NHC-TP was eliminated with a GM apparent terminal t1/2 of 13.1 to 17.9 hours.

- AUC and Cmax for NHC-TP in PBMC generally increased with increasing dose following single-oral dose administration of MOV 200 to 1600 mg in the fasted state.

- The GM and corresponding 90% CI for accumulation ratio (Day 6/Day 1) at 800 mg was 2.65 (2.31, 3.03) and 2.42 (1.93, 3.02) for AUC0-12 and Cmax, respectively, consistent with t1/2 of NHC-TP and Q12H dosing.

For discussion and interpretation of results refer to [Sec. 2.7.2-covid19txallpop: 3.1.1].

2.3 Extrinsic Factor Studies

No extrinsic factor clinical studies have been conducted due to lack of anticipated DDIs [Sec. 2.7.2-covid19txallpop: 3.3.1].

2.4 Pharmacodynamic and Other Safety Endpoint Studies

No dedicated pharmacodynamic or other safety endpoint studies were conducted. A concentration-QTc assessment was conducted using 12-lead Holter ECG data collected in the initial safety, tolerability and PK study (P004) to evaluate the relationship of plasma NHC concentration and QTcF [Sec. 2.7.2-covid19txallpop: 2.4.1]. Therefore, no dedicated TQT study was conducted.

2.4.1 Effect of MOV and NHC on QT/QTc

2.4.1.1 Concentration-QT Analysis of Data Collected in P004 (A Randomized, Double-blind, Placebo-controlled, First-in-human Study Designed to Evaluate the Safety, Tolerability, and Pharmacokinetics of MOV Following Oral Administration to Healthy Volunteers)

Analysis of C-QTc was conducted using ECG Holter data collected in P004 up to a dose of 1600-mg MOV (for study design see [Sec. 2.7.2-covid19txallpop: 2.1.1]). Data from 60 participants were pooled from Part 1 and Part 3 of the study for the C-QTc analysis. No relationship was found between increases in NHC plasma concentrations and changes in QTcF [Ref. 5.3.5.3: 06G3K2]. The following are key results from this analysis:

- QTcF was found to be generally not dependent on HR.
- The slope indicating the strength of relationship between QTcF change from baseline and NHC plasma concentration obtained from the analysis was very close to zero and not statistically significant (estimate [90% CI] = -0.00005 [-0.00058, 0.00049], p>0.892) suggesting that NHC plasma concentrations up to that obtained at 1600 mg are not associated with an increased risk of QT prolongation.
- The predicted mean ΔΔQTcF and corresponding 90% CI at Cmax (6347 ng/mL) for the highest dose (1600 mg) are -0.565 (-4.785, 3.655) with the 90% CI falling below 10 msec, the threshold of regulatory concern according to ICH E14.
- Categorical analysis of other ECG parameters generally indicated no effect of NHC on HR, PR or QRS intervals. No treatment-related changes were seen in U-wave and T-wave morphologies.
- Overall, NHC did not prolong QTc at concentrations observed with MOV doses up to 1600 mg providing approximately a 2.14-fold Cmax margin to the 800-mg dose of MOV Q12H.

For discussion and interpretation of results refer to [Sec. 2.7.2-covid19txallpop: 3.4.3].

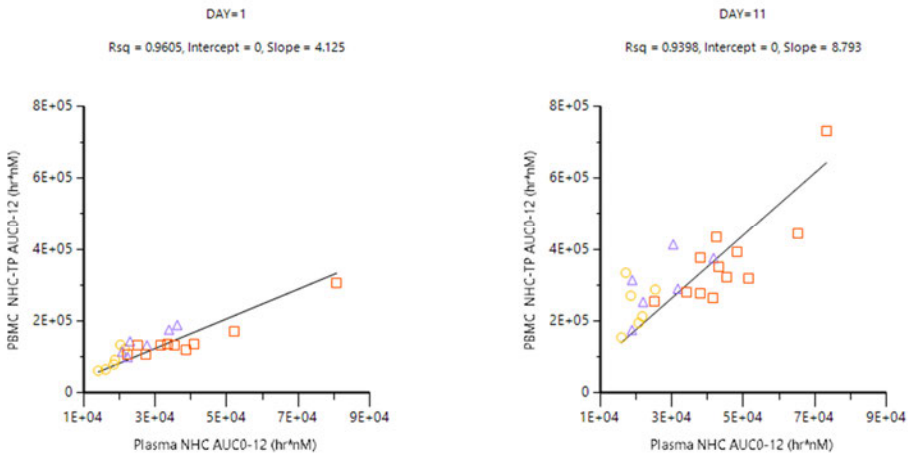
2.5 Summary of Data Analyses from More than One Study

2.5.1 NHC and NHC-TP Correlation Analysis

NHC widely distributes to tissues and is subsequently converted to the pharmacologically active triphosphate form (NHC-TP). In order to evaluate the PK of NHC-TP, PBMCs were collected in 3 Phase 1 studies (P004, P008, and P012) in healthy participants and from a small subset of COVID-19 participants in a Phase 2 (P001) and a Phase 2/3 (P002) study. The NHC-TP concentrations obtained from healthy participants in P004 were not considered reliable due to a sample stability issue that was later addressed by a change in sample handling procedures. Sampling of PBMCs for quantification of NHC-TP in P001 and P002 was sparse and therefore overall exposures (ie, Cmax and AUC) could not be calculated. Therefore, correlation of NHC-TP exposures in PBMC with NHC exposures in plasma included data from P008 [Sec. 2.7.2-covid19txallpop: 2.2.1] and P012 [Sec. 2.7.2-covid19txallpop: 2.1.2] only.

The objectives of this analysis were to: (1) evaluate whether NHC PK in the plasma is predictive of NHC-TP PK in PBMCs; and (2) determine which NHC PK parameter (AUC, Cmax, Ctrough) correlates best with NHC-TP exposures (AUC, Ctrough) in PBMCs. Overall, the AUC of NHC in the plasma was highly correlated with the AUC of NHC-TP in PBMCs [Ref. 5.3.5.3: 07ZL42]. The relationship between the AUC of NHC and NHC-TP from P012 is provided in [Figure 2.7.2-covid19txallpop: 4]. The AUC of NHC in the plasma was a strong and consistent predictor of NHC-TP exposures in PBMCs, based on the adjusted coefficient of determination. These findings support the use of plasma NHC AUC as the primary exposure measure in the Phase 2 and 3 E-R analyses. Additional detail is provided in [Ref. 5.3.5.3: 07ZL42].

Figure 2.7.2-covid19txallpop: 4
Individual AUC0-12 of NHC in Plasma vs NHC-TP in PBMC Following Administration of Multiple Ascending Oral Doses of 400-mg (Yellow Circles), 600-mg (Purple Triangles) and 800-mg (Red Squares) MOV Q12H for 10.5 Days to Healthy Participants (P012) (Left panel: Day 1; Right Panel: Day 11)



AUC0-12=area under the concentration-time curve from 0 to 12 hours; MOV=molnupiravir, MK-4482, EIDD-2801; NHC=N-hydroxycytidine, EIDD-1931; NHC-TP=N-hydroxycytidine triphosphate, EIDD-2061; P=protocol (number); PBMC=peripheral blood mononuclear cells; Q12H=once every 12 hours

n=6 (400-mg group), n=6 (600-mg group), n=12 (800-mg group)

Source: [Ref. 5.3.5.3: 07ZL42]

2.5.2 Population Pharmacokinetic Analyses

This section summarizes the PopPK analyses conducted to characterize the PK of NHC, explore the potential influence of intrinsic and extrinsic factors such as age, gender, weight, BMI, race, or concomitant medications on the PK of NHC, and provide individual exposure estimates to inform E-R analyses. Two PopPK analyses are provided in support of this submission. The End-of-Phase 2 PopPK model was developed based on Phase 1 and Phase 2 data and included a formal covariate analysis. This model was later updated and refined by expansion of the prior PopPK dataset to include data from all randomized participants in the Phase 3 study (P002 Part 2).

2.5.2.1 Population Pharmacokinetic Analysis – End of Phase 2

The objectives of this analysis were to: (1) develop a PopPK model for MOV using NHC plasma concentrations; (2) identify and quantify the effects of intrinsic and extrinsic factors; and (3) estimate individual exposures to be used for viral dynamics and E-R models. Details for this analysis are summarized in the modeling report [Ref. 5.3.5.3: 07ZXLB].

The data used in this analysis were collected in one Phase 1 study in healthy participants (P004), 1 Phase 2 study in nonhospitalized participants with COVID-19 (P006), and the

Phase 2 parts of 2 studies, one in hospitalized participants with COVID-19 (P001), and one in nonhospitalized participants with COVID-19 (P002). The PopPK dataset consisted of 100 healthy participants, 189 hospitalized participants with COVID-19, and 260 nonhospitalized participants with COVID-19.

The PK of NHC was described by a linear 2-compartment model with sigmoid absorption (implemented using a zero-order input process into a depot compartment followed by first-order absorption into the central compartment) and first-order elimination. Distinct residual variability models were implemented for healthy participants and participants with COVID-19. All model parameters were estimated precisely and without correlation. Predictive performance of the selected model was assessed by (prediction corrected) visual predictive checks, which showed the model captured to observed data generally well.

Covariate effects included in the final model as statistically significant predictors of the PK parameters were: a less-than-proportional power function of body weight on CL/F, a less-than-proportional power function of BMI on Vc/F, a 31.3% decrease in Vc/F in females compared to males, a 568% increase in the duration of the zero-order absorption process (D1) following a high-fat meal compared to fasting, a 64.4% decrease in D1 for oral solution (PIB) compared to DFC (administered orally either as a whole capsule or as capsule contents in a suspension), and a 26.5% decrease in D1 for hospitalized participants compared to healthy or nonhospitalized participants.

The impact of the covariate effects included in the final plasma NHC PK model was evaluated on the basis of distribution of exposure metrics (Ctrough, Cmax, and area under the NHC AUC0-12) predicted assuming a hypothetical 800-mg Q12H dosing regimen for 5 days. For all subgroups of age, body weight, BMI, sex, racial classification, ethnicity, patient hospitalization status, renal function, and hepatic function, the GMRs (relative to the reference subgroup for each intrinsic factor) of AUC0-12 were within the 0.8 to 1.25 bioequivalency range, except for BMI ≥40 kg/m^2, where the GMR fell just below this range.

2.5.2.2 Population Pharmacokinetic Analysis for Phase 3

The objectives of this analysis were to: (1) apply the previously developed PK model for NHC plasma concentrations to the pooled analysis dataset including the data collected in the Phase 3 portion of P002: and (2) quantify the effects of intrinsic and extrinsic factors on model-predicted exposures. The Phase 3 model was used to estimate individual exposures for use in Phase 3 E-R modeling. Compared to the Phase 2 model, the pooled analysis dataset for Phase 3 contained 7 additional hospitalized participants with COVID-19 from P001 and 651 additional nonhospitalized participants with COVID-19 from the Phase 3 portion (Part 2) of P002 (all receiving 800-mg MOV). Details for this analysis are summarized in the modeling report [Ref. 5.3.5.3: 07ZRF9].

The selected PK model was obtained by refinement of the End-of-Phase 2 model discussed in the preceding section. The overall structure of the model remained the same; however, the absorption process was characterized using transit compartments in this updated model as opposed to sequential zero and first order transfer in the End-of-Phase 2 model. Both functions allow drug to be absorbed according to a prototypical ‘S’ shape function of time,

but the model based on transit compartments is generally more flexible and described absorption kinetics slightly better. The covariate effects selected in the End-of-Phase 2 model were assumed to apply to the dataset used in this analysis and carried forward to this model. A univariate stepwise backward elimination analysis was run to test the statistical significance ($\alpha = 0.001$) of the covariate effects selected in the previous analysis. All covariate parameter relationships, except the shift in MTT for the hospitalized patients, were found to be statistically significant and, thus, remained in the model. The final model described the central tendency and variability of NHC plasma concentrations in participants with COVID-19 generally well.

Based upon a reference individual defined as a male participant with a 78-kg body weight and 28-kg/m^2 BMI, the typical population estimate of CL/F was 70.6 L/h. Typical estimates of volume of distribution for Vc/F of 63.9 L and Vp/F of 68.3 L were obtained. Assuming a 5-day course of MOV 800 mg Q12H, NHC concentration is predicted to peak at 11400 nM/L approximately 1.5 hours after the last dose, with half-lives associated with the first and second phase of disposition of approximately 0.6 hours (t1/2, α) and 16.5 hours (t1/2, β), respectively. Assuming that NHC was administered by IV bolus, the first[t] and second phase of disposition would typically account for 96% and 4% of the overall exposure, respectively.

In order to characterize the expected impact of intrinsic and extrinsic factors on MOV (NHC) plasma PK, simulations were performed based on the final NHC plasma PK model using covariate data from the participants included in the analysis dataset and their individual Bayesian estimates of PK parameters. Simulations assumed hypothetical 800-mg Q12H dosing for 5 days for all individuals in the analysis dataset. Forest plots of the GMRs and 90% CIs of exposure measures for covariates of interest were constructed to illustrate the relative differences in impact of various covariates. The resulting forest plot for AUC as well as discussion of results regarding the effect of specific factors effects on the PK of NHC are described in [Sec. 2.7.2-covid19txallpop: 3.2].

2.5.3 Exposure-Response Analyses

This section summarizes the analyses conducted to characterize E-R relationship between NHC and clinical endpoints, including viral load, infectivity, and hospitalization and/or death. Two E-R modeling reports are included with this submission: One is based on data available at the end of Phase 2 [Ref. 5.3.5.3: 08074R] and the second is based on Phase 3 data [Ref. 5.3.5.3: 07YDDS].

2.5.3.1 Exposure-Response Analyses from End-of-Phase 2

The E-R analysis was conducted using the virologic, mutation and efficacy data from 3 Phase 2 studies (P001 Part 1, P002 Part 1, P006). E-R models were developed for the virologic data from P001, P002 and P006. E-R analyses for the mutation endpoints utilized data from P001 and P002 only. Exploratory E-R analysis for the primary efficacy endpoint of hospitalization and/or death was conducted using only data from P002 Part 1. Full Phase 2 efficacy results are discussed in [Sec. 2.7.3-covid19txallpop: 2].

Details for the end of Phase 2 E-R analysis are provided in the modeling report [Ref. 5.3.5.3: 08074R]. A high-level summary and interpretation of results from this analysis with regards to MOV development decisions (including choice of dose for Phase 3) is provided in [Sec. 2.7.2-covid19txallpop: 1.5.1].

2.5.3.1.1 Exposure-Efficacy Analyses

Mutation Endpoints:

Characterization of the E-R relationship from the mutation data obtained from NGS to evaluate nucleotide changes in the viral RNA from NP samples from MOV-treated and placebo-treated participants was conducted to provide information on the exposure-dependency of the mechanism of action of MOV against SARS-CoV-2 in the clinical setting. Two different mutation E-R datasets were evaluated and separate E-R models developed, which differed in terms of which variants were counted based on differing cut-offs established for VAFs. The first E-R dataset and model, referred to as the TESNV, was based on the reported NGS data from 2 CSRs [Ref. 5.3.5.1: P001V01MK4482] [Ref. 5.3.5.1: P002V01MK4482], where the sequence variants provided for the mutation rate analyses were restricted to those with a VAF of ≥2%. It was later recognized that a VAF cutoff of ≥2% does not capture all minor variants present in the NGS datasets. Therefore, a separate analysis of the results of NGS data analyses, including all minor variants with a VAF between 0.4% and 10% (ie, including those with a VAF of <2%) was conducted and reported in [Ref. 5.3.5.3: 07W3MS] A second E-R model and dataset, referred to as the LNS, was created using the mutation data based on this updated VAF cut-off. This dataset will be referred to as the LNS dataset. Because MOV's MOA is expected to generate widely distributed substitutions in the viral RNA, the second dataset (LNS version) with lower VAF cutoff is expected to better reflect the full drug effect and, as such, this E-R model and dataset was considered the primary one for the E-R analyses.

The LNS error count increases over time, hence day since treatment initiation was included as a covariate in the model. There was a strong association between LNS error counts and viral load RNA levels, so viral load was also included as a covariate. Both sigmoidal and linear functional forms for E-R were tested with a sigmoidal E-R relationship (Emax model) selected as the final structural model with Day included as a covariate on Emax and viral load as a covariate on E0. EC50 was estimated to be 4387.7 nM*hr.

In addition to modeling the error counts, the LNS mutation data was categorized into a binary response (yes/no) using 3 different thresholds: >20, >35 and >50 errors/10000 nucleotides of SARS-CoV-2 RNA relative to baseline. Logistic E-R models were constructed to model the probability of achieving the thresholds. Both linear and Emax logistic regression models were tested with Emax versions selected as the final models. All 3 models show a significant drug effect, with the exposure effect plateauing at 800 mg.

The TESNV mutation data were evaluated as binary endpoints based on achievement of mutation rates defined by threshold of 3, 6, 9 mutations (per 10,000 bases relative to baseline) at any of the post baseline visits. Three separate E-R models were developed based on these thresholds. Both linear and Emax logistic regression model forms were evaluated.

Overall, results from this evaluation were consistent with the key interpretations from the LNS mutation E-R analysis.

Virology Endpoints

The virology E-R dataset was composed of pooled data from P001, P002 (Phase 2 portion only), and P006 [Ref. 5.3.5.3: 08074R]. Longitudinal SARS-CoV-2 RNA viral load data included in this dataset included observed values as measured by quantitative or qualitative PCR at baseline, Day 3, Day 5 (EOT), Day 10, Day 15, and Day 29 from NP and OP swabs. Additionally, the following derived viral load endpoints were included:

1. Change from baseline at EOT (Day 5), Day 10, 15, 29 from quantitative PCR data for NP and OP swabs

2. Decline slope from baseline to EOT (taking Day 3 measure into calculation) from quantitative PCR data for NP and OP swabs

3. Percentage of participants BLOQ at EOT, Day 10, 15, 29 from qualitative PCR data for NP and OP swabs

The Phase 2 virology E-R dataset comprised 292, 299 and 202 participants from P001, P002 and P006, respectively, who were randomized and treated and had at least 1 viral load record.

A strong influence of baseline viral load on CFB and viral load decline slope from Day 1 to Day 5 was identified during data exploration and baseline viral load was included as a covariate in all models. Exploration of the influence of TSSO on the CFB viral load profiles suggested that drug effect and dose response is stronger in the shorter TSSO subpopulation. No analyses beyond these data explorations were made with the OP data as the NP data appeared to have a clearer effect signal to allow for modeling and the OP data trends, when apparent, did not appear to be different than that suggested by NP data.

The final E-R models (for CFB on Day 5, 10 and viral load decline slope) were based on data from the nonhospitalized studies only (P002 and P006), where a significant exposure dependency was identified for NHC AUC. The TSSO ≤5 days subpopulation demonstrated a greater effect of exposure on response, and a lack of exposure effect was found in the subgroup of participants with TSSO >5 days. The data from placebo to exposures from 800 mg were well represented by a linear E-R relationship and an Emax E-R relationship could not be estimated, indicating limited evidence supporting a saturating effect.

To identify the PK driver, E-R model development was also conducted with NHC Ctrough as the exposure metric and no significant E-R relationships were identified in any model run, which supported the use of AUC as the PK driver.

The potential for E-R in the proportion of BLQ participants at Days 5, 10, 15 and 29 were explored, but no significant E-R relationships were identified for this endpoint.

Clinical Endpoint Data

The primary endpoint in P002, hospitalization or death, was evaluated for E-R in the Phase 2 portion only. The results should be interpreted with caution given the small sample size and number of events but suggest a potential drug and dose effect and the importance of early treatment on the clinical outcome of hospitalization. For participants who had a TSSO of ≤5 days, nonsignificant trends were observed in the dose- and E-R relationships for the endpoint of hospitalization, suggesting that the MOV 800-mg Q12H dose provides an increased clinical effect over lower MOV doses. The E-R analyses included only participants with available PK data. Three participants in the 400-/800-mg groups were hospitalized before completing the 5-day course of treatment. These participants only received between 1 to 3 doses of study drug before hospitalization and therefore had no PK samples collected [Ref. 5.3.5.3: 08074R].

The final model was parametrized as a linear logistic model with the hospitalization rates were modeled as a binary response (hospitalized vs not) with NHC AUC as the exposure predictor. A nonsignificant E-R trend (p=0.0932) towards a reduction of hospitalization/deaths through Day 29 was found with increasing exposure in the subset defined by TSSO ≤5 days [Ref. 5.3.5.3: 08074R].

2.5.3.2 Exposure-Response Analyses for Phase 3

E-R modeling of Phase 2 and Phase 3 data in participants with mild or moderate COVID-19 from P002 (Parts 1 and 2) and P006 was conducted to support the proposed market dose [Sec. 2.7.2-covid19txallpop: 1.3.1] and define the clinical comparability bounds for dose justification [Sec. 2.7.2-covid19txallpop: 1.5]. This section provides a summary of E-R analyses that were conducted between NHC PK and efficacy and safety endpoints. Additional details are provided in the Phase 3 E-R report [Ref. 5.3.5.3: 07YDDS].

2.5.3.2.1 Exposure-Efficacy Analyses

Exposure-Response for Clinical Endpoints

The analysis dataset for the E-R analysis for clinical endpoints was composed of all data from Part 2 (Phase 3 portion) of P002 [Ref. 5.3.5.3: 07YDDS] . The primary endpoint of the study was all-cause hospitalization (for ≥24 hours) or death through Day 29. A total of 1433 participants were 1:1 randomized to receive either MOV 800 mg (n=716) or placebo (n=717) Q12H for 5 days. Not all participants included in the efficacy population had available PK data and hence an exposure estimate available. After excluding patients with missing baseline viral load (treatment and placebo groups) or missing posthoc PK parameters (treatment group only), the analysis dataset for the E-R analyses included data from 683 participants who received placebo and 630 participants who received MOV.

The hospitalization/death incidence was treated as a binary response (0=no, 1=yes) and these data were modeled as a logistic regression. The covariate model selection was performed using stepwise backward elimination based on a statistical significance level α of 0.05 (requiring a 3.8 increase in log likelihood for 1 degree of freedom). Other acceptance criteria included AIC, BIC, improvement in parameter estimate precision, and model run stability.

The clinical relevance of any relationship was also considered. Additional assessment of collinearity between covariates was conducted using the variance inflation factor criteria.

Based on the exploratory analysis, a number of potentially confounding relationships were identified. For example, baseline covariates (eg, clade, disease severity, age, bodyweight) seemed to influence the clinical outcome. To avoid potential confounding of these relationships with the exposure-dependency in drug effect, it was important to develop a covariate model using placebo arm data only to allow assessment of the covariate effect independent of the drug effect. The final placebo model was a logistic regression model with covariates for baseline viral load, baseline disease severity, age, weight, clade, flag for active cancer participants (yes/no) and a flag for diabetic participants (yes/no). The BIC value decreases by almost 120 points from 475.8 in the full covariate model to 356.4 in final refined covariate model.

An E-R model for the primary outcome measure (probability of hospitalization or death) in P002 Part 2 (Phase 3) was developed building off the placebo model. Different model structures for the E-R term were tested on the data. Drug effect in the final model was parametrized as an additive Emax term with NHC AUC as the exposure predictor. The data were well described by the model. The AUC50 is estimated to be 19900 nM*hr with bootstrapped 95% CI as (9270, 32700) nM*hr.

Exposure-Response for Virology Endpoints

The E-R analysis for virology endpoints was based on pooled data from P002 (Part 1 and Part 2) and P006, with Phase 2 data from patients with TSSO >5 days excluded to match the Phase 3 inclusion/exclusion criteria. E-R models were developed for the following viral load endpoints:

1. Change from baseline at EOT (Day 5), Day 10, and 15 from quantitative PCR data for NP swabs

2. Decline slope from baseline to EOT (taking Day 3 measure into calculation) from quantitative PCR data for NP swabs

The virology analysis dataset for the Phase 2 portion of these studies (ie, P001, P002 [Part 1]) and P006 has been summarized in the end of Phase 2 report [Ref. 5.3.5.3: 08074R]. The data in the current analysis dataset coming from the Phase 2 portion is largely the same as that included in the Phase 2 E-R dataset from the prior analysis, with the exception that several additional covariates (baseline antibody status, risk factors) have been added. A total of 756 placebo participants and 797 participants receiving MOV across P002 (Part 1 and Part 2) and P006 were included in the final dataset. Not all participants who had viral load data had available PK data and hence an exposure estimate available. Participants who received MOV were only included if the posthoc PK parameters were available.

Separate E-R relationships were assessed for viral load change from baseline on Days 5, 10 and 15 and slope of viral load decline. In E-R model development for viral load endpoints, a similar multi-step process was followed for each endpoint. First, data from placebo participants were modeled to identify covariates that influence viral load outside of drug

effect. Baseline viral load and baseline disease severity were identified as significant covariates in the initial round of modeling for Day 5 and 10 CFB and baseline viral load, diabetes, and clade for Day 15 CFB and baseline viral load, age, and diabetes for slope. Next, participants who were treated with MOV were added to the model. The final E-R model structure for viral load change from baseline on Day 5 was an Emax model with an additional covariate for the presence of diabetes (yes/no) on Emax. A linear model best characterized the relationship between exposure and viral load change from baseline on Day 10. No exposure-dependency was identified for viral load change form baseline on Day 15 or slope of decline.

2.5.3.2.2 Exposure-Safety Analyses

Individual exposures estimated for individuals from P002 were predicted using the Phase 3 PopPK model [Ref. 5.3.5.3: 07ZRF9]. These exposures were stratified into quartiles and the incidence of high-level safety categories (including the number of participants with any AEs, drug-related AEs, or SAEs) was compared across exposure quartiles. Results for P002 Part 2 only are provided in the Phase 3 E-R report [Ref. 5.3.5.3: 07YDDS]. Results for a pooled analysis of all 800-mg data from P002 (Parts 1 and 2) are provided in the ISS [Sec. 5.3.5.3.3-covid19txallpop]. A summary of key findings is also provided in Sec. 2.7.2-covid19txallpop: 1.5.1.2.

2.5.4 Viral Dynamics Modeling

Viral dynamics modeling, an established application of the quantitative systems pharmacology approach, was conducted to describe mechanistic basis for the time course of viral load and response to treatment for MOV. This model was incrementally refined throughout MOV development and is described in detail in [Ref. 5.3.5.3: 05R5Z5]. The viral dynamics model provided a framework for integrating data across the development program to further understanding of the mechanisms of the disease, MOV drug action and drivers of clinical viral response. The objectives of the VDM analysis were to: (1) develop a model that adequately describes the viral dynamics in untreated participants and the response to treatment for MOV; (2) support mechanistic understanding of virologic response for MOV; and (3) support understanding of likely response in situations not studied, or with limited clinical study data.

The VDM dataset merged longitudinal viral load data from NP swabs from hospitalized (P001) and nonhospitalized (P002 and P006) participants with mild, moderate and severe COVID-19 and included a number of potential covariates. Model development occurred in a step-wise fashion with model updates and refinement conducted as further data became available. A high-level summary of the sequence of models developed is as follows:

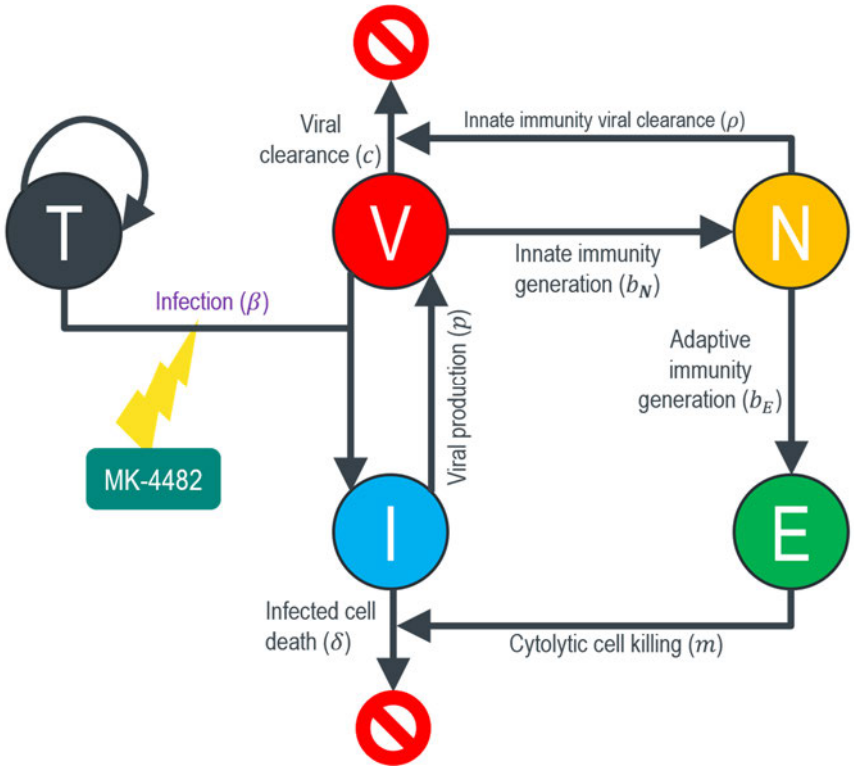
- IVDM-1, model of natural disease course (no treatment) based on early data available from literature

- IVDM-2, early model incorporating MOV drug action and expanded description of the innate and adaptive immune response based on emerging Phase 2 study data from P001 and P002 and published ferret data developed in Berkeley Madonna using a deterministic model structure.

- IVDM-3, expansion of IVDM-2 to a full population model implementing in Monolix and fit to end-of-Phase 2 data from P001, P002, and P006. A model reduction exercise to identify the minimum model structure needed to reproduce all the patterns of behavior in the observed clinical data then yielded the IVDM-3 model.

- IVDM-4, re-estimation and refinement of IVDM-3 based on expansion of the end-of-Phase 2 dataset to also include the Phase 3 data from P002. An extensive analysis of covariate effects was included in IVDM-4 development.

Figure 2.7.2-covid19txallpop: 5
Final Viral Dynamics Model Structure (representing final model from IVDM-4 step) Implemented to Account for the Natural Time Course of SARS-Cov-2 Infection, the Innate and Adaptive Immune Response, and MOV Drug Action



IVDM=integrated viral dynamics model; MOV=molnupiravir, MK-4482, EIDD-2801; SARS-CoV-2=sever acute respiratory syndrome coronavirus 2

Source: [Ref. 5.3.5.3: 05R5Z5]

The core mechanisms of the SARS-CoV-2 viral infection process and COVID-19 disease progression are incorporated in all the models, as depicted in [Figure 2.7.2-covid19txallpop: 5]. Models from IVDM-2 onwards mathematically represent the cellular infection process by the SARS-CoV-2 virus and the induced innate and adaptive immunity responses to the infection, which together describe the expected rise and fall of viral load during the natural (untreated) disease course. MOV drug effect was represented as inhibition of viral infection rate by reducing the infectivity consistent with the catastrophic mutational error mechanism of action.

Details on the data utilized, parameter estimation approaches, and model qualification results for each step are provided in the IVDM report [Ref. 5.3.5.3: 05R5Z5]. The report also describes a number of modeling results explorations and simulations untaken to further understanding of the mechanism of response with respect to variation in infection characteristics and response across individuals, nature of MOV's drug effect including model-predicted dose-response, impact of variation in immune response (including the immunocompromised subpopulation) on the viral profile and drug effect, and projection of response if MOV were used for pre- and post-exposure prophylaxis.

The key findings and interpretations from the IVDM modeling effort are provided in [Sec. 2.7.2-covid19txallpop: 3.4.1].

3 COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

This sections describes the PK of MOV with an emphasis on the recommended clinical dose of 800 mg administered Q12H for 5 days. An integrated summary and discussion of results from the clinical pharmacology studies and PopPK/E-R analyses are provided in this section. This section also outlines the results from the intrinsic/extrinsic factor evaluation and includes integrated assessment of pharmacodynamic and special safety studies and viral dynamics modeling. A summary of the PK characteristics of NHC as assessed in the Phase 1 studies in healthy participants is provided in [Appendix 2.7.2-covid19txallpop: 2].

3.1 Pharmacokinetics in Humans

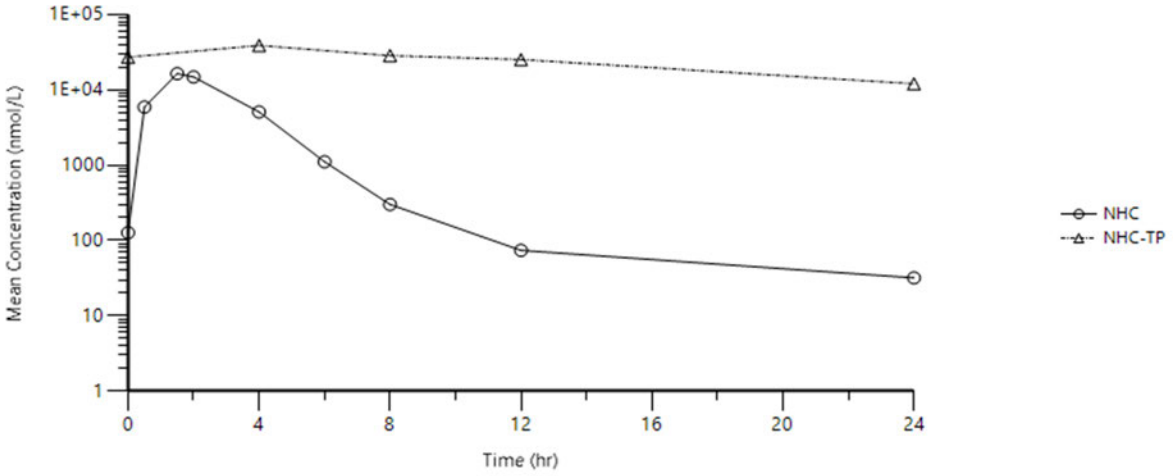
3.1.1 MOV, NHC and NHC-TP Pharmacokinetic Profile

The PK of MOV, NHC and NHC-TP were evaluated in healthy participants in P004 (MOV and NHC only) [Sec. 2.7.2-covid19txallpop: 2.1.1] and P008 (NHC and NHC-TP only) [Sec. 2.7.2-covid19txallpop: 2.2.1] following single doses up to 1600 mg and multiple doses of MOV up to 800 mg administered Q12H for 5.5 days (11 total dose administrations). In P012, the PK of NHC and NHC-TP were evaluated in healthy participants following multiple doses of MOV up to 800 mg administered Q12H for 10.5 days (21 total dose administrations) [Sec. 2.7.2-covid19txallpop: 2.1.2]. The PK of NHC were also evaluated following multiple doses up to 800 mg Q12H for 5 days in participants with COVID-19 (P001 Part 1, P002 Part 1 and Part 2, P006) using sparse sample collection, which was interpreted using PopPK modeling [Sec. 2.7.2-covid19txallpop: 2.5.2].

MOV is an orally administered prodrug of NHC. Rapid hydrolysis of MOV occurs during absorption/first pass to deliver NHC to systemic circulation. MOV largely converts to NHC

before entering systemic circulation and was generally not detected in plasma (any measurable MOV concentrations were <0.5% of NHC Cmax). NHC is the primary circulating analyte and is taken up into tissues and anabolized to the active moiety, NHC-TP. The mean plasma-concentration time profile for NHC and NHC-TP at steady-state at the 800-mg dose level following Q12H administration for 10.5 days in P012 is shown in [Figure 2.7.2-covid19txallpop: 6].

Figure 2.7.2-covid19txallpop: 6
Mean Plasma NHC and PBMC NHC-TP Concentration-Time Profiles at Day 11 in Healthy Adults (N=12) Following Administration of MOV 800 mg Q12H for 10.5 Days



MOV=molnupiravir, MK-4482, EIDD-2801; NHC=N-hydroxycytidine, EIDD-1931; NHC-TP=N-hydroxycytidine triphosphate, EIDD-2061; Q12H=every 12 hours

Source: [Ref. 5.3.5.3: 07ZL42]

Following administration of MOV as a DFC, NHC reached maximum plasma concentrations at approximately 1.5 hours and then declined in a biphasic manner. A short distributional t1/2 (reflecting the α-phase) of approximately 0.6 hours accounted for the majority of AUC (~ 96%) [Sec. 2.7.2-covid19txallpop: 2.5.2.2], consistent with minimal accumulation observed after multiple Q12H dosing. This is followed by a longer terminal t1/2 (reflecting the β-phase) of 20.6 hours [Sec. 2.7.2-covid19txallpop: 2.1.2]. An effective t1/2 of 3.3 hours was calculated based on the dosing interval of 12 hours and the accumulation ratio observed (1.09) at the 800-mg Q12H dose level for 5.5 days in P004. Steady-state of NHC is likely reached after the first dose.

Based on Phase 1 data in healthy participants and the PopPK analysis, the PK of NHC are linear and time-independent. A linearity index (multiple dose AUC0-12/single dose AUC0-inf) was estimated based on the Day 1 PK and Day 6 PK of at 800 mg [Sec. 2.7.2-covid19txallpop: 2.1.1] to assess for time-dependent PK: a ratio of 1 indicates linear kinetics. The linearity index for NHC was ~ 1, reflecting time-independent PK.

Overall, PK exposures for NHC increased approximately proportionally with dose, with single-dose PK being predictive of multiple dose PK. In P004 on Day 6, Cmax increased in a dose proportional manner, with a slope (90% CI) estimate of 0.971 (0.915, 1.03). AUC increased roughly in a dose proportional manner; however, the slope was modestly >1 and the 90% CI did not include unity (1.08 [90% CI: 1.02 to 1.14]; between-treatment pairwise analysis using an ANOVA model and ln-transformed dose-normalized AUC indicated that the 90% CI for the ratio of GLSMs spanned unity for the majority of comparisons up to 800 mg Q12H. Following single dose administration in P008, AUC0-inf increased in a slightly greater than dose proportional manner with the slope estimate (95% CI) of 1.152 (1.092, 1.213). Cmax increased in a slightly less than dose proportional manner with the slope estimate (95% CI) of 0.866 (0.755, 0.978). The slight suprapproportional increase in AUC observed in P004 and P008 may be explained by the assay LLOQ. At lower doses in particular, the terminal phase of the concentration-time profile is not quantifiable. As a result, a small portion of the AUC is not captured at low doses but is apparent at higher doses. This limitation in characterizing AUC at lower doses explains why slopes estimates fall above 1 for AUC.

Based on PopPK modeling, the PK of NHC were found to be similar between healthy participants and participants with COVID-19. A summary of steady-state PK parameter values following 800-mg Q12H dosing in healthy participants (observed values obtained from P004) and patients with COVID-19 (model-predicted values obtained from the Phase 3 PopPK analysis) is provided [Table 2.7.2-covid19txallpop: 3].

Table 2.7.2-covid19txallpop: 3
PK of Plasma NHC Following Multiple Oral Administration of 800-mg MOV Q12H

	NHC Geometric Mean (%CV)	
PK Parameter	**Healthy Participants[a]** (N=5)	**Participants with COVID-19[b]**
AUC0-12 (ng*hr/mL)	8330 (17.9)	8810 (41.2)
Cmax (ng/mL)	2970 (16.8)	2600 (31.7)
C12 (ng/mL)	16.7 (42.8)	30.9 (115)

AUC0-12=area under the concentration-time curve from time 0 to 12 hours; C12=concentration at time 12 hours; Cmax=maximum concentration; %CV=percent coefficient of variation; COVID-19=coronavirus disease 2019; MOV=molnupiravir, MK-4482, EIDD-2801; NHC=N-hydroxycytidine, EIDD-1931; PK=pharmacokinetic(s); Q12H=once every 12 hours

[a]Values were obtained from a Phase 1 study of healthy participants (P004).

[b]Values were obtained from population PK analysis.

Source: [Ref. 5.3.5.3: 07ZRF9] [Ref. 5.3.3.1: P004MK4482]

As expected, the Tmax of NHC-TP in PBMCs was longer compared to the Tmax of NHC in plasma (4.00 hours versus 1.50 hours) at steady-state. Overall, the profile of NHC-TP is flatter than NHC, owing to differences in the distribution and kinetics compared NHC in plasma. The AUC of NHC in the plasma was a strong and consistent predictor of NHC-TP exposures in PBMCs [Sec. 2.7.2-covid19txallpop: 2.5.1], suggesting that NHC AUC is the driver for uptake and conversion to NHC-TP intracellularly. Although plasma NHC

concentrations decline to low trough concentrations prior to the next dose, the overall profile of NHC-TP is supportive of Q12H dosing. The flatter profile and longer dominant t1/2 of NHC-TP in PBMCs are consistent with the ~ 2-fold accumulation observed. This results in high levels of the active NHC-TP maintained intracellularly across the dosing interval from Day 1 onwards to Day 5 and supports the proposed 12-hour dosing interval.

3.1.2 Human ADME Profile

3.1.2.1 Absorption

MOV is a BCS Class 1 compound [Sec. 2.7.1: 1.2.1]. The absolute human bioavailability of MOV (the prodrug) has not been determined but is considered to be negligible, given that little or no intact MOV has been detected systemically. Preclinical data suggest that MOV delivers NHC with moderate to high oral bioavailability [Sec. 2.6.4: 3]. This is consistent with the early Tmax (1.5 to 3 hours, depending on meal status) and low variation in the extent of absorption observed clinically following administration of MOV as the final market formulation capsule.

Administration of MOV as a single 200-mg dose with a high-fat meal to healthy participants in P004 delayed median NHC Tmax by 2 hours and reduced geometric mean NHC Cmax by 35.6%, but did not impact the AUC of NHC [Sec. 2.7.1: 2.3.1]. Similar findings were observed in healthy Japanese participants in P008 [Sec. 2.7.1: 2.3.2], where the median NHC Tmax was delayed by 1.50 hours and geometric mean NHC Cmax was reduced by 24% but NHC AUC was comparable. In the PopPK analysis, absorption was complex and best captured by a series to transit compartments. Administration of MOV with a high-fat meal increased the MTT by a factor of 5.22. Similarly, formulation was found to impact MTT, as shown by the 61.6% decrease for oral solution compared to capsule or suspension. Food, hospitalization status, and formulation were all statistically significant covariates on absorption rate or duration terms, in the PopPK model. This variation in rate affects the NHC Cmax but not the AUC, because the extent of absorption was consistent across individuals [Sec. 2.7.1: 3.3]. Since NHC AUC is the PK parameter expected to be most closely related to efficacy and safety, MOV may be administered without regard to food, consistent with the dosing instructions for Phase 2 and pivotal Phase 3 studies.

MOV does not show significant pH-dependent solubility over gastrointestinal pH values [Sec. 2.7.1: 1.2.1]; therefore, gastric pH reducing agents would not be expected to alter the PK of NHC.

3.1.2.2 Distribution and Protein Binding

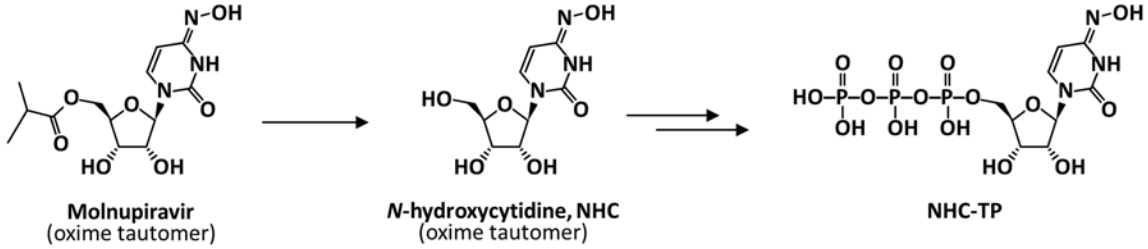
Based on PopPK analysis, V/F is 131.9 L (sum of Vc and Vp: 63.8 L and 68.1 L) indicating that NHC distributes in peripheral tissues [Ref. 5.3.5.3: 07ZRF9]. Sex and BMI were statistically significant covariates for volume of distribution. NHC does not bind to plasma proteins in vitro [Sec. 2.7.2-covid19txallpop: 1.4.1] [Sec. 2.6.4: 4]. Based on nonclinical in vitro transporter data, NHC is a substrate of nucleoside uptake transporters (CNTs and ENTs) which are widely expressed across mammalian tissue types [Sec. 2.7.2-covid19txallpop: 1.4.4] [Sec. 2.6.4: 7.1]. Based on animal tissue distribution studies where both NHC and

NHC-TP were measured, NHC in humans is expected to widely distribute into a majority of tissue types.

3.1.2.3 Metabolism

Following oral administration, MOV is converted to NHC during absorption/first pass, involving the high capacity and widely distributed CES1 and CES2 carboxylesterases, which are also expressed in the GI tract and/or liver [Sec. 2.6.4: 7.1]. Clinically, MOV is only detected at very low levels in systemic circulation [Ref. 5.3.3.1: P004MK4482: 2].

Figure 2.7.2-covid19txallpop: 7
Metabolism of MOV



Source: [Sec. 2.6.4: 5]

Based on nonclinical data, the majority of the MOV-related absorbed dose is expected to be converted in humans to NHC, which is then taken up into tissues and anabolized to the active moiety NHC-TP via endogenous pyrimidine metabolism pathways [Figure 2.7.2-covid19txallpop: 7]. Ultimately, metabolism to uridine and/or cytidine is the main route of NHC elimination [Sec. 2.6.4: 5]. At least 3 widely distributed cellular enzymes have demonstrated the ability to metabolize NHC to endogenous pyrimidines. mARC1 and mARC2 have been reported to convert NHC to cytidine in vitro [Ref. 5.4: 06CBPM]. Additionally, cytidine deaminase readily converts NHC to uridine in vitro [Sec. 2.6.4: 7.1].

These nonclinical findings are corroborated clinically by a semiquantitative analysis of urine collected in P004 following Q12H doses of 100- and 800-mg MOV. NHC, along with relatively low levels of cytidine, uridine and a glucuronide of NHC were all detected in urine with concentrations that increased in an approximately dose-dependent manner from the 100-mg Q12H dose (0 to 12 hour) to the 800-mg Q12H dose (0 to 12 hour) [Sec. 2.6.4: 5.1.3]. In a separate semiquantitative analysis conducted using pooled human plasma samples (0 to 12 hour samples, both Day 1 and Day 11) from human healthy participants treated with multiple Q12H oral doses of 400- or 800-mg MOV for 10.5 days (P012), NHC and uridine were detected in human plasma from both dose groups, and exposures increased in an approximately dose-dependent manner [Sec. 2.6.4: 5.1.3]. In addition, trace levels of a glucuronide metabolite of NHC and a glucose conjugate of NHC were detected in plasma from both dose groups. Cytidine was not detected in plasma from either dose group [Sec. 2.6.4: 5.1.3]. All of the major metabolites detected in human plasma have also been observed previously in either rats and/or dogs. The dose-dependent increases of the 2 natural

pyrimidine bases cytidine and uridine in human urine, as well as uridine in human plasma, suggest that some amount of these were derived from the oral dose of MOV. These data are consistent with the expectation that the majority of the MOV-related dose in humans is converted to NHC, NHC-TP, and then ultimately to uridine and/or cytidine which then mix with the endogenous pyrimidine nucleotide pool. This explains the low recoveries (<13%) of [^{14}C]MOV-related radioactivity that were observed in rat (with >50% retained in the carcass) and dog excretion studies. In these studies, low amounts of [^{14}C]-labelled NHC, uridine, cytidine, or metabolites of these were also observed in urine, feces, or plasma [Sec. 2.6.4: 5.1]. The low recovery of the [^{14}C]MOV-related radioactivity would not further contribute to the understanding of MOV and/or NHC elimination routes. This, in addition to the potential for long-term retention of radiolabeled drug, precludes the conduct of a human ADME study.

3.1.2.4 Elimination

Based on the PopPK analysis, CL/F was 70.6 L/h. A covariate effect of body weight on clearance was identified during modeling [Sec. 2.7.2-covid19txallpop: 2.5.2.2].

The amount of MOV and NHC excreted renally was evaluated in healthy participants in P004. MOV was generally detected only at very low levels in urine following administration of single doses of MOV 50 to 1600 mg and multiple doses up to 800 mg [Sec. 2.7.2-covid19txallpop: 2.1.1]. A small amount of NHC was detected in the urine following both single and multiple doses of MOV [Sec. 2.7.2-covid19txallpop: 2.1.1]. The percentage of the dose administered recovered in urine over the time interval 0 to 24 hours postdose (Fe0-24) detected as NHC ranged from 0.820% following a 50-mg single dose to 6.70% following the 1600 mg single dose. Following multiple dosing with 800 mg Q12H for 5.5 days, 3% of the administered dose was excreted in urine as NHC over the time interval 0 to 12 hours postdose (Fe0-12) on Day 6. The majority of renal elimination of NHC occurred during the first 4 hours postdose and increased supraproportionally with dose.

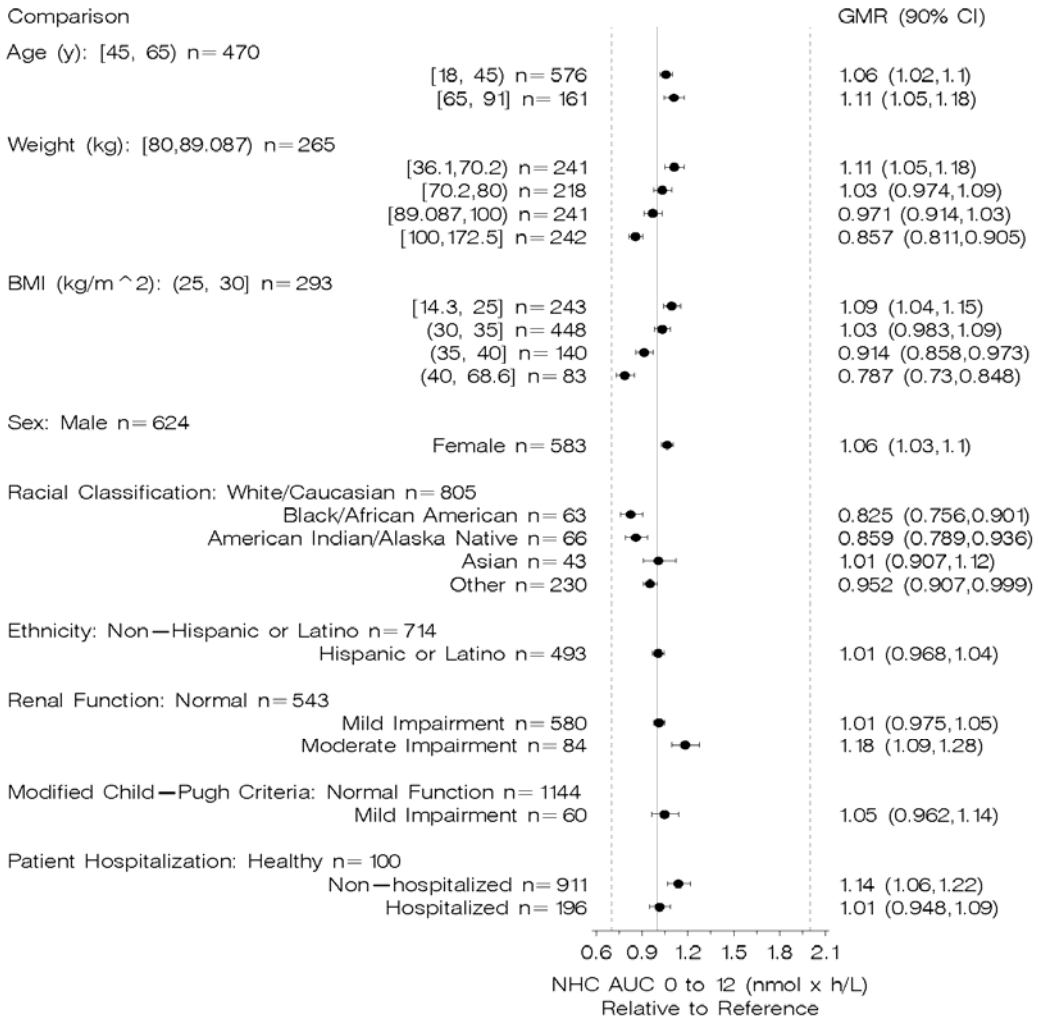
Additionally, low amounts of cytidine, uridine, and a glucuronide of NHC were observed in human urine (P004) using a semiquantitative analysis [Sec. 2.6.4: 5.1.3] [Sec. 2.7.2-covid19txallpop: 3.1.2.3].

3.2 Intrinsic Factor Evaluation

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, race, or ethnicity. Measures of body size (body weight and BMI) did influence NHC exposures; however, the magnitude of the effect was not large enough to warrant dose adjustment. Further, patients with renal impairment and patients with hepatic impairment do not require dose adjustment.

The effects of intrinsic factors on the AUC of NHC as evaluated via the Phase 3 PopPK analysis are summarized in the forest plot [Figure 2.7.2-covid19txallpop: 8]. The dashed vertical lines on the plot represent the clinical bounds of 0.7 to 2.0, as discussed in [Sec. 2.7.2-covid19txallpop: 1.5.2].

Figure 2.7.2-covid19txallpop: 8
Forest Plot of Intrinsic Factor GMRs (90% CI) for Model-Estimated AUC0-12 for NHC After 800-mg MOV Q12H



n is the number of subjects in each group.
[or] indicates respective endpoint is included in the interval.
(or) indicates respective endpoint is not included in the interval.

AUC0-12=area under the concentration-time curve from time 0 to 12 hours; BMI=body mass index; CI=confidence interval; GMR=geometric mean ratio; MOV=molnupiravir, MK-4482, EIDD-2801; NHC=N-hydroxycytidine, EIDD-1931

The vertical solid line represents 1; the vertical dashed lines represent the clinical bounds (0.7, 2.0)

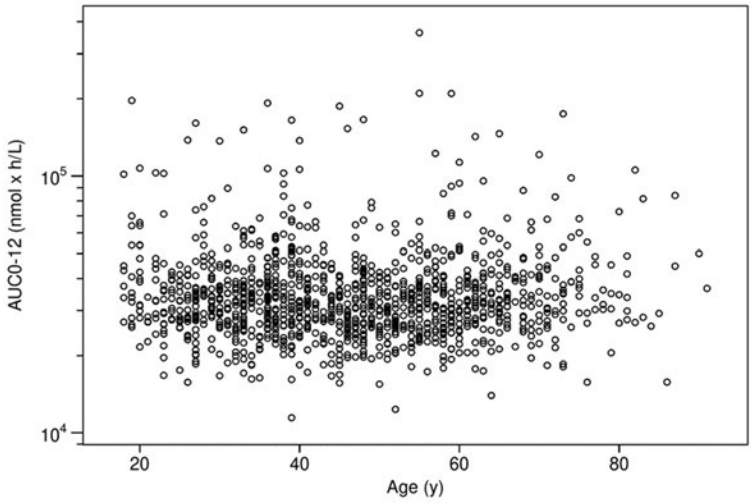
Source: [Ref. 5.3.5.3: 07ZRF9]

The PK evaluation is consistent with the statistical analysis of efficacy [Sec. 2.7.3-covid19txallpop] and safety [Sec. 2.7.4-covid19txallpop] across subpopulations, which also inform dosing recommendations in subgroups and special populations. Subgroup analyses for efficacy were conducted for key patient subpopulations (eg, by age, gender, race, ethnicity, BMI). Overall, subgroup analyses showed consistency of the effect of treatment, supporting the position that dose adjustment is not needed for any subpopulation. Results of an integrated safety analyses at the 800-mg dose level in P002 Part 1 (Phase 2) and Part 2 (Phase 3) indicate that 800-mg MOV is generally well tolerated [Sec. 2.7.4-covid19txallpop: 2.1]. Overall, the incidence of AEs in participants treated with MOV was comparable to, or lower than, placebo.

3.2.1 Age

NHC exposures were consistent across a wide range of ages in adults. Out of 1207 individuals included in the PopPK analysis, 161 (13%) were ≥ 65 years and 42 (3.5%) were ≥75 years. Age was not identified as a statistically significant covariate in the model. Posthoc NHC exposures in terms of AUC were plotted against age in [Figure 2.7.2-covid19txallpop: 9] with no clear trend identified. The NHC AUC GMR for all age groups fell within the clinical bounds described in [Sec. 2.7.2-covid19txallpop: 1.5.2].

Figure 2.7.2-covid19txallpop: 9
Relationship between Posthoc NHC AUC Estimates and Age from PopPK Analysis



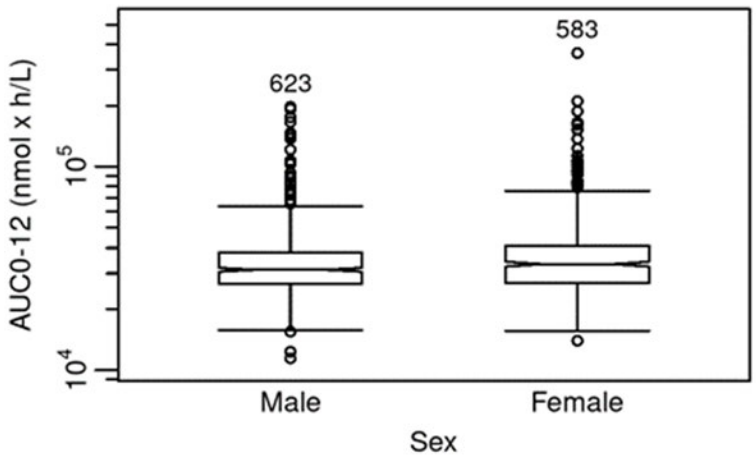
AUC=area under the concentration-time curve; AUC0-12=area under the concentration-time curve from time 0 to 12 hours; NHC=N-hydroxycytidine, EIDD-1931; PopPK=population PK

Source: [Ref. 5.3.5.3: 07ZRF9]

3.2.2 Sex

No meaningful trend between sex and NHC exposures was identified. Out of 1207 individuals included in the PopPK analysis, 624 (51.7%) were male and 583 (48.3%) were female. Sex was identified as a significant covariate on Vc/F in the model with females typically having a 15% higher Cmax than males; however, there was no meaningful difference in NHC exposure in terms of AUC between males and females [Figure 2.7.2-covid19txallpop: 10]. The NHC AUC GMR for females fell within the clinical bounds described in [Sec. 2.7.2-covid19txallpop: 1.5.2].

Figure 2.7.2-covid19txallpop: 10
Relationship between Posthoc NHC AUC Estimates and Sex from PopPK Analysis



AUC=area under the concentration-time curve; AUC0-12=area under the concentration-time curve from time 0 to 12 hours; NHC=N-hydroxycytidine, EIDD-1931; PopPK=population PK

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

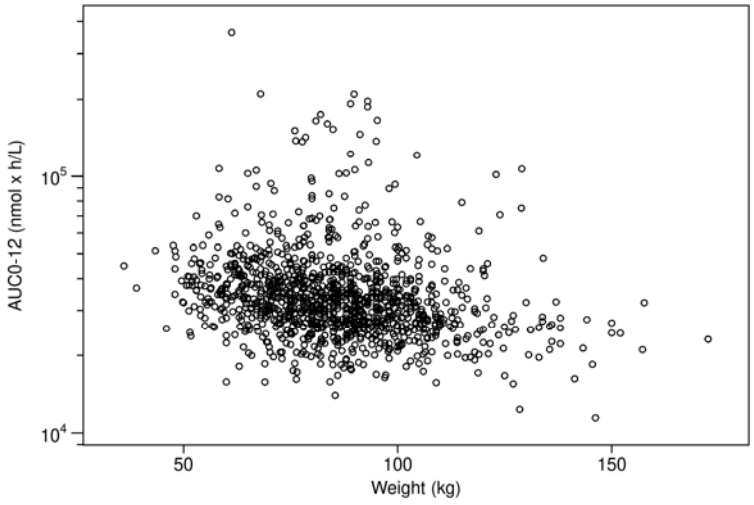
Source: [Ref. 5.3.5.3: 07ZRF9]

3.2.3 Body Weight and BMI

Measures of body size (body weight and BMI) were the most influential intrinsic factors identified in the PopPK model of NHC exposures. The PopPK analysis included 1207 participants with a median (range) body weight of 85 kg (36.1 to 172 kg) and a median (range) BMI of 30.4 kg/m^2 (14.3 to 68.6 kg/m^2). In the final PopPK model, body weight was a statistically significant covariate on CL/F and BMI was a statistically significant covariate on Vc/F. An inverse trend was identified between body weight [Figure 2.7.2-covid19txallpop: 11] or BMI [Figure 2.7.2-covid19txallpop: 12] and posthoc NHC exposures in terms of AUC.

Of note, the highest BMI category (BMI>40 kg/m^2) was the subpopulation (n=83) associated with the lowest NHC AUC of all the intrinsic factor groups examined with a GM (%CV) AUC of 26600 (33.1) nM*hr. This value exceeds the AUC50 from the hospitalization E-R modeling indicating that although exposures are low in this population, they can be expected to achieve more than 50% of the maximal drug benefit. This is consistent with the GMR (90% CI) of 0.787 (0.73, 0.848) in this population (compared to the reference BMI category of >25 to ≤30 kg/m^2) contained within the 0.7 to 2.0 bounds of clinical significance. These findings are further supported by efficacy subgroup analyses, which demonstrated no clear reduction in efficacy based on BMI [Ref. 5.3.5.1: P002V03MK4482: Figure 14.2-5]. Therefore, no dose adjustment for this subpopulation is recommended.

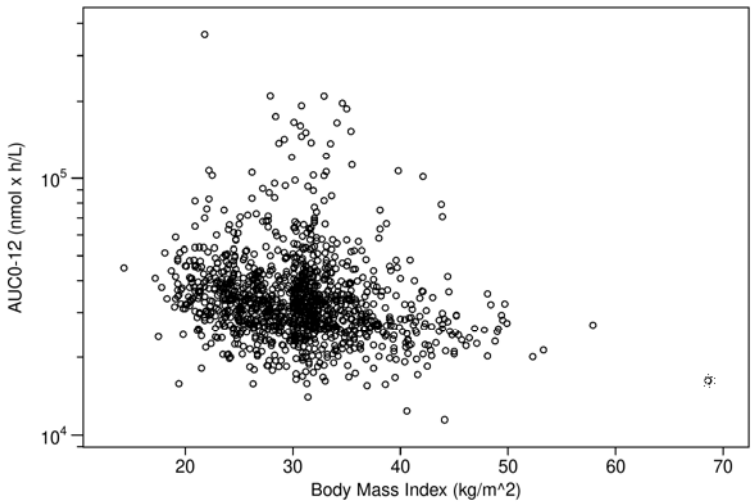
Figure 2.7.2-covid19txallpop: 11
Relationship between Posthoc NHC AUC Estimates and Body Weight from PopPK Analysis



AUC=area under the concentration-time curve; AUC0-12=area under the concentration-time curve from time 0 to 12 hours; NHC=N-hydroxycytidine, EIDD-1931; PopPK=population PK

Source: [Ref. 5.3.5.3: 07ZRF9]

Figure 2.7.2-covid19txallpop: 12
Relationship between Posthoc NHC AUC Estimates and BMI from PopPK Analysis



AUC=area under the concentration-time curve; AUC0-12=area under the concentration-time curve from time 0 to 12 hours; NHC=N-hydroxycytidine, EIDD-1931; PopPK=population PK

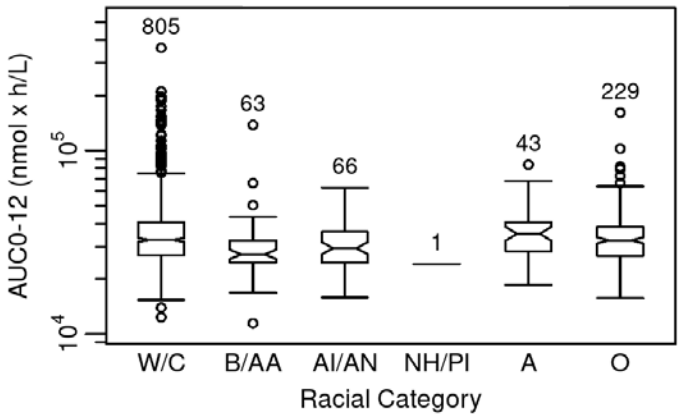
Source: [Ref. 5.3.5.3: 07ZRF9]

3.2.4 Race and Ethnicity

Race and ethnicity were evaluated as covariates in the PopPK analysis. A total of 714 (59.2%) participants identified as non-Hispanic or Latino while 493 (40.8%) participants identified as Hispanic or Latino. The majority (66.7%) of participants identified as white or Caucasian, while 63 (5.22%) participants identified as black or African American, 66 (5.47%) participants identified as American Indian or Alaska Native, 43 (3.56%) participants identified as Asian, and a single participant identified as Native Hawaiian or other Pacific Islander. The remaining 229 (19%) participants were classified as other, which includes those participants that identify as mixed race.

Overall, there was no meaningful relationship identified between NHC exposures and race [Figure 2.7.2-covid19txallpop: 13] or ethnicity [Figure 2.7.2-covid19txallpop: 14]. The GMRs of NHC AUC fell within the clinical bounds for all race and ethnicity subgroups [Sec. 2.7.2-covid19txallpop: 1.5.2]. A large portion of participants were classified as other. The AUCs observed in this subgroup fell within the range of other race categories that were evaluated. Lower exposures seen in Black/African American (GMR 0.825) and American Indian/Alaska Native (GMR 0.86) were likely driven by higher body weights/higher BMI in these subpopulations [Figure 2.7.2-covid19txallpop: 15]. Efficacy subgroup analyses demonstrated no relationship between efficacy and race or ethnicity subgroups [Sec. 2.7.3-covid19txallpop: 2.1.2.1.2]. Based on these findings, no dose adjustment is recommended on the basis of race or ethnicity.

Figure 2.7.2-covid19txallpop: 13
Relationship between Posthoc NHC AUC Estimates and Race from PopPK Analysis

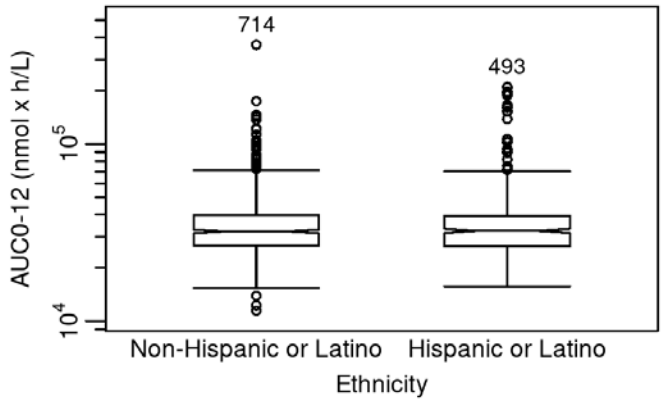


A=Asian; AI/AN=American Indian or Alaska Native; AUC=area under the concentration-time curve; AUC0-12=area under the concentration-time curve from time 0 to 12 hours; B/AA=Black or African American; NH/PI=Native Hawaiian or other Pacific Islander; NHC=N-hydroxycytidine, EIDD-1931; O=other; PopPK=population PK; W/C=white or Caucasian

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

Source: [Ref. 5.3.5.3: 07ZRF9]

Figure 2.7.2-covid19txallpop: 14
Relationship between Posthoc NHC AUC Estimates and Ethnicity from PopPK Analysis

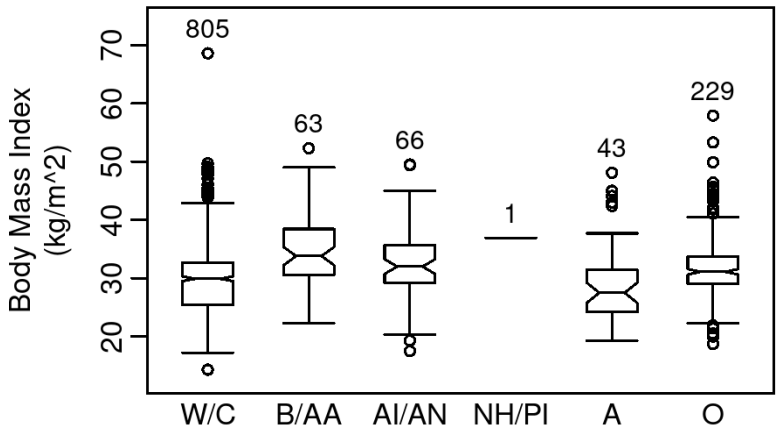


AUC=area under the concentration-time curve; AUC0-12=area under the concentration-time curve from time 0 to 12 hours; NHC=N-hydroxycytidine, EIDD-1931; PopPK=population PK

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

Source: [Ref. 5.3.5.3: 07ZRF9]

Figure 2.7.2-covid19txallpop: 15
Distribution of BMI by Race for Participants Included in the PopPK Analysis



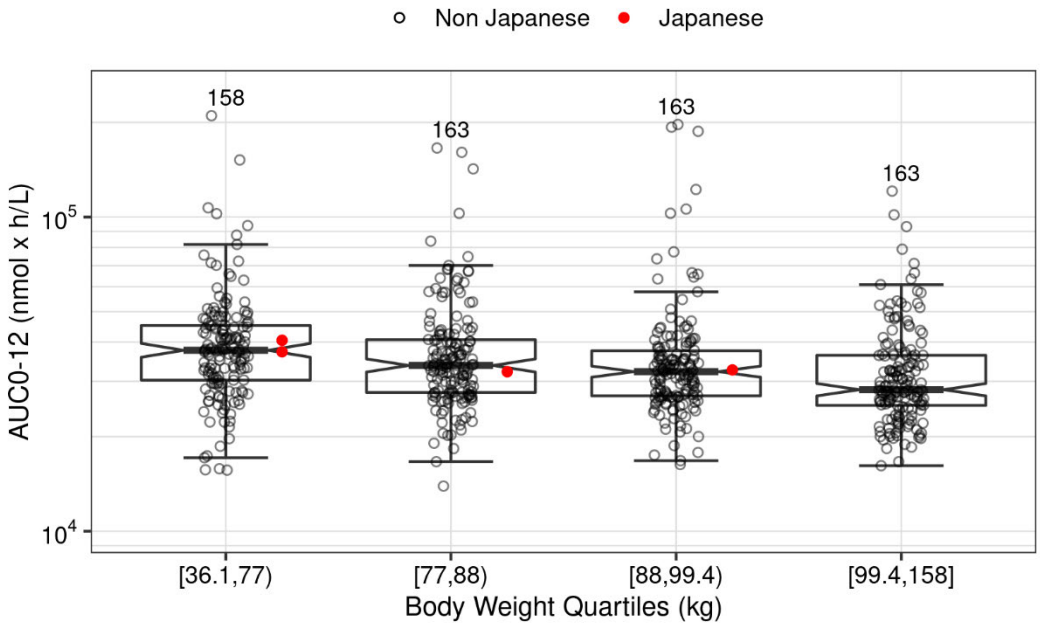
BMI, body mass index; PopPK=population PK; A, Asian; AI/AN, American Indian/Alaska Native; Asia Pac., Asia Pacific; B/AA, Black/African American

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

Source: [Ref. 5.3.5.3: 07ZRF9]

Lack of a meaningful impact of race on PK is further supported by data from Japanese participants. Overall, exposures, for a dose of 800 mg Q12H x 5 days, exposures in terms of NHC Cmax and AUC tended to be higher in healthy Japanese participants from P008 [Sec. 2.7.2-covid19txallpop: 2.2.1] compared to healthy non-Japanese participants from P004 [Sec. 2.7.2-covid19txallpop: 2.1.1]. However, these differences can be largely explained by an imbalance in body size between the 2 studies (median body weight of 60.8 kg and 75.8 kg in P008 and P004, respectively) [Ref. 5.3.3.3: P008MK4482: Table 10-3, 10-4] [Ref. 5.3.3.1: P004MK4482: Table 14.1-2.1, 14.1-2.2, 14.1-2.3]. Body weight is known to influence the PK of NHC, as discussed in [Sec. 2.7.2-covid19txallpop: 3.2.3]. Exposures from Japanese participants in P008 were compared to those from non-Japanese participants with similar body weights (ie, the first quartile) in P001 Part 1 and P002 Part 1 [Ref. 5.4: 06GCWS]. The mean NHC AUC was 49300 nM*hr and 47900 nM*hr in Japanese and non-Japanese (from first quartile) participants, respectively. This suggests that exposures in Japanese are not meaningfully different compared to those in non-Japanese participants with similar body weight and are included within the range of exposures in non-Japanese [Ref. 5.4: 06GCWS]. This conclusion is further supported by PopPK analysis of 4 participants enrolled at sites in Japan in the Phase 3 portion of P002. A comparison of posthoc NHC AUC values were not noticeably different in Japanese participants when compared to non-Japanese participants of similar body weight [Figure 2.7.2-covid19txallpop: 16].

Figure 2.7.2-covid19txallpop: 16
Comparison of PopPK Predicted NHC AUC Between Japanese and Non-Japanese Participants Enrolled in Phase 3 of P002 by Body Weight Quartile



Boxes represent the 25th and 75th percentiles and lines the median. Notches provide an approximate 95% C.I. about the median. Whiskers extend to the most extreme values within the 1.5 interquartile range. Values beyond the whisker limits are marked with open circles. The numbers of included values are displayed above each box.

AUC=area under the concentration-time curve; AUC0-12=area under the concentration-time curve from time 0 to 12 hours; NHC=N-hydroxycytidine, EIDD-1931; P=protocol (number); PopPK=population PK

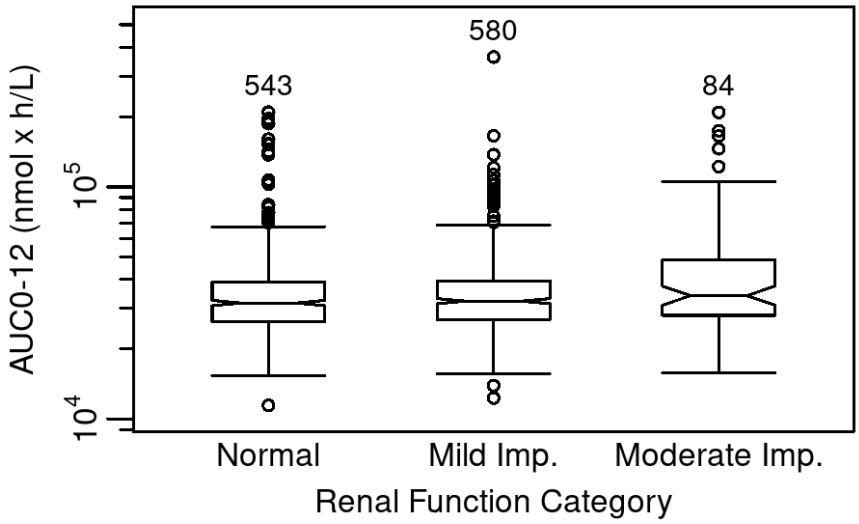
Source: [Ref. 5.3.5.3: 07ZRF9]

3.2.5 Renal Impairment

Preclinical and clinical data indicate that renal impairment is unlikely to meaningfully impact the PK of NHC. Minimal renal elimination of NHC was observed in healthy adults. Only 3% of the 800-mg dose was excreted renally as NHC at steady-state over the 12-hour dosing interval [Sec. 2.7.2-covid19txallpop: 2.1.1].

The impact of renal impairment on NHC exposures was evaluated in a PopPK analysis [Figure 2.7.2-covid19txallpop: 17]. A total of 1207 participants with data on renal function (evaluated based on MDRD) were included in the analysis: 543 participants with normal renal function (eGFR ≥90 mL/min/1.73 m^2), 580 participants with mild renal impairment (eGFR <90 to ≥60 mL/min/1.73 m^2), and 84 participants with moderate renal impairment (eGFR <60 to ≥30 mL/min/1.73 m^2). Renal impairment was not identified as a statistically significant covariate in the model. Compared to participants with normal renal function, the GMR (90% CI) of AUC was 1.01 (0.975, 1.05) and 1.18 (1.09, 1.28) in participants with mild and moderate renal impairment, respectively. These estimates fall within the clinical bounds, as described in [Sec. 2.7.2-covid19txallpop: 1.5.2], indicating no need for dose adjustment in participants with mild and moderate renal impairment.

Figure 2.7.2-covid19txallpop: 17
Relationship between Posthoc NHC AUC Estimates and Renal Function Category from PopPK Analysis



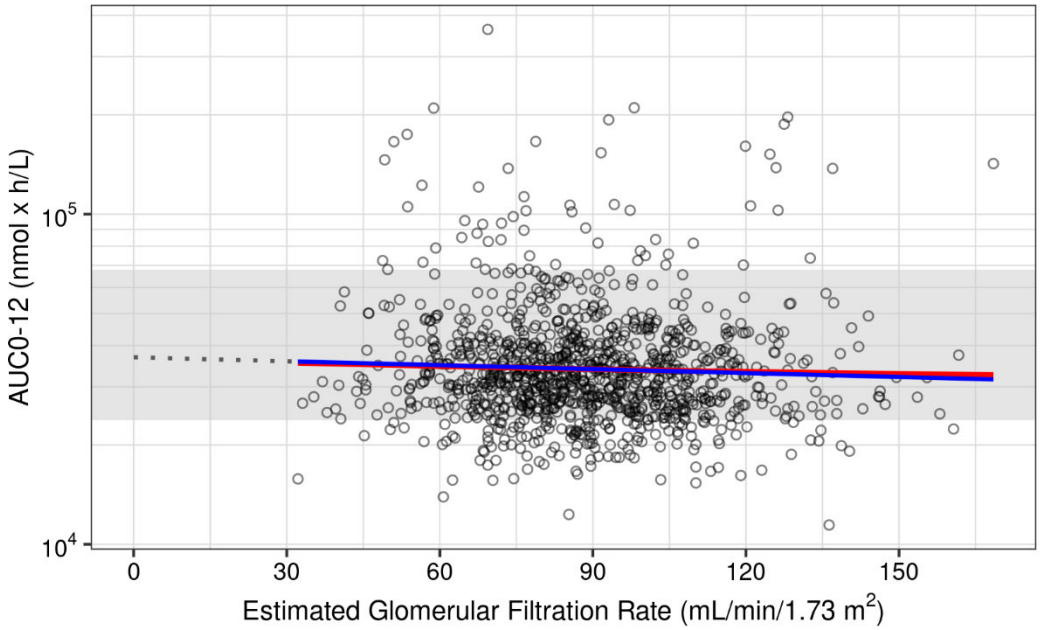
AUC=area under the concentration-time curve; AUC0-12=area under the concentration-time curve from time 0 to 12 hours; NHC=N-hydroxycytidine, EIDD-1931; PopPK=population PK

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

Source: [Ref. 5.3.5.3: 07ZRF9]

Individuals with severe renal impairment (eGFR <30 mL/min/1.73 m^2) were excluded from these clinical studies. To evaluate the potential impact in this subpopulation, NHC exposures from mild and moderate populations were extrapolated to eGFR values associated with severe renal impairment [Ref. 5.3.5.3: 07ZRF9]. [Figure 2.7.2-covid19txallpop: 18] shows the distribution of PopPK estimated AUC0-12 as a function of eGFR following 800-mg MOV Q12H for all patients through the end of Phase 3 (P006, Part 1 of P001, and Parts 1 and 2 of P002). Overall, the slope of the regression line in modest and the extrapolated portion falls well within the clinical bounds (indicated by the grey shaded region). Further, was no visible difference between the lines representing a log linear regression and a smoothed conditional averaging over the range of observed eGFR, in particular at the lower end of this range. This suggests that there was no apparent acceleration of the increase in AUC0-12 with decreasing eGFR in participants with moderate renal impairment and projected very minimal difference in the expected AUC0-12 in individuals with moderate or severe impairment.

Figure 2.7.2-covid19txallpop: 18
Relationship Between eGFR and Predicted NHC Exposures in Participants Following MOV 800 mg Q12H Dosing



AUC=area under the concentration-time curve; AUC0-12=area under the concentration-time curve from time 0 to 12 hours; eGFR=estimated glomerular filtration rate; MDRD=Modification of Diet in Renal Disease study; MOV=molnupiravir, MK-4482, EIDD-2801; NHC=N-hydroxycytidine, EIDD-1931; PopPK=population PK; Q12H=every 12 hours

A log-linear regression is represented as a solid blue line within the range of observed data and as a dotted black line in the extrapolated range. The red line represents a smoothing function. The shaded area delineates the limits of the clinical comparability bounds. This plot shows data from P001 (Part 1), P006, and P002 (Parts 1 and 2). The MDRD equation was used to calculate eGFR.

Source: [Ref. 5.3.5.3: 07ZRF9]

Although severe renal impairment may disrupt CYP450 expression, altering PK of some hepatically eliminated drugs, NHC is not a substrate of these enzymes. Therefore, this mechanism of effect of severe renal impairment on NHC PK is not anticipated. In conclusion, based on the minimal difference in NHC PK observed in mild and moderate renal impairment, the minimal renal elimination of NHC observed clinically, the lack of CYP450-mediated clearance of NHC, and the lack of safety signals associated with MOV, severe renal impairment is not expected to result in a meaningful change in NHC exposure. Therefore, no dose adjustment is recommended for patients with severe renal impairment.

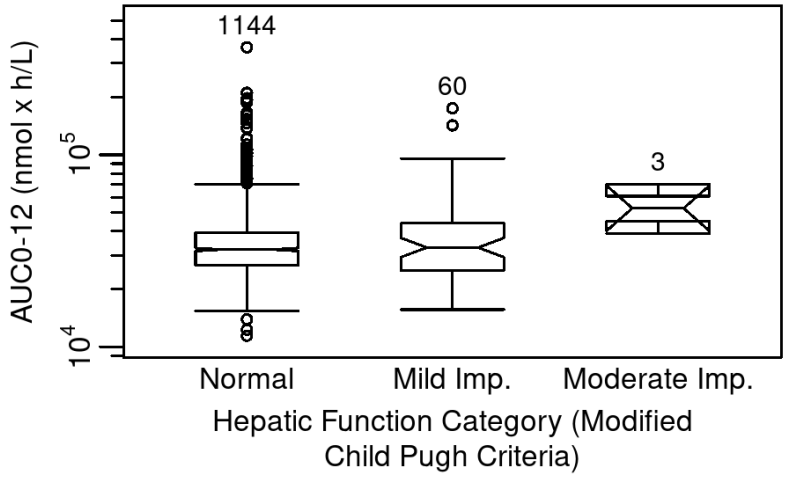
3.2.6 Hepatic Impairment

Hepatic elimination is not expected to be a major route of elimination for NHC based on nonclinical data [Sec. 2.7.2-covid19txallpop: 3.1.2]. NHC is metabolized to uridine and/or cytidine via the same pathways as those involved in endogenous pyrimidine metabolism. These processes would not be expected to be affected by hepatic impairment. Decreased protein binding in hepatic impairment may alter PK in unexpected ways; however, NHC is not bound to plasma proteins [Sec. 2.7.2-covid19txallpop: 1.4.1]. In addition, MOV absorption is not expected to be altered in hepatic impairment due to high solubility in buffers with and without bile acids [Sec. 2.7.1: 1.2.1].

Hepatic function (ie, Child-Pugh score) was not explicitly captured in the clinical database. In order to evaluate the impact of hepatic impairment on NHC PK in the PopPK analysis, the degree of hepatic impairment was approximated using a modified Child-Pugh score. This modified Child-Pugh score was based on reported lab values for total bilirubin and albumin, while encephalopathy, ascites, and INR were assumed to be normal as these parameters were not collected in the clinical dataset [Ref. 5.3.5.3: 07ZRF9]. Based on PopPK results, the GMR (90% CI) of exposures for participants with mild hepatic impairment (n=60) compared to participants with no hepatic impairment (n=1144) was 1.05 (0.962, 1.14) [Figure 2.7.2-covid19txallpop: 19]. Only 3 participants were classified as having moderate hepatic impairment so a GMR was not calculated for this group.

While it is acknowledged that the modified Child-Pugh score may underestimate the true number of participants with higher degrees of hepatic impairment, the available data in mild and moderate hepatic impairment participants do not identify a distinguishable trend in NHC exposures with hepatic dysfunction. Hepatic impairment of any degree is not expected to result in a meaningful change in NHC exposure.

Figure 2.7.2-covid19txallpop: 19
Relationship between Posthoc NHC AUC Estimates and Hepatic Function Category from PopPK Analysis



AUC=area under the concentration-time curve; AUC0-12=area under the concentration-time curve from time 0 to 12 hours; NHC=N-hydroxycytidine, EIDD-1931; PopPK=population PK

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

Source: [Ref. 5.3.5.3: 07ZRF9]

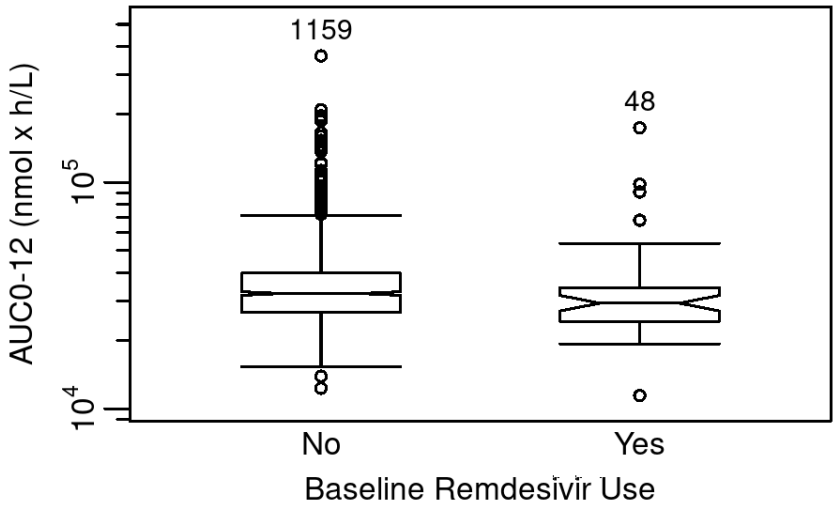
3.3 Extrinsic Factor Evaluation

3.3.1 Evaluation of Drug-Drug Interaction: MOV as a Perpetrator

Based on in vitro data, MOV is unlikely to be a perpetrator of DDIs due to inhibition or induction of major metabolic enzymes or inhibition of transporters [Sec. 2.7.2-covid19txallpop: 2.3]. MOV and NHC are not inhibitors of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 or inhibitors of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2K, MRP2, MDR1 and BCRP or inducers of CYP1A2, 2B6, and 3A4 [Sec. 2.7.2-covid19txallpop: 1.4.3]. 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: 3.1.2.3]. It is unlikely that coadministered drugs will impact the exposure of NHC in plasma or NHC-TP in tissues. Therefore, no clinical DDI studies were conducted.

The impact of remdesivir use on NHC exposures was evaluated in a PopPK analysis [Figure 2.7.2-covid19txallpop: 20]. In total, 48 (4%) of participants in P001 received concomitant remdesivir during MOV treatment, while 1159 (96%) did not. NHC exposures in participants on concomitant remdesivir were similar to those in the no remdesivir group. The geometric mean ratio (90% CI) of exposures for participants with concomitant remdesivir use compared to without was 0.929 (0.846, 1.02).

Figure 2.7.2-covid19txallpop: 20
Relationship between Posthoc NHC AUC Estimates and Concomitant Remdesivir Use from PopPK Analysis



AUC=area under the concentration-time curve; AUC0-12=area under the concentration-time curve from time 0 to 12 hours; NHC=N-hydroxycytidine, EIDD-1931; PopPK=population PK

Note: 1 = concomitant use of remdesivir, 0 = no concomitant remdesivir use. The solid line within the box represents the median. The lower and upper hinges represent the 25th and 75th percentiles, respectively. The whiskers extend to the most extreme values within 1.5 times the interquartile range.

Source: [Ref. 5.3.5.3: 07ZRF9]

Lastly, 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 3TC, abacavir, FTC, hydroxychloroquine, nelfinavir, ribavirin, sofosbuvir, or tenofovir [Sec. 2.6.2: 5.1]. Further, no synergy or antagonism is expected when MOV is used with commonly administered antivirals for HIV, HBV, or HCV.

MOV may be coadministered with other medications without dose adjustment.

3.4 Pharmacodynamic and Other Safety Endpoints

3.4.1 Insights into Disease Process and Determinants of Response from Viral Dynamics Modeling and Exposure-Response Analyses

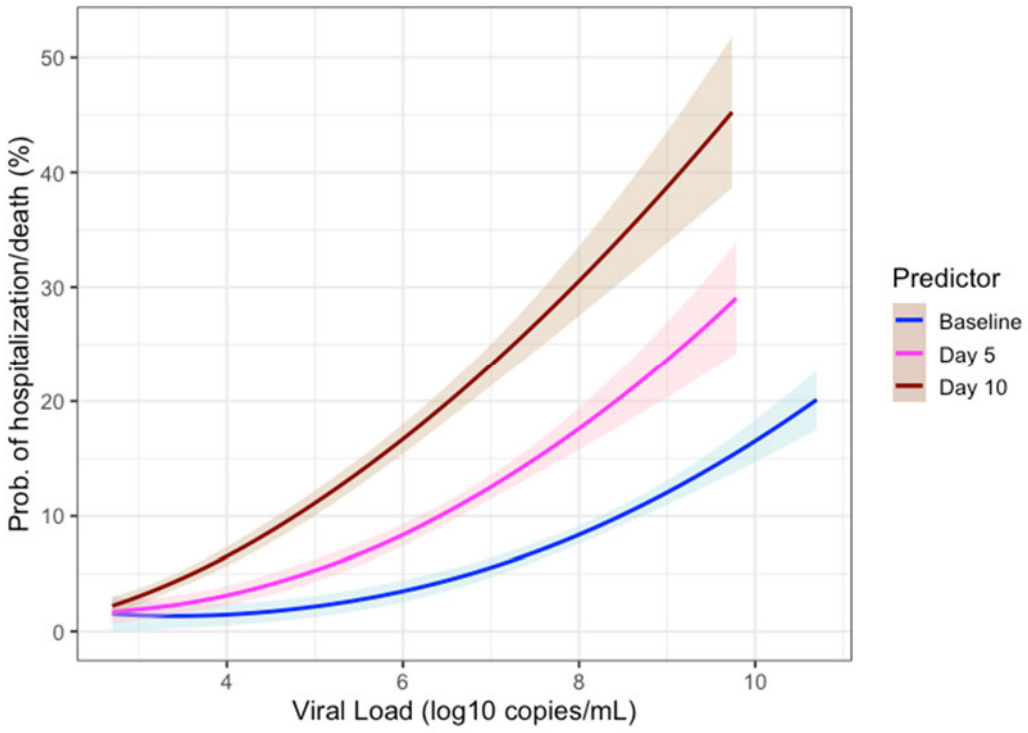
The E-R results which informed the choice of dose and the clinical equivalence bounds for MOV for the treatment of COVID-19 were discussed in [Sec. 2.7.2-covid19txallpop: 1.5]. In this section, additional insights into SARS-COV-2 infection process and the determinants of antiviral drug response in COVID-19 treatment obtained from the E-R and the viral dynamics analyses are discussed.

3.4.1.1 Natural Disease Process and Relationship with Clinical Outcomes

The final IVDM for COVID-19 describes the clinical data from the MOV Phase 2 and 3 studies well, including appropriately representing variation in response across individual and subpopulations [Ref. 5.3.5.3: 05R5Z5]. This mechanistic representation of disease indicated that the processes of cellular infection, viral production, and immune response are in a time-varying, nonequilibrium state throughout the course of SARS-CoV-2 infection, such that the characteristics of the viral load profile (magnitude and timing of peak viral load, slope of decline post peak, and duration of viral load) are determined by a complex interplay of these processes.

In the empiric E-R analysis of the Phase 3 data [Ref. 5.3.5.3: 07YDDS], models were investigated to characterize the link between the key pharmacodynamic biomarker of viral load and the primary clinical outcome to better facilitate holistic interpretation of results for both measures in appropriate context. Both the data exploration and the modeling clearly point to the importance of viral load in clinical outcomes. Participants with high baseline viral load are at greater risk for more severe symptomology, hospitalization, need for supplemental oxygen, need for ventilation, and death than those with lower baseline viral load. However, there was an even stronger relationship with sustained high viral loads as measured on Day 5 or Day 10 with these outcomes [Figure 2.7.2-covid19txallpop: 21]. This points to high and sustained viral load as being a key driver of poorer outcomes in COVID-19. As such antiviral therapies, such as molnupiravir, likely exert their influence on outcomes by reducing viral loads more quickly than the natural immune response alone. In characterizing drug effects on viral load, change from baseline measures relative to placebo are typically reported to more clearly separate drug effects from the natural viral load time course. However, this additional change from baseline is not itself the driver of clinical outcome, but rather it is the resulting absolute viral load (natural immune response + drug effect) that likely influences the outcome. This suggests that the magnitude of drug effect on viral load needed to avoid negative outcomes such as hospitalization or death will likely vary across individuals depending on the magnitude of their infection and their immune response.

Figure 2.7.2-covid19txallpop: 21
Estimated Relationship of Viral Load (Baseline, Day 5, or Day 10) and Probability of Hospitalization/Death based on Linear Logistic Regression Models of the Placebo Arm Data in P002 Part 2 (Phase 3)



Top curve: Day 10

Middle curve: Day 5

Lower curve: Baseline

Source: [Ref. 5.3.5.3: 05R5Z5]

3.4.1.2 Molnupiravir Mechanism of Action

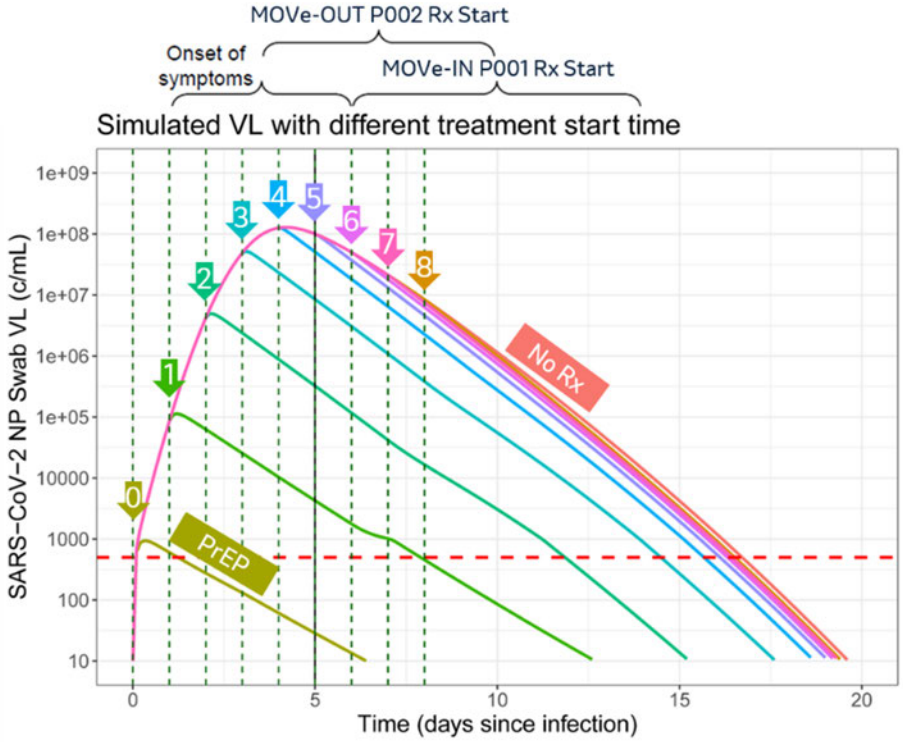
In the IVDM analysis, MOV mechanism of action was best described as an inhibitory process on the infectivity term in the model. An Emax term with estimated NHC AUC50 of 10544.94 nM*hr and fixed maximal response of 100% was adequate to describe the dose- and exposure-dependent drug effect on viral load. At the geometric mean exposure from the 800-mg Q12hr dose, the resulting drug effect is estimated to be an 76.2% reduction in viral infectivity. The results from the mechanistic modeling were consistent with results from the empiric E-R modeling where an NHC AUC50 estimate of 10260 nM*hr was obtained for viral load change from baseline at Day 5.

3.4.1.3 Influence of Time-Since-Symptom-Onset on Response

In the Phase 2 E-R analyses [Ref. 5.3.5.3: 08074R], early data exploration suggested that the presence and magnitude of drug effect could be influenced by patient population (nonhospitalized vs hospitalized) as well as the timing of the treatment start relative to the course of infection, as reflected by TSSO at baseline. The clearest drug effect signals and exposure-dependency were identified in the nonhospitalized patients (P002 and P006) with a TSSO ≤5 days. Viral load profile measures did not demonstrate statistically significant drug effect or exposure-dependency in the hospitalized patients (P001) or in the subset of P002 and P006 with TSSO >5 days. These and similar observations in the statistical analysis of the Phase 2 data informed the decision to study nonhospitalized patients with TSSO ≤5 days in the Phase 3 portion of P002.

The timing of therapeutic intervention relative to onset of symptoms was also investigated in the mechanistic viral dynamics analysis [Ref. 5.3.5.3: 05R5Z5]. Simulations suggest that due to the rapid dynamics, the timing of treatment start can strongly influence the drug effect achieved on the viral load profile. The IVDM-based simulation shown in [Figure 2.7.2-covid19txallpop: 22] illustrate that when untreated, the virus grows rapidly to reach the peak around day 4 postinfection before gradually declining. When the treatment is started early in the infection, MOV can achieve meaningful reductions in viral replication and shorten the duration of detectable viral load relative to no treatment. However, when the treatment is started late, such as after 5 days, the virology drug effect is substantially diminished as the process of ongoing cellular level infections is much less influential on the viral profile relative to the processes of infection clearance at these later timepoints.

Figure 2.7.2-covid19txallpop: 22
Simulated Typical Patient Viral Load Profiles for a Range of Treatment Start Times (Treatment Start Depicted as Numbered Downward Arrows) from 0-Day to 8-Days After Infection Using the Phase 2 Version of the Viral Dynamics Model (IVDM-2)



Source: [Ref. 5.3.5.3: 05R5Z5]

3.4.1.4 Variation in Response Across Individuals and Subpopulations

There is considerable overlap in the covariates identified as influential determinants of response variations in the empiric E-R analyses and in the mechanistic viral dynamics analysis. In the E-R model of the primary clinical outcome, covariates included baseline viral load, baseline disease severity, age, weight, clade, and comorbidities of active cancer and diabetes, and in the E-R models for virologic endpoints diabetes, baseline viral load and baseline disease severity were identified [Ref. 5.3.5.3: 07YDDS]. In the viral dynamics analysis, covariates identified included baseline viral load, age, baseline disease severity, clade, and diabetes [Ref. 5.3.5.3: 05R5Z5]. The IVDM covariates were mostly identified on the immune response parameters except for baseline viral load on infectivity. This suggests that the variation in the human response (eg, immune response) is more influential in COVID-19 disease than variations in the virus kinetics. This interpretation is also supported by the magnitude of IIV assessed on IVDM-4 parameters representing differing processes, where a 2.5-fold range in infectivity (beta) was estimated versus 14.5-fold range in viral clearance rate due to innate immunity (rho), 346-fold range in innate immunity activation rate (bN) and 89.7-fold range in adaptive immunity cell killing rate (m). Variations in

infectivity, innate and adaptive immune response appear to all contribute to the variation in baseline viral load across individuals, which is consistent with baseline viral load being an important covariate in all the E-R models. Variations related to clade for IVDM-4 were most apparent for the Delta clade with Delta clade associated with faster activation and increased viral clearance by the innate immune response, leading to a more rapid natural decline in viral load versus other clades, which is consistent with the reduced hospitalization rate identified with Delta in the outcomes E-R analysis. Increased age and comorbidity of diabetes were associated with reduced rate of viral clearance from the innate immunity response, suggesting that influential factors identified empirically in the hospitalization E-R modeling may be related to slower or less effective immune response leading to slower rate of decline in the viral load profile. Although not identified as a significant covariate, the subset of patient considered immunocompromised (due to HIV, organ transplant, active cancer, immunosuppressive therapies) was explored by examining Bayesian parameter estimates in these participants and through simulation in the viral dynamics analysis. Overall, the results suggest that this subpopulation is able to develop an immune response to SARS-CoV-2 and that molnupiravir is effective in further reducing viral loads in the immunocompromised population.

Across the E-R and viral dynamics analyses very few covariate relationships were identified on molnupiravir drug effect and overall the results are consistent with the drug effect being maintained across a range of subpopulations. Diabetes was a covariate identified on Emax in the Day 5 viral load E-R model. Although it is difficult to mechanistically explain a basis for this relationship, it would be appropriate to continue to check whether this association is reproduced in other studies or in additional datasets. Enrollment bin was found to be not significant in the outcomes E-R model after accounting for other influential factors suggestive of a consistent drug effect across the study. Drug effect in the primary outcome model was best represented as an additive term on the other covariate terms, suggesting that caution is warranted in comparing relative risk reduction values between studies or among groups without a careful understanding of how the other influential factors may differ in these comparisons. As an external validation, the primary outcome event rate in the placebo arm was projected for a patient population similar to that studied in the Paxlovid EPIC-HR study using the E-R model developed from the MOV study data. The prediction from this exercise was 7.2% hospitalization or death, which is similar to the 6.4% rate reported for this study [Ref. 5.4: 07Z89H] which further illustrates the influence of patient population factors on outcomes.

3.4.2 Safety Evaluation

No clinically meaningful trends were observed in AEs, SAEs, drug-related AEs, discontinuations due to AEs or clinical laboratory values as a function of dose or treatment. No clinically meaningful hematological or liver function laboratory test result abnormalities were observed. Safety data are detailed in [Sec. 2.7.4-covid19txallpop]. A quartile analysis was conducted based on posthoc exposures for high-level safety categories (including the number of participants with COVID-19 with any AEs, drug-related AEs, or SAEs) to evaluate any safety-related exposure-dependency [Ref. 5.3.5.3: 07YDDS]. The findings of this evaluation are discussed in [Sec. 2.7.2-covid19txallpop: 1.5.2].

3.4.3 QTc Evaluation

Data from GLP safety pharmacology studies and Phase 1 clinical data support a lack of risk for QTc prolongation. In vitro hERG assays demonstrated a safety margin of >1000-fold for MOV and >28-fold for NHC (no IC50 determinable with highest evaluated exposures) based on unbound Cmax at the therapeutic dose [Sec. 2.6.2: 4.2, 4.3]. Additionally, no ECG changes (including QTc prolongation) were observed in the cardiovascular telemetry study in conscious dogs up to the highest dose tested of 50 mg/kg (5-fold above the NHC Cmax value of 10.8 μM at the 800-mg Q12H human dose) [Sec. 2.6.2: 4.5].

A concentration (NHC)-QTc analysis was conducted using Holter ECG data collected in the single and multiple ascending dose study (P004) [Sec. 2.7.2-covid19txallpop: 2.4.1.1]. Only data from the capsule formulation were used, single doses of 1200 and 1600 mg, and multiple doses from 50 to 600 mg Q12H. After completion of the study, the baseline Holter data at the 800-mg Q12H dose were lost when they were inadvertently not backed up prior to a system modification and could not be retrieved for the purposes of this analysis. A total of 60 participants were included in the analysis [Ref. 5.3.5.3: 06G3K2].

Based on the results of this analysis, no relationship was found between increases in NHC plasma concentrations and changes in QTcF. The placebo-corrected change from baseline in QTcF (ΔΔQTcF) estimate at a GM Cmax and corresponding 90% CIs for 1600 mg was -0.57 (-4.79, 3.65), with the upper 90% CI limit falling well below 10 msec, the threshold of regulatory concern according to ICH E14, and with the point estimate and lower 90% CI limit falling below zero. The observed NHC geometric mean Cmax (6350 ng/mL) at a 1600-mg dose in P004 was ~ 2-fold higher than the observed Cmax at a dose of 800 mg in P004 (fasted administration) and ~ 2.5-fold higher than the PopPK predicted geometric mean Cmax in COVID-19 participants (dosed without regard to food) at the 800-mg dose of 2590 ng/mL [Ref. 5.3.5.3: 07ZRF9]. In addition, no relationship was found between increases in NHC plasma concentrations and changes in QTcF in a Japan Phase 1 study (P008) within the dose range up to 1600 mg (observed NHC GM Cmax of 8910 ng/mL) [Ref. 5.3.5.3: 07ZK36].

There was no evidence of hysteresis; therefore, the lack of meaningful change in QTc at Cmax indicates that no meaningful effect on QTc throughout the dosing interval would be expected. AUC of NHC is similar in participants with COVID-19 and the healthy participants enrolled in P004 and accumulation with Q12H dosing is minimal. Differences in exposures associated with intrinsic/extrinsic factors (COVID-19 status, food, demographics, drug-drug interaction or organ impairment) were considered not clinically meaningful [Sec. 2.7.2-covid19txallpop: 3.2, 3.3] and were small relative to the exposures observed at the 1600-mg dose level. Furthermore, the in vitro hERG inhibition potential is low (IC50/free clinical Cmax >28 for NHC and >1000 for MOV) and is confirmed by the lack of QTc prolongation in clinical ECGs seen in this Phase 1 study. Taken together, the risk of QTc prolongation for the drug in the clinical setting is considered minimal.

4 SPECIAL STUDIES

No additional clinical pharmacology studies were conducted.

5 CONCLUSIONS

The key findings of the MOV clinical pharmacology assessments are as follows:

Conclusions for Pharmacokinetics and ADME:

- Following oral administration, MOV is converted to NHC during absorption/first-pass, likely involving the high capacity and widely distributed CES1 and CES2 carboxylesterases. MOV was quantifiable in only a minority of participants and only near Tmax with peak concentrations of MOV <0.5% of NHC.

- Uptake by nucleoside transporters and intracellular anabolism/catabolism of NHC involves the same pathways as those involved in endogenous pyrimidine distribution and metabolism. NHC in cells is converted to the active moiety NHC-TP.

- NHC is eliminated primarily by metabolism to cytidine and uridine involving at least 3 widely distributed enzymes; mARC1 and mARC2 (forms cytidine) and cytidine deaminase (forms uridine).

- NHC is not bound to plasma proteins.

- NHC has a median Tmax of approximately 1.5 hours following administration of DFC in the fasted state. The rate of absorption was slowed with a high-fat meal, resulting in a lower maximum concentration. However, this is not expected to be clinically meaningful as the extent of absorption remained consistent.

- NHC AUC and Cmax increase approximately dose proportionally.

- Plasma concentrations of NHC decline in a biphasic manner with an α-phase (distributional t1/2) of 0.6 hours which accounts for the majority of AUC and a β-phase (terminal t1/2) of 21 hours. The effective t1/2 of NHC is 3.3 hours. There is minimal accumulation with Q12H dosing.

- NHC PK is similar in participants with COVID-19 and healthy participants.

- Based on the Phase 3 PopPK model, the geometric mean (%CV) AUC0-12, Cmax, and C12 of NHC at steady-state following administration of MOV 800 mg Q12H for 5 days to participants with COVID-19 were 34000 nM*hr (41.2), 10000 nM (31.7), 119 nM (115), respectively.

- Intracellular NHC-TP exhibited a longer effective t1/2 than plasma NHC, resulting in a flatter PK profile with ~ 2-fold accumulation following Q12H dosing. The terminal half-life of NHC-TP in PBMCs is consistent with the terminal t1/2 of NHC in plasma.

- Despite the short effective t1/2 of NHC in the plasma, dosing MOV Q12H is appropriate based on the durable presence of meaningful intracellular NHC-TP concentrations throughout the dosing interval from Day 1 onwards.

- Individual NHC-TP PK in PBMCs correlated with individual NHC PK in plasma, with plasma NHC AUC shown to be a consistent, strongly correlated predictor of NHC-TP AUC in PBMCs.

Conclusion for effect of MOV on QTc:

- Based on the results of a concentration/QTc analysis, no relationship was found between increases in NHC plasma concentrations and changes in QTcF. This analysis together with nonclinical cardiovascular safety data indicate no meaningful risk of QTc prolongation for the drug in the clinical setting.

Conclusions for Dose and Bounds:

- A clinical dose of 800 mg Q12H for 5 days for patients with COVID-19 was selected based on the totality of the virologic data, trends in the clinical efficacy in Part 1 of P002, safety data in healthy participants and those with COVID-19, and E-R modeling.

- Clinical comparability bounds of (0.7, 2.0) are established to reflect the range of relative change in NHC AUC that would be expected to be clinically comparable with respect to efficacy and safety. Intrinsic and extrinsic factor effects that fall within this range are considered not clinically relevant and no alteration in the dosing guidance would be needed for those factors.

Intrinsic Factors:

- MOV can be used in patients with COVID-19 with no dose adjustment regardless of age, sex, body weight, BMI, race, ethnicity, or renal or hepatic impairment.

Extrinsic Factors:

- Coadministration of MOV with food does not have a clinically meaningful effect on the plasma exposures of NHC. Therefore, MOV may be administered without regard to food.

- MOV is not a substrate, inhibitor or inducer of major metabolic enzymes and is not a substrate or inhibitor of major transporters and therefore is not expected to meaningfully interact with other drugs.

6 APPENDIX

Appendix 2.7.2-covid19txallpop: 1
Overview of Clinical Pharmacology Program

Study Number	Brief Description of Study	Study Design	Treatment	Enrolled/ Completed (Male/Female)
Module 5.3.3.1 Healthy Participant PK and Initial Tolerability Study Reports				
MK-4482-004 (P004, EIDD-2801-1001)	A Randomized, Double-Blind, Placebo-Controlled, First-in-human Study Designed to Evaluate the Safety, Tolerability, and Pharmacokinetics of EIDD-2801 Following Oral Administration to Healthy Volunteers	Part 1:Multi-panel, sequential, double-blind, randomized, placebo-controlled, single ascending dose study	Part 1: MOV 50, 100, 200, 400, 600, 800, 1200, 1600 mg or placebo single dose	64/64 (53/11)
		Part 2: Open-label, randomized, 2-period crossover food effect study (fasted period and fed period)	Part 2: MOV 200 mg single dose	10/10 (7/3)
		Part 3: Multi-panel, sequential, double-blind, placebo-controlled, multiple ascending dose study	Part 3: MOV 50, 100, 200, 300, 400, 600, 800 mg or placebo Q12H × 5.5 days	56/56 (49/7)
MK-4482-012 (P012)	A Multiple Ascending Dose Clinical Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Molnupiravir in Healthy Participants	Double blind, randomized, placebo-controlled, multiple-ascending dose study	MOV 400, 600 or 800 mg or placebo Q12H × 10.5 days	32/32 (16/16)
Module 5.3.3.3 Intrinsic Factor PK Study Reports				
MK-4482-008 (P008)	A Single and Multiple Dose Clinical Study to Evaluate the Safety, Tolerability and Pharmacokinetics of MK-4482 in Healthy Japanese Adult Participants	Part 1: Multi-panel, 2-period, double-blind, placebo-controlled, single ascending dose study	Part 1 Panel A: MOV 200, 1600 mg or placebo single dose Part 1 Panel B: MOV 400 mg or placebo single dose Part 1 Panel C: 800 mg or placebo single dose	25/25 (25/-)
		Part 2: 2-panel, sequential, double-blind, placebo-controlled, multiple dose study	Part 2 Panel E: MOV 400 placebo Q12H × 5.5 days Part 2 Panel F: MOV 800 mg or placebo Q12H × 5.5 days	40/40 (40/-)

Appendix 2.7.2-covid19txallpop: 2
Tabular Summary of NHC PK Parameter Values by Study

PN	Short Title/ Design	MOV Dose/ Treatment	Day	N	GM (GCV%)					GMR (90% CI)		
					Cmax (ng/mL)	Tmax[a] (hr)	AUC0-inf (ng/mL*hr)	AUC0-last (ng/mL*hr)	t1/2 (hr)	AUC0-inf	Cmax	Ref
P004	A Randomized, Double-blind, Placebo-controlled, First-in-human Study Designed to Evaluate the Safety, Tolerability, and Pharmacokinetics of EIDD-2801 Following Oral Administration to Healthy Volunteers/ Part 1: SAD Part 2: Food effect Part 3: MAD	50 mg PIB	1	6	223 (46.2)	1.00 (0.517-1.00)	432 (26.5)	415 (27.4)	0.945 (12.1)			
		100 mg PIB	1	6	454 (42.2)	1.00 (0.500-1.50)	932 (27.0)	917 (27.5)	0.907 (10.1)			
		200 mg PIB	1	6	926 (12.6)	1.00 (0.500-1.00)	1830 (19.6)	1810 (20.0)	1.02 (16.4)			
		400 mg PIB	1	6	1850 (22.7)	1.00 (0.500-1.00)	4010 (20.2)	4000 (20.2)	1.03 (8.86)			
		600 mg PIB	1	6	2720 (27.0)	1.00 (1.00-1.00)	6130 (21.4)	6120 (21.6)	1.06 (10.3)			
		800 mg PIB	1	6	3640 (13.4)	1.00 (0.500-1.00)	8740 (10.4)	8720 (10.4)	1.29 (7.10)			
		1200 mg DFC	1	6	4500 (17.9)	1.75 (1.00-2.50)	13800 (11.8)	13800 (11.7)	1.81 (73.5)			
		1600mg DFC	1	6	6350 (20.6)	1.50 (1.00-2.00)	20700 (31.4)	20700 (31.4)	4.59 (71.6)			
		200 mg DFC (fasted)	1	10[b]	893 (36.8)	1.00 (1.00-2.50)	1980 (29.3)	1950 (29.9)	0.977 (13.0)	0.955 (0.881, 1.03)	0.644 (0.535, 0.775)	Fed versus Fasted
		200 mg DFC (fed)	1	10[b]	575.0 (27.7)	3.00 (2.00-4.00)	1890 (28.8)	1950 (29.0)	1.09 (16.3)			
		50 mg DFC Q12H x 5.5d	1	6	223 (19.4)	1.00 (1.00-1.00)	461 (15.7)	444 (17.3)	0.937 (14.0)			
			6	6	188 (8.67)	1.00 (1.00-1.50)	NC	414 (16.2)	0.968 (15.5)			
		100 mg DFC Q12H x 5.5d	1	6	395 (18.5)	1.25 (1.00-2.03)	855 (19.8)	835 (19.9)	0.918 (9.08)			

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PN	Short Title/ Design	MOV Dose/ Treatment	Day	N	GM (GCV%)					GMR (90% CI)		
					Cmax (ng/mL)	Tmax[a] (hr)	AUC0-inf (ng/mL*hr)	AUC0-last (ng/mL*hr)	t1/2 (hr)	AUC0-inf	Cmax	Ref
			6	6	434 (14.0)	1.25 (1.00-1.50)	NC	947 (15.7)	0.970 (15.8)			
		200 mg DFC Q12H x 5.5d	1	6	766 (16.3)	1.50 (1.00-1.50)	1660 (15.3)	1640 (15.5)	0.960 (10.4)			
			6	6	742 (32.1)	1.50 (0.500-1.50)	NC	1720 (26.0)	1.24 (36.4)			
		300 mg DFC Q12H x 5.5d	1	6	1280 (15.2)	1.50 (1.00-1.50)	3090 (17.4)	3080 (17.4)	1.09 (17.7)			
			6	6	1100 (20.6)	1.50 (1.00-2.00)	NC	2980 (16.3)	1.71 (47.1)			
		400 mg DFC Q12H x 5.5d	1	6	1530 (23.2)	1.50 (1.00-2.00)	3800 (19.5)	3790 (19.5)	1.05 (13.1)			
			6	6	1470 (20.9)	1.50 (1.00-1.50)	NC	3730 (21.6)	1.20 (9 58)[d]			
		600 mg DFC Q12H x 5.5d	1	6	2160 (31.4)	1.75 (1.00-6.00)	6680 (17.6)[d]	6110 (26.9)	1.16 (3 50)[d]			
			6	6	2240 (20.9)	1.75 (1.50-2.50)	NC	7250 (28.1)	NC			
		800 mg DFC Q12H x 5.5d	1	6	2770 (13.3)	1.75 (1.50-2.50)	8200 (21.6)	8180 (21.5)	1.18 (7.28)			
			6	5	2970 (16.8)	1.50 (1.00-2.02)	NC	8450 (18.5)	7.08 (154)[f]			
P008	A Randomized, Double-blind, Placebo-Controlled Clinical Study to Evaluate the Safety, Tolerability and Pharmacokinetics of MK-4482 in Healthy Japanese Adult Participants Part 1: Single dose	200 mg DFC	1	6	1210 (58.8)	1.00 (0.50-5.00)	2310 (21.7)	2310 (21.7)	1.28 (13.9)			
		400 mg DFC	1	6	3160 (11.6)	1.00 (1.00-1.50)	6410 (18.0)	6390 (18.0)	8.37 (15.1)			
		800 mg DFC (fasted)	1	7[c]	4750 (20.0)	1.50 (0.52-2.50)	12400 (15.4)	12400 (15.5)	3.95 (113.3)	1.11 (1.02, 1.20)	0.76 (0.67, 0.86)	Fed versus Fasted
		800 mg DFC (fed)	1	6[c]	3760 (17.0)	3.00 (2.00-3.00)	13800 (17.7)	13700 (17.8)	3.74 (78.5)			

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PN	Short Title/ Design	MOV Dose/ Treatment	Day	N	GM (GCV%)					GMR (90% CI)		
					Cmax (ng/mL)	Tmax[a] (hr)	AUC0-inf (ng/mL*hr)	AUC0-last (ng/mL*hr)	t1/2 (hr)	AUC0-inf	Cmax	Ref
	and food effect Part 2: MAD	1600 mg DFC	1	6	8910 (21.5)	2.00 (1.00-2.00)	26300 (13.5)	26300 (13.5)	5.50 (57.1)			
		400 mg DFC Q12H x 5.5d	1	15	2340 (24.1)	1.50 (1.00-2.00)	NC	5240 (17.1)[e]	NC			
			6	15	2320 (27.9)	1.50 (1.00-2.00)	NC	5410 (19.9)[e]	11.5 (18.6)			
		800 mg DFC Q12H x 5.5d	1	15	5000 (15.5)	1.50 (1.00-2.00)	NC	12100 (15.6)[e]	NC			
			6	13	4650 (20.8)	1.50 (1.00-2.50)	NC	12600 (15.6)[e]	10.2 (49.4)			

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PN	Short Title/ Design	MOV Dose/ Treatment	Day	N	GM (GCV%)					GMR (90% CI)		
					Cmax (ng/mL)	Tmax[a] (hr)	AUC0-inf (ng/mL*hr)	AUC0-last (ng/mL*hr)	t1/2 (hr)	AUC0-inf	Cmax	Ref
P012	A Randomized, Double-blind, Placebo-Controlled, Multiple ascending dose Clinical Study to Evaluate the Safety, Tolerability and Pharmacokinetics of MK-4482 in Healthy Adult Participants[g]	400 mg DFC Q12H x10.5d	1	6	2157 (19.6)	1.50 (0.50 - 1.55)	NC	4666 (15.6)	NC			
			11	6	2177 (25.8)	1.50 (0.57 – 2.00)	5314 (17.8)	5262 (17.6)	16.4 (117.0)			
		600 mg DFC Q12H x 10.5d	1	6	2851 (29.4)	1.50 (1.50 – 2.00)	NC	6921 (23.4)	NC			
			11	6	2312 (33.3)	1.75 (1.50 – 2.00)	7077 (32.2)	7025 (32.6)	20.6 (22.7)			
		800 mg DFC Q12H x10.5d	1	12	3629 (54.5)	1.98 (1.50 – 4.00)	NC	9876 (38.3)	NC			
			11	12	4199 (34.2)	1.50 (1.50 – 2.02)	11795 (28.6)	11743 (28.5)	20.6 (11.0)			

AUC0-inf = area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC0-last = area under the plasma concentration-time curve from time 0 to the last measurable non-zero concentration (tlast); CI=confidence interval; Cmax = maximum observed concentration; DFC=dry-filled capsule; GCV%= percent coefficient of variation based on geometric mean; GM=geometric mean; MAD=multiple ascending dose; MOV=molnupiravir, MK-4482, EIDD-2801; N = number of participants with valid observations; NC = not calculated; NHC=N-hydroxycytidine; PIB=powder-in-bottle; PK=pharmacokinetic; PN=protocol number; Q12H=every 12 hours; SAD=single ascending dose; t1/2 = apparent terminal elimination half-life; tmax = time of the maximum observed concentration

[a] Median (minimum- maximum) values are presented for Tmax

[b] n=10 received 2 single oral 200 mg DFC doses in fasted and fed state separated by a 14 day washout

[c] n=6 received 2 single oral 800 mg DFC doses in the fasted and fed state separated by a 14 day washout

[d] n=5

[e] AUC0-12

[f] n=4

[g] original geometric mean Cmax and AUC data in CSR was presented as a nM and was converted to ng/mL by multiplying value by 259.22/1000

Data source: [Ref. 5.3.3.1: P004MK4482] [Ref. 5.3.3.3: P008MK4482] [Ref. 5.3.3.1: P012MK4482

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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, treatment, and medication

Abbreviation	Definition
AE	Adverse event
AUC	Area under the concentration time curve
BMI	Body mass index
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CSR	Clinical study report
EIDD	Emory Institute for Drug Development
EOT	End of Treatment
IA	Interim analysis
LNS	Low frequency nucleotide substitutions
MITT	Modified intent-to-treat
MOV	Molnupiravir, MK-4482, EIDD-2801
NEWS	National Early Warning Score
NHC	N-hydroxycytidine
NP	Nasopharyngeal
OP	Oropharyngeal
PCR	Polymerase chain reaction
PK	Pharmacokinetic(s)
PopPK	Population PK
Q12H	Every 12 hours
RdRp	RNA-dependent RNA polymerase
RNA	Ribonucleic acid
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAP	Statistical Analysis Plan

Abbreviation	Definition
SD	Standard Deviation
sSAP	Supplemental Statistical Analysis Plan
WHO	World Health Organization

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1 BACKGROUND AND OVERVIEW OF CLINICAL EFFICACY

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. MOV has demonstrated activity against SARS- CoV-2 both in vitro and in animal infection models and has a high barrier to development of viral resistance. MOV is orally administered and reduces the risk of hospitalization or death in non-hospitalized, adult patients with mild or moderate laboratory-confirmed COVID-19 at high risk for disease progression.

This Summary of Clinical Efficacy provides an overview of the clinical efficacy profile of MOV from 3 clinical studies evaluating the efficacy and safety of MOV for the treatment of COVID-19 in adults.

1.1 General Design and Rationale for Clinical Efficacy Studies Comprising the Development Program

The scientific background and rationale for the MOV clinical development program is provided in [Sec. 2.5-covid19txallpop: 1].

The data contributing to the evaluation of efficacy are from 3 clinical studies. The clinical efficacy of MOV is primarily based on the Phase 3 (Part 2) results for the pivotal, ongoing, Phase 2/3 study (MK-4482-002 [P002]). Other supportive efficacy results are also included from the analysis of the completed Phase 2 (Part 1) portion of P002, the completed Phase 2a study (MK-4482-006 [P006], also known as EIDD-2801-2003), and the completed Phase 2 study (MK-4482-001 [P001]).

Phase 3 (Part 2) results for P002 includes data from an IA (combined IA3/IA4, 50% of Phase 3 participants completed Day 29 Visit) and data from all participants randomized in Phase 3 through Day 29. At the IA3/IA4 time point, the prespecified statistical criterion for success was met and the study's formal evaluation of efficacy was considered complete (the null hypothesis was rejected based on the results). Descriptive summaries of efficacy for all participants randomized in Phase 3 (Part 2) through Day 29 are considered supportive of the analyses reported at the IA3/IA4 timepoint.

These 3 included studies enrolled a diverse population of adults with COVID-19 [Table 2.7.3-covid19txallpop: 1].

1.2 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 protocol-specific SAP/sSAP or are contained in the protocols for the 3 included studies [Ref. 5.3.5.1: P002V03MK4482: 16.1.9, 16.1.1] [Ref. 5.3.5.1: P002V01MK4482: 16.1.9, 16.1.1] [Ref. 5.3.5.1: P006MK4482: 16.1.9, 16.1.1] [Ref. 5.3.5.1: P001V01MK4482: 16.1.9, 16.1.1].

Due to differences in study populations, severity of illness, laboratory methodologies, and other design factors, no integration of efficacy across studies was planned.

2 SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

An overall description of all studies contributing to efficacy 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 final analyses of prespecified exploratory virology endpoints for 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] and summary of these results are in [Sec. 2.7.3-covid19txallpop: 2.1.1.3.1].

Table 2.7.3-covid19txallpop: 1
Summary of Clinical Efficacy Studies with MOV

<table>
<tr><th>Study Number (Status) [CTD Location] Regions</th><th>Study Design</th><th>Number of Participants by Intervention Group (Randomized/Treated/Completed)</th><th>Study Population</th><th>Efficacy Endpoints</th></tr>
<tr><td colspan="5">Phase 2/3 Study</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>Title: A Phase 2/3, Randomized, Placebo-controlled, Double-Blind Clinical Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MK-4482 in Non-Hospitalized adults with COVID-19
Design: Randomized, placebo-controlled, double-blind study
Treatment duration: 5 days</td>
<td>Part 1: Dose ranging (Phase 2)- Completed
1:1:1:1 200 mg, 400 mg, 800 mg, or placebo, oral Q12H x 5 days
Part 1 (Day 29 Visit):
<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>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: Evaluation of selected dose (Phase 3)- Ongoing[a]
1:1 selected dose of MOV vs placebo oral Q12H x 5 days
Part 2 (Day 29 Visit): Combined IA3/IA4
<table>
<tr><th>Group</th><th>R</th><th>T</th><th>C</th></tr>
<tr><td>MOV 800 mg</td><td>387</td><td>386</td><td>369</td></tr>
<tr><td>Placebo</td><td>388</td><td>379</td><td>358</td></tr>
</table>
Part 2 (Day 29 Visit): All participants randomized</td>
<td>Males/females, ≥18 years of age, with laboratory-confirmed SARS-CoV-2 infection, non-hospitalized, at high risk for disease progression
Part 1 (Phase 2): symptom onset ≤7 days
<table>
<tr><th>Group</th><th>Sex Male/Female</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 (Day 29 Visit): Combined IA3/IA4: symptom onset ≤5 days
<table>
<tr><th>Group</th><th>Sex Male/Female</th><th>Median Age (range) years</th></tr>
<tr><td>MOV 800 mg</td><td>187 M/200 F</td><td>41.0 (18-87)</td></tr>
<tr><td>Placebo</td><td>217 M/171 F</td><td>43.0 (18-88)</td></tr>
</table>
Part 2 (Day 29 Visit): All participants randomized: symptom onset ≤5 days</td>
<td>• Primary endpoint:
- Hospitalization or death
• Secondary endpoints:
- COVID-19 signs and symptoms
- WHO 11-point scale score
• Exploratory endpoints:
- Acute Care Visits
- COVID-19-related acute care visits
- NHC and NHC-TP concentrations
- SARS-CoV-2 RNA
- SARS-CoV-2 RNA sequences
- SARS-CoV-2 infectivity</td>
</tr>
</table>

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<table>
<tr><th>Study Number (Status) [CTD Location] Regions</th><th>Study Design</th><th>Number of Participants by Intervention Group (Randomized/Treated/Completed)</th><th>Study Population</th><th>Efficacy Endpoints</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><th>Group</th><th>R</th><th>T</th><th>C</th></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>
<table>
<tr><th>Group</th><th>Sex Male/Female</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></td></tr>
<tr><td colspan="5">Phase 2a Study</td></tr>
<tr><td>MK-4482-006 (also known as EIDD-2801-2003) (completed) [Ref. 5.3.5.1: P006MK4482]
North America</td><td>Title: A Phase IIa, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Safety, Tolerability, and Efficacy of EIDD-2801 to Eliminate SARS-CoV-2 Viral RNA Detection in Persons with COVID-19
Design: Randomized, double-blind, placebo-controlled study
Treatment duration: 5 days</td><td>Part 1:
1:1 200 mg or placebo, oral BID x 5 days, Oral
Parts 2 to 9:
3:1 MOV up to 800 mg or placebo, oral BID x 5 days
Parts 1-9 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 1-9 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>• Primary endpoint: Time to SARS-CoV-2 RNA negativity
• Secondary endpoints:
- SARS-CoV-2 infectivity
- SARS-CoV-2 RNA
- SARS-CoV-2 RNA mutation rate
- Patient-reported symptoms
- Time to improvement of new or worsened symptoms
- Hospitalization
- NHC concentrations</td></tr>
</table>

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<table>
<tr><th>Study Number (Status) [CTD Location] Regions</th><th>Study Design</th><th>Number of Participants by Intervention Group (Randomized/Treated/Completed)</th><th>Study Population</th><th>Efficacy Endpoints</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 and Africa
Asia Pacific</td>
<td>Title: A Phase 2/3 Randomized, Placebo-Controlled, Double-Blind Clinical Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MK-4482 in Hospitalized Adults with COVID-19
Design: Randomized, placebo-controlled, double-blind study
Treatment duration: 5 days</td>
<td>Part 1: Dose ranging (Phase 2) – Completed
1:1:1:1 200 mg, 400 mg, 800 mg, or placebo, oral Q12H x 5 days
Part 1 (Day 29 Visit):
<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>
Part 2: Evaluation of selected dose (Phase 3) – not conducted</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 (Day 29 Visit):
<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>• Primary endpoint: Time to sustained recovery
• Secondary endpoints:
- All-cause mortality
• Exploratory endpoints:
- NHC and NHC-TP concentrations
- SARS-CoV-2 RNA
- SARS-CoV-2 RNA sequences
• Additional Analyses:
- SARS-CoV-2 infectivity</td>
</tr>
<tr><td colspan="5">[a] Completed through Day 29 (efficacy evaluation); participants continuing through Late Follow-up Visit.
BID=twice daily; COVID-19=coronavirus disease 2019; EIDD=Emory Institute for Drug Development; IA=interim analysis; MOV=molnupiravir (MK-4482, EIDD-2801); NHC=N-hydroxycytidine; NHC-TP=N-hydroxycytidine-5′-triphosphate; P=protocol number; Q12H=every 12 hours; RNA=ribonucleic acid; SARS-CoV-2=severe acute respiratory syndrome coronavirus-2; WHO=World Health Organization.</td></tr>
</table>

Source: [Ref. 5.3.5.1: P002V01MK4482: Table 10-1, 14.1-5] [Ref. 5.3.5.1: P002V03MK4482: Table 10-1, 10-2, 14.1-13, 14.1-15] [Ref. 5.3.5.1: P006MK4482: Table 14.1.1.1, 14.1.3.1.1, 2] [Ref. 5.3.5.1: P001V01MK4482: Table 14.1-1, 14.1-4] [Ref. 5.3.5.1: P001V01MK4482: 16.1.3.1].

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2.1 Phase 2/3 Study Results

2.1.1 P002 (Part 2)

2.1.1.1 Primary Efficacy Endpoint - Hospitalization or Death

2.1.1.1.1 Combined IA3/IA4

A full analysis and summary of the IA3/IA4 results are included in the P002 Part 2 CSR [Ref. 5.3.5.1: P002V03MK4482].

Hospitalization or death through Day 29 was selected as the primary endpoint as 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. In the MITT population, participants were included in the intervention group to which they were randomized.

At the IA3/IA4 timepoint, MOV met the protocol-defined criterion (one-sided p-value boundary <0.0092) for demonstration of superiority to placebo for the primary efficacy endpoint [Table 2.7.3-covid19txallpop: 2].

- 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 2.7.3-covid19txallpop: 2].
    - One participant in the placebo group with unknown Day 29 survival status was counted as having an outcome of hospitalization or death in the analysis of the primary endpoint [Table 2.7.3-covid19txallpop: 3].
- The 8 participants who died through Day 29 were all in the placebo group and were hospitalized prior to their death. No participants in the MOV group died [Table 2.7.3-covid19txallpop: 3].

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Table 2.7.3-covid19txallpop: 2
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%.).

Source: [P002V02MK4482: adam-adeff1]

Table 2.7.3-covid19txallpop: 3
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.

Source: [P002V02MK4482: adam-adsl; adeff1]

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 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, and an analysis excluding participants who received <5 doses of study intervention or were hospitalized or died before their fifth 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].

2.1.1.1.2 All Participants Randomized in Part 2

The efficacy results for all participants randomized in Part 2 and followed through Day 29 are included in the P002 Part 2 CSR [Ref. 5.3.5.1: P002V03MK4482: 11] 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 2.7.3-covid19txallpop: 4] [Table 2.7.3-covid19txallpop: 5] [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 percentage point 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 2.7.3-covid19txallpop: 4].
  - One participant in the placebo group with unknown Day 29 survival status was counted as having an outcome of hospitalization or death in the analysis of the primary endpoint [Table 2.7.3-covid19txallpop: 5].
- Nine participants in the placebo group and 1 participant in the MOV group died through Day 29 [Table 2.7.3-covid19txallpop: 5].

Table 2.7.3-covid19txallpop: 4
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]

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Table 2.7.3-covid19txallpop: 5
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 fifth dose, an analysis imputing unknown hospitalization status as failure, and an analysis which 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 2.7.3-covid19txallpop: 6] [Table 2.7.3-covid19txallpop: 7] [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 2.7.3-covid19txallpop: 6
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 2.7.3-covid19txallpop: 7
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)

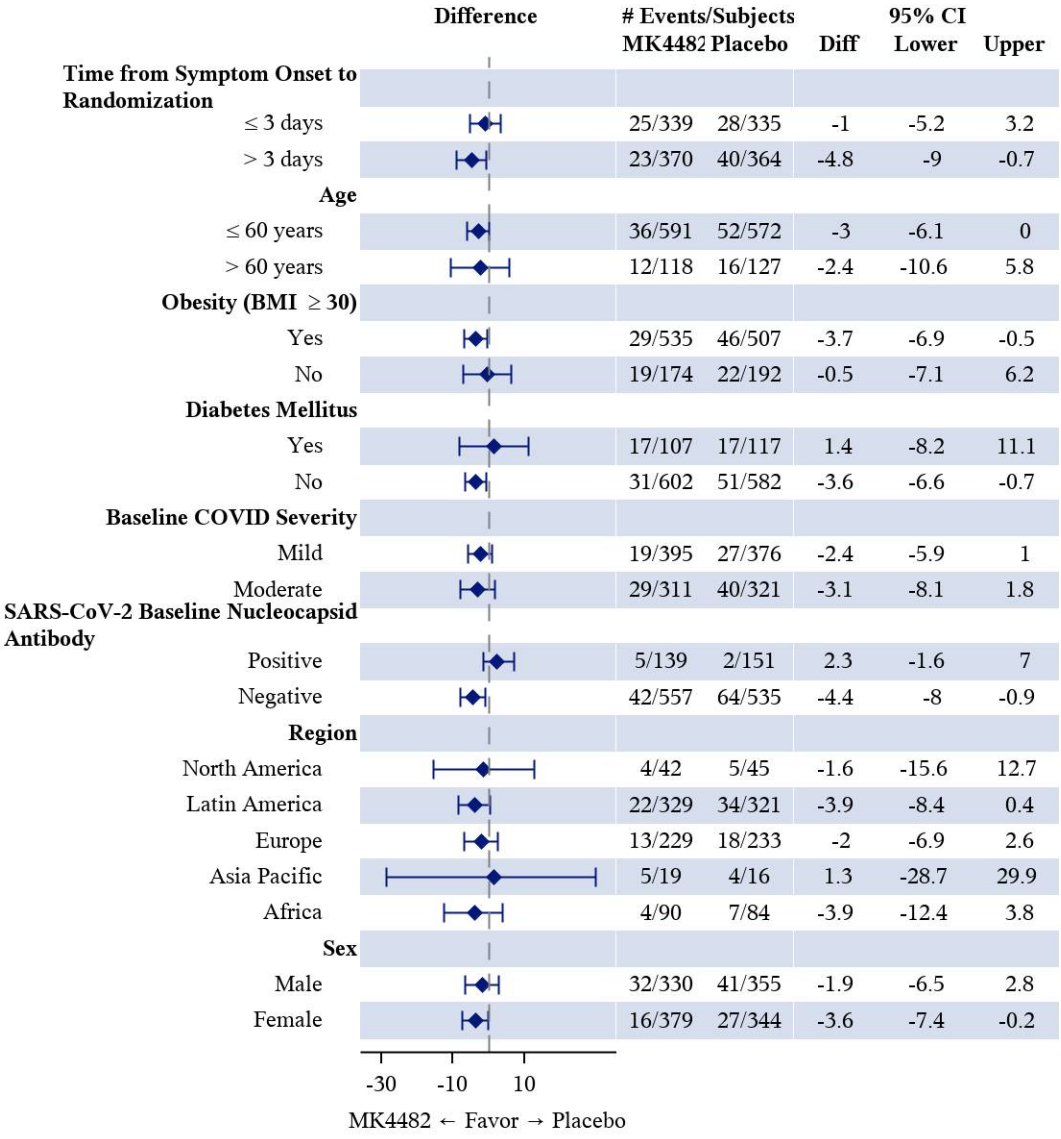
n= number of participants with the corresponding event.
Every participant is counted a single time for each applicable row and column. Participants who died were hospitalized prior to death; such participants are counted once each in the hospitalization and death rows.

Source: [P002V03MK4482: adam-adsl; adeff3]

Subgroup Analyses

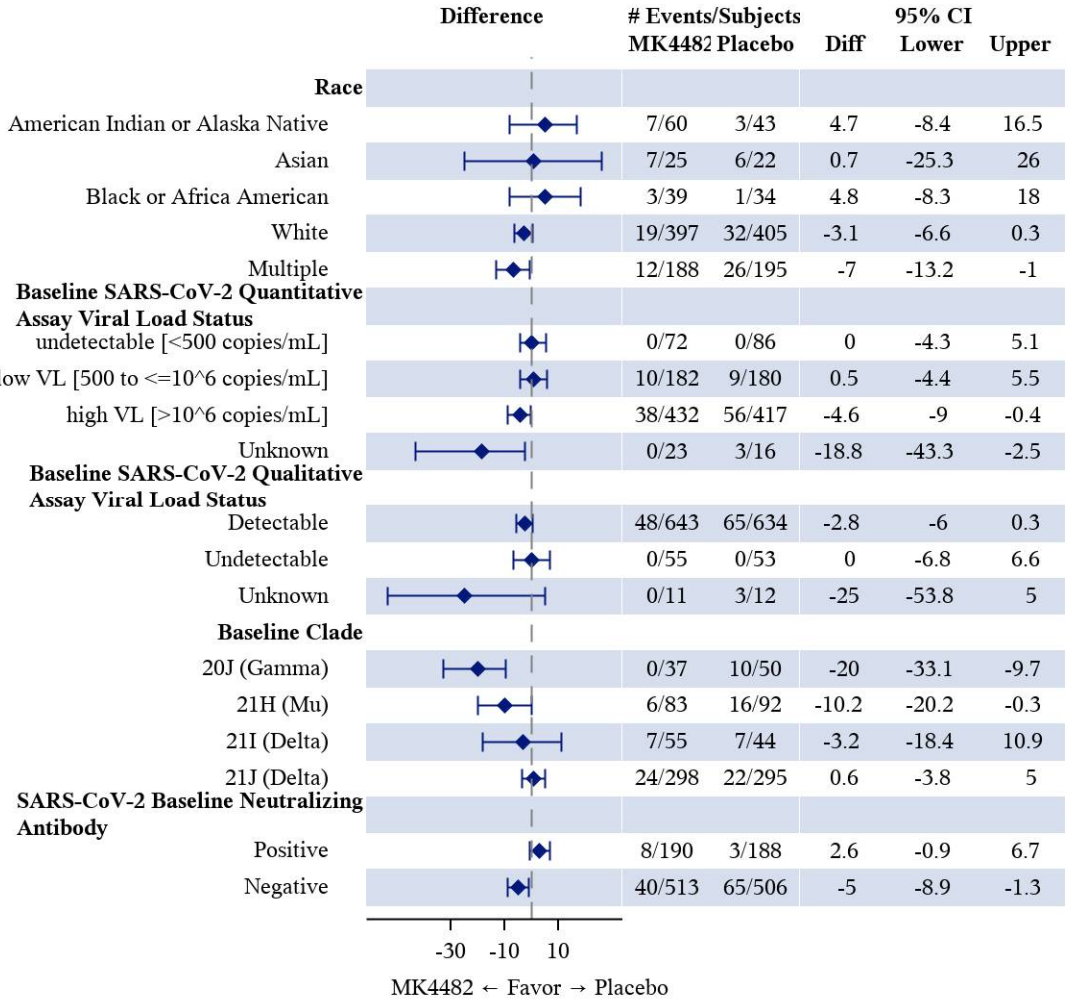
Results of subgroup analyses of the primary endpoint based on prespecified baseline characteristics, including updated virology characteristics, are presented in [Figure 2.7.3-covid19txallpop: 1] [Appendix 2.7.3-covid19txallpop: 1].

Figure 2.7.3-covid19txallpop: 1
Incidence of Hospitalization or Death Through Day 29 by Subgroup
Modified Intent-To-Treat Population
MK-4482-002 Part 2 Day 29 Virology DBL



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Incidence of Hospitalization or Death Through Day 29 by Subgroup
Modified Intent-To-Treat Population
MK-4482-002 Part 2 Day 29 Virology DBL (Continued)



	# Events/Subjects MK4482	Placebo	Diff	95% CI Lower	Upper
Race					
American Indian or Alaska Native	7/60	3/43	4.7	-8.4	16.5
Asian	7/25	6/22	0.7	-25.3	26
Black or Africa American	3/39	1/34	4.8	-8.3	18
White	19/397	32/405	-3.1	-6.6	0.3
Multiple	12/188	26/195	-7	-13.2	-1
Baseline SARS-CoV-2 Quantitative Assay Viral Load Status					
undetectable [<500 copies/mL]	0/72	0/86	0	-4.3	5.1
low VL [500 to <=10^6 copies/mL]	10/182	9/180	0.5	-4.4	5.5
high VL [>10^6 copies/mL]	38/432	56/417	-4.6	-9	-0.4
Unknown	0/23	3/16	-18.8	-43.3	-2.5
Baseline SARS-CoV-2 Qualitative Assay Viral Load Status					
Detectable	48/643	65/634	-2.8	-6	0.3
Undetectable	0/55	0/53	0	-6.8	6.6
Unknown	0/11	3/12	-25	-53.8	5
Baseline Clade					
20J (Gamma)	0/37	10/50	-20	-33.1	-9.7
21H (Mu)	6/83	16/92	-10.2	-20.2	-0.3
21I (Delta)	7/55	7/44	-3.2	-18.4	10.9
21J (Delta)	24/298	22/295	0.6	-3.8	5
SARS-CoV-2 Baseline Neutralizing Antibody					
Positive	8/190	3/188	2.6	-0.9	6.7
Negative	40/513	65/506	-5	-8.9	-1.3

The corresponding confidence interval is based on Miettinen & Nurminen method.
Time from symptom onset to randomization is based on the value of the stratification factor collected at randomization.
Source: [P002VRV03MK4482: adam-adsl; adeff1]

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2.1.1.1.3 Summary of Differences 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. The reduced treatment effect among all participants randomized in Part 2 compared to IA3/IA4 is due to the results in the post-IA3/IA4 cohort. 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.

2.1.1.2 Secondary Efficacy Endpoints

To further evaluate the efficacy of MOV administered to non-hospitalized participants, additional relevant endpoints were selected, which 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].

2.1.1.2.1 All Participants Randomized in Part 2

2.1.1.2.1.1 COVID-19 Signs and Symptoms

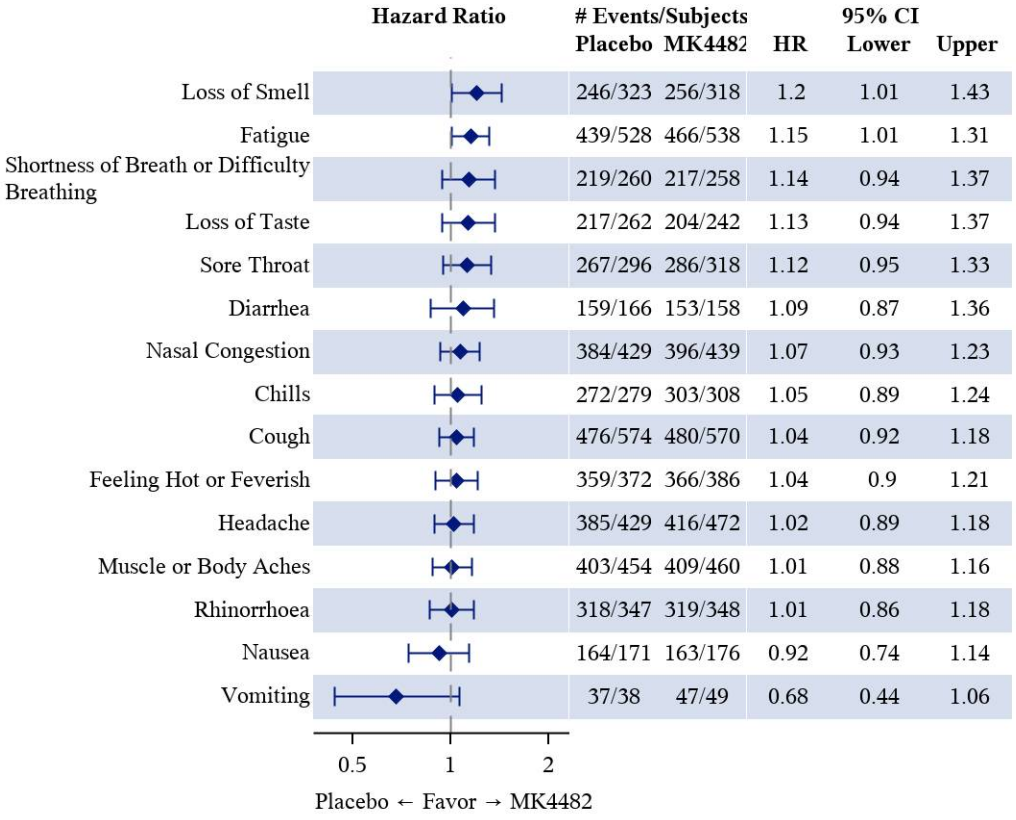
The analyses of self-reported signs and symptoms attributable to COVID-19 were based on data collected from a daily, 15-item paper symptom diary completed by the participant. The diary completion rates were comparable in the intervention groups, with greater than 92% completion for any sign/symptom through 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 hazard ratio >1) for participants treated with MOV compared with placebo [Figure 2.7.3-covid19txallpop: 2]. 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].

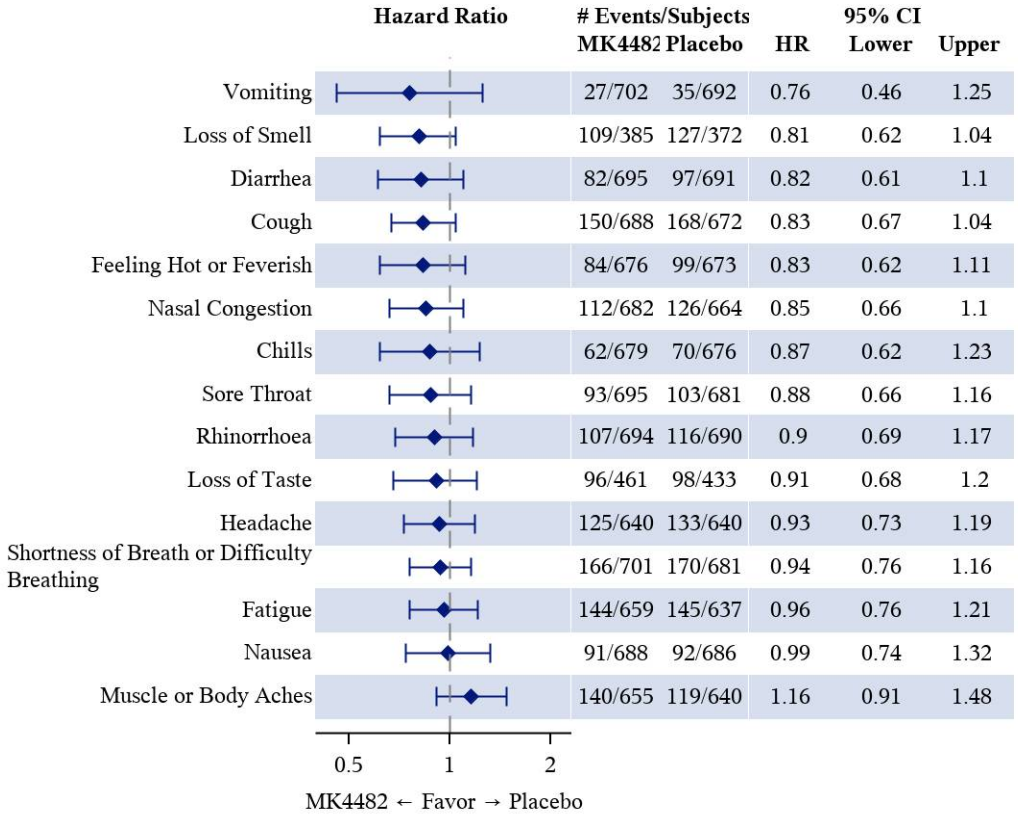
Progression (worsening) was less likely (indicated by hazard ratio <1) for participants treated with MOV for most self-reported COVID-19 signs and symptoms compared with placebo [Figure 2.7.3-covid19txallpop: 3]. A lower proportion of participants reported progression in the MOV group compared with the 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 2.7.3-covid19txallpop: 2
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



Based on Cox regression model with Efron's method of tie handling with treatment and randomization stratification factor as covariates. Hazard ratio > 1 favors the MK-4482 800 mg group.
Source: [P002V03MK4482: adam-adtte]

Figure 2.7.3-covid19txallpop: 3
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



Based on Cox regression model with Efron's method of tie handling with treatment and randomization stratification factor as covariates. Hazard ratio < 1 favors the MK-4482 800 mg group.
Source: [P002V03MK4482: adam-adtte]

2.1.1.2.1.2 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 trajectory over the course of illness.

2.1.1.3 Exploratory Endpoints

2.1.1.3.1 All Participants Randomized in Part 2

2.1.1.3.1.1 Acute Care Visits

The percentage of participants who have 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 health care 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].

2.1.1.3.1.2 Virology

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 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. The mechanism of antiviral activity of MOV is viral error catastrophe predicated on increasing the viral mutation rate beyond a biologically tolerable threshold resulting in impairment of viral fitness and infectivity leading to viral elimination.

Combined IA3/IA4

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

All Participants Randomized in Part 2

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

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Table 2.7.3-covid19txallpop: 8
Mean Change from Baseline Over Time in SARS-CoV-2 RNA Titer (Log10 Copies/mL)
Based on Quantitative Assay
Nasopharyngeal Sample
Modified Intent-To-Treat Population
MK-4482-002 Part 2 Day 29 Virology DBL

	MK-4482 800 mg			Placebo		
Visit	N	Mean[a]	Mean Change[a] (SD)	N	Mean[a]	Mean Change[a] (SD)
SARS-CoV-2 RNA Titer (log10 copies/ml)						
Baseline	614	6.89		597	6.91	
Day 3	570	5.75	-1.17 (1.450)	570	5.96	-0.97 (1.352)
EOT (Day 5)	558	4.68	-2.25 (1.633)	547	4.96	-1.95 (1.580)
Day 10	518	3.59	-3.30 (1.737)	510	3.75	-3.16 (1.773)
Day 15	515	3.14	-3.73 (1.880)	506	3.22	-3.69 (1.913)
Day 29	516	2.84	-4.00 (1.814)	513	2.85	-4.08 (1.843)
SARS-CoV-2 RNA Titer (log10 copies/ml) in Participants with Baseline RNA Titer ≤ 10^6 copies/ml						
Baseline	182	4.62		180	4.62	
Day 3	167	3.98	-0.63 (1.377)	170	4.25	-0.36 (1.241)
EOT (Day 5)	162	3.53	-1.08 (1.223)	166	3.65	-0.96 (1.357)
Day 10	152	3.02	-1.58 (1.000)	157	3.13	-1.46 (1.251)
Day 15	154	2.99	-1.63 (1.154)	156	3.08	-1.55 (1.222)
Day 29	153	2.78	-1.76 (0.946)	154	2.77	-1.83 (0.967)
SARS-CoV-2 RNA Titer (log10 copies/ml) in Participants with Baseline RNA Titer > 10^6 copies/ml						
Baseline	432	7.84		417	7.90	
Day 3	403	6.49	-1.39 (1.422)	400	6.69	-1.23 (1.314)
EOT (Day 5)	396	5.15	-2.73 (1.534)	381	5.53	-2.39 (1.474)
Day 10	366	3.83	-4.02 (1.452)	353	4.02	-3.92 (1.409)
Day 15	361	3.21	-4.63 (1.335)	350	3.28	-4.64 (1.292)

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Mean Change from Baseline Over Time in SARS-CoV-2 RNA Titer (Log10 Copies/mL)
Based on Quantitative Assay
Nasopharyngeal Sample
Modified Intent-To-Treat Population
MK-4482-002 Part 2 Day 29 Virology DBL

	MK-4482 800 mg			Placebo		
Visit	N	Mean[a]	Mean Change[a] (SD)	N	Mean[a]	Mean Change[a] (SD)
SARS-CoV-2 RNA Titer (log10 copies/ml) in Participants with Baseline RNA Titer > 10^6 copies/ml						
Day 29	363	2.87	-4.95 (1.136)	359	2.88	-5.04 (1.168)

[a] Mean and mean change from baseline is based on the measurements of participants with values at both baseline and the time point assessed.

Baseline measurements are defined as the latest record before first dose for each participant.

SD=Standard deviation.

N=Number of participants with baseline and at least one postbaseline test result at the time point assessed.

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

The quantitative assay is the Q2 SARS-CoV-2 Viral Load Quantitation Assay by RT-PCR.

The assay LLOQ is 500 copies/ml and ULOQ is 500,000,000 copies/ml. Postbaseline results that are below LLOQ are included in the mean and mean change from baseline with the imputed value 499. Postbaseline samples with values that are above ULOQ were diluted by a factor of 100 for measurement, and remeasured results were included in the mean and mean change from baseline.

Analysis only includes participants with baseline SARS-CoV-2 RNA titer ≥ 500 copies/mL.

Source: [P002VRV03MK4482: adam-adrna]

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Table 2.7.3-covid19txallpop: 9
Proportion of Participants With Undetectable SARS-CoV-2 RNA Over Time Based on Qualitative Assay
Nasopharyngeal Sample
Modified Intent-To-Treat Population
MK-4482-002 Part 2 Day 29 Virology DBL

Visit	MK-4482 800 mg		Placebo		Difference
	n/N	% (95% CI)[a]	n/N	% (95% CI)[a]	% (95% CI)[b]
All Participants					
Baseline	0/643	0.0 (0.0, 0.6)	0/634	0.0 (0.0, 0.6)	0.0 (-0.6, 0.6)
Day 3	20/612	3.3 (2.0, 5.0)	17/611	2.8 (1.6, 4.4)	0.5 (-1.5, 2.5)
EOT (Day 5)	44/606	7.3 (5.3, 9.6)	42/594	7.1 (5.1, 9.4)	0.2 (-2.8, 3.2)
Day 10	119/563	21.1 (17.8, 24.7)	105/547	19.2 (16.0, 22.8)	1.9 (-2.8, 6.7)
Day 15	236/547	43.1 (38.9, 47.4)	240/554	43.3 (39.1, 47.6)	-0.3 (-6.1, 5.6)
Day 29	398/536	74.3 (70.3, 77.9)	419/546	76.7 (73.0, 80.2)	-2.6 (-7.7, 2.5)
Participants with Baseline RNA Titer ≤ 10^6 copies/ml[c]					
Baseline	0/198	0.0 (0.0, 1.8)	0/212	0.0 (0.0, 1.7)	0.0 (-1.8, 1.9)
Day 3	16/187	8.6 (5.0, 13.5)	14/205	6.8 (3.8, 11.2)	1.7 (-3.7, 7.4)
EOT (Day 5)	35/186	18.8 (13.5, 25.2)	34/198	17.2 (12.2, 23.2)	1.7 (-6.1, 9.5)
Day 10	72/177	40.7 (33.4, 48.3)	69/188	36.7 (29.8, 44.0)	4.4 (-5.6, 14.3)
Day 15	109/172	63.4 (55.7, 70.6)	125/194	64.4 (57.3, 71.2)	-0.9 (-10.6, 8.6)
Day 29	142/168	84.5 (78.2, 89.6)	160/187	85.6 (79.7, 90.3)	-1.1 (-8.7, 6.3)
Participants with Baseline RNA Titer > 10^6 copies/ml[c]					
Baseline	0/431	0.0 (0.0, 0.9)	0/415	0.0 (0.0, 0.9)	0.0 (-0.9, 0.9)
Day 3	3/412	0.7 (0.2, 2.1)	2/400	0.5 (0.1, 1.8)	0.2 (-1.2, 1.7)
EOT (Day 5)	8/406	2.0 (0.9, 3.8)	5/389	1.3 (0.4, 3.0)	0.7 (-1.2, 2.7)
Day 10	42/373	11.3 (8.2, 14.9)	34/353	9.6 (6.8, 13.2)	1.6 (-2.9, 6.1)
Day 15	121/363	33.3 (28.5, 38.4)	111/355	31.3 (26.5, 36.4)	2.0 (-4.9, 8.8)

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Proportion of Participants With Undetectable SARS-CoV-2 RNA Over Time Based on Qualitative Assay
Nasopharyngeal Sample
Modified Intent-To-Treat Population
MK-4482-002 Part 2 Day 29 Virology DBL

Visit	MK-4482 800 mg		Placebo		Difference
	n/N	% (95% CI)[a]	n/N	% (95% CI)[a]	% (95% CI)[b]
Day 29	247/357	69.2 (64.1, 73.9)	254/353	72.0 (67.0, 76.6)	-3.0 (-9.6, 3.7)

[a] 95% CI is based on Clopper-Pearson method.
[b] The corresponding confidence interval is based on Miettinen & Nurminen method stratified by randomization strata.
[c] The subgroups are classified based on the Q2 SARS-CoV-2 Viral Load Quantitation Assay.
n=Number of participants with undetectable SARS-CoV-2 RNA at the corresponding visit.
N=Number of participants with a qualitative assay result of SARS-CoV-2 RNA at the corresponding visit.
Day 3 includes post-baseline records up to day 4 relative to randomization. EOT (Day 5) includes post-baseline records from day 5 (relative to randomization) up to day 7. End of treatment visits occurring earlier than day 5 (relative to randomization) are included in the Day 3 visit.
The qualitative assay is the Roche cobas® SARS-CoV-2 RT-PCR.
Analysis only includes participants with detectable SARS-CoV-2 RNA at baseline.

Source: [P002V03MK4482: adam-adrna]

SARS-CoV-2 Infectivity

Infectious SARS-CoV-2 virus was predominately detected in NP samples collected 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].

A comparable percentage of participants in the MOV group (14.3% [96/671]) and placebo group (14.5% [97/670]) had detectable infectious virus at baseline [Ref. 5.3.5.3: 07X2GY: Table 14]. Infectious virus was detected at Day 3, (EOT) Day 5, and Day 10 for 0.5% (3/637), 0.0% (0/623), and 0.2% (1/583) of participants in the MOV group compared with 4.7% (30/643), 1.0% (6/616), and 0.2% (1/582) of participants in the placebo group, respectively. No infectious virus was recovered from any participant sample in the MOV or placebo intervention groups at Day 15 or Day 29.

Note: The 1 participant in the MOV group with infectious virus detected on Day 10 was suspected to have initially presented with symptomatic human metapneumovirus infection and not COVID-19 at baseline (undetectable SARS-CoV-2 PCR with positive testing for human metapneumovirus on Day 1), and subsequently developed a new SARS-CoV-2 infection with a high viral load and infectious virus detected at Day 10. Refer to [Ref. 5.3.5.3: 07X2GY: 4.4] for additional details.

Among participants with infectious virus detected at baseline, no participants in the MOV group had infectious virus detected at Day 3 or later, whereas infectious virus was detected for participants in the placebo group at Day 3 (20.8% [20/96]) and EOT (Day 5) (2.2% [2/89]) [Table 2.7.3-covid19txallpop: 10].

Table 2.7.3-covid19txallpop: 10
Proportion of Participants With Undetectable SARS-CoV-2 Infectivity Titers Over Time
Nasopharyngeal Sample
Modified Intent-To-Treat Population With Detectable SARS-CoV-2 RNA Infectivity Titers at Baseline
MK-4482-002 Part 2 Day 29 Virology DBL

Visit	MK-4482 800 mg		Placebo	
	n/N	% (95% CI)	n/N	% (95% CI)
Baseline	0/96	0.0 (0.0, 3.8)	0/97	0.0 (0.0, 3.7)
Day 3	92/92	100.0 (96.1, 100.0)	76/96	79.2 (69.7, 86.8)
EOT (Day 5)	91/91	100.0 (96.0, 100.0)	87/89	97.8 (92.1, 99.7)
Day 10	82/82	100.0 (95.6, 100.0)	86/86	100.0 (95.8, 100.0)
Day 15	78/78	100.0 (95.4, 100.0)	83/83	100.0 (95.7, 100.0)
Day 29	77/77	100.0 (95.3, 100.0)	89/89	100.0 (95.9, 100.0)

N= number of participants with positive baseline infectivity result and with available post baseline SARS-CoV-2 RNA samples at the timepoint of analysis.
n= number of participants with undetectable infectious titer at each timepoint among N. Infectivity results are imputed as undetectable if the sample was not sent for infectivity testing due to SARS-CoV-2 RNA copies being lower than 10^5 copies/ml.
95% CI is based on Clopper-Pearson method.
Day 3 includes post-baseline records up to day 4 relative to randomization. EOT (Day 5) includes post-baseline records from day 5 (relative to randomization) up to day 7. End of treatment visits occurring earlier than day 5 (relative to randomization) are included in the Day 3 visit.

Source: [P002VRV03MK4482: adam-adinf]

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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 postbaseline 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 placebo (2.9) [Table 2.7.3-covid19txallpop: 11]. The small number of participants with samples that met the criteria for analyses at the later time points (Days 10, 15, and 29) 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 Day 5 compared with the placebo group [Table 2.7.3-covid19txallpop: 12].

Table 2.7.3-covid19txallpop: 11
Mean of SARS-CoV-2 RNA Mutation Rate Compared to Baseline Sequence by Visit
Nasopharyngeal Sample
Modified Intent-To-Treat Population
MK-4482-002 Part 2 Day 29 Virology DBL

Visit	MK-4482 800 mg		Placebo	
	N	Mean (SD)	N	Mean (SD)
SARS-CoV-2 RNA Mutation Rate (per 10,000 bases)				
Baseline	448		440	
EOT (Day 5)	205	7.3 (9.96)	233	2.9 (5.13)
Day 10	31	9.8 (13.26)	41	2.7 (3.84)
Day 15	15	3.8 (7.49)	14	6.0 (10.87)
Day 29	1	2.7 (N/A)	4	7.3 (7.70)

SD=Standard deviation.
N=Number of participants with baseline and at least one postbaseline test result in the specified analysis window.
The mutation rate is calculated as number of nucleotide mutations compared to the baseline sequence per 10,000 bases across the entire viral genome (30,000 bases).
EOT (Day 5) includes post-baseline records from day 5 (relative to randomization) up to day 7.

Source: [P002VRV03MK4482: adam-adsl; adngs]

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Table 2.7.3-covid19txallpop: 12
Participants With Number of SARS-CoV-2 RNA Mutation > 3, 6 or 9 (Per 10,000 bases) Compared to Baseline Sequence by Visit
Nasopharyngeal Sample
Modified Intent-To-Treat Population
MK-4482-002 Part 2 Day 29 Virology DBL

Visit	MK-4482 800 mg		Placebo	
	n/m	(%)	n/m	(%)
Number of SARS-CoV-2 RNA Mutation > 3 Compared to Baseline Sample (per 10,000 bases)				
EOT (Day 5)	102/205	(49.8)	49/233	(21.0)
Day 10	12/31	(38.7)	9/41	(22.0)
Day 15	5/15	(33.3)	4/14	(28.6)
Day 29	0/1	(0.0)	2/4	(50.0)
Number of SARS-CoV-2 RNA Mutation > 6 Compared to Baseline Sample (per 10,000 bases)				
EOT (Day 5)	72/205	(35.1)	14/233	(6.0)
Day 10	10/31	(32.3)	2/41	(4.9)
Day 15	2/15	(13.3)	3/14	(21.4)
Day 29	0/0	(0.0)	1/4	(25.0)
Number of SARS-CoV-2 RNA Mutation > 9 Compared to Baseline Sample (per 10,000 bases)				
EOT (Day 5)	50/205	(24.4)	8/233	(3.4)
Day 10	10/31	(32.3)	1/41	(2.4)
Day 15	1/15	(6.7)	2/14	(14.3)
Day 29	0/1	(0.0)	1/4	(25.0)

n=Number of participants with number of mutations meets the criterion in the report title.
m=Number of participants with baseline and at least one postbaseline test result in the specified analysis window.
EOT (Day 5) includes post-baseline records from day 5 (relative to randomization) up to day 7.

Source: [P002VRV03MK4482: adam-adsl; adngs]

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2.1.1.4 Post-hoc Efficacy Analyses

2.1.1.4.1 All Participants Randomized in Part 2

2.1.1.4.1.1 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].

2.1.1.4.1.2 Oxygen Therapy

The percentage of participants requiring 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 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 oxygen therapy by highest level of oxygen need also show that participants in the MOV group had less requirement for any oxygen therapy compared with the placebo group [Ref. 5.3.5.1: P002V03MK4482: Table 14.2-112, 14.2-113].

2.1.1.4.1.3 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].

2.1.2 P002 (Part 1)

The efficacy results for Part 1 of P002 that are presented in this application are comprised of results primarily from IA2 (for dose selection, which occurred at the completion of Phase 2 after approximately 300 participants had 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. 2.7.3-covid19txallpop: 2.1.2.2].

2.1.2.1 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; 1 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 try and identify patient subgroups who were most likely to benefit from treatment with MOV, post-hoc subgroup analyses of the primary endpoint were conducted for 1) participants >60 years of age, 2) participants at increased risk for severe illness from COVID-19, 3) participants with ≤5 days from symptom onset to randomization and at increased risk for severe illness from COVID-19, and 4) 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].

2.1.2.2 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 at 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. Results for the 200 mg MOV group were generally comparable to placebo at all timepoints [Ref. 5.3.5.1: P002V01MK4482: Table 14.2-43]. The results for OP samples were generally consistent with those from NP samples [Ref. 5.3.5.1: P002V01MK4482: Table 14.2-44]. 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

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 [Appendix 2.7.3-covid19txallpop: 4] based on the lack of positive results in samples with

viral RNA <10^6 copies/mL [Appendix 2.7.3-covid19txallpop: 5]. Thirty-six of 214 participants in the combined MOV groups and 8 of 70 participants in the placebo group had detectable infectious virus at baseline [Appendix 2.7.3-covid19txallpop: 4] [Appendix 2.7.3-covid19txallpop: 6]. Positive infectivity was observed mostly in samples from participants with a higher viral load (>10^6 copies/mL) and in participants with shorter times from symptom onset [Appendix 2.7.3-covid19txallpop: 5]. 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

Mutation Rate Analyses

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 800 mg group in NP samples. At Day 5, the mutation rates (number of mutations/10,000 bases [SD]) for the 800 mg, 400 mg, and 200 mg groups were 8.7 [8.4], 6.7 [7.8], and 7.9 [14.6] compared with 2.0 [3.4] for the placebo group [Ref. 5.3.5.1: P002V01MK4482: Table 14.2-38]. A higher proportion of participants in the 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].

For the primary analysis, a variant frequency cutoff of ≥2% was used to calculate viral mutation rates in post-baseline sequences relative to baseline. An additional post-hoc analysis of next-generation sequencing data from Part 1 was also conducted to include only minor variants with an allele frequency between 0.4% to 10% in NP and OP samples. Results of this analysis demonstrated a linear dose-response relationship for MOV in the geometric mean number of minor variants in both NP and OP samples at Day 3 and Day 5 [Ref. 5.3.5.3: 07W3MS: Table 1, 2] [Appendix 2.7.3-covid19txallpop: 7] (panels b, c, e, and f).

At Day 3, approximate increases of 5- and 8-fold were observed in the geometric mean number of mutations for the 800 mg MOV group compared with placebo, in NP and OP samples [Ref. 5.3.5.3: 07W3MS: Table 1, 2]. At Day 5, approximate increases of 11- and 10-fold were observed in the geometric mean number of mutations observed for the 800 mg MOV group compared with placebo, in NP and OP samples [Ref. 5.3.5.3: 07W3MS: Table 1, 2].

Higher mean numbers of C to U and G to A transition mutations were observed in NP samples from MOV-treated participants compared with placebo. On Day 3, the mean number of C to U and G to A transitions were 2.2 and 1.5 in the MOV 800 mg group compared with 1.1 and 0.1 in the placebo group. On Day 5, the mean number of C to U and G to A transitions were 9.0 and 5.7 in the MOV 800 mg group compared with 2.6 and 0.2 in the placebo group [Appendix 2.7.3-covid19txallpop: 8]. Transversion mutations were less frequently observed in all groups. Results for OP samples were generally consistent with

results from NP samples, although the number of evaluable OP samples in some groups was small [Appendix 2.7.3-covid19txallpop: 9]. These results are consistent with the mechanism of action of MOV and findings from preclinical animal model studies that showed an increase in C to U and G to A mutations in viral RNA recovered from MOV-treated animals infected with SARS-CoV-2 [Ref. 5.4: 05R3LW].

Treatment-Emergent Amino Acid Changes

An analysis was performed to determine if MOV treatment resulted in selection for specific amino acid substitutions in the replicase complex proteins (nsp7-nsp14), possibly associated with development of MOV resistance. To distinguish between low frequency mutations caused by the mechanism of action of MOV and resistance associated mutations, a higher variant frequency cutoff of ≥5% was used. Treatment-emergent variants were defined as amino acid substitutions in the protein coding sequence that differed between baseline and post-baseline samples at a frequency of ≥5% in 2 or more participants in the combined MOV groups and in no participants in the placebo group. Among the 103 participants in the combined MOV groups with paired baseline and post-baseline samples, 2 treatment-emergent amino acid substitutions were identified. A nsp13-A446T substitution was detected in NP samples from 2 participants, 1 each in the 200 and 800 mg groups. A nsp14-V466I substitution was detected in NP samples from 2 participants, 1 in the 400 mg and 1 in 800 mg groups. The impact of these substitutions on MOV activity is unknown. No treatment-emergent substitutions were detected in the viral polymerase protein (nsp12) [Appendix 2.7.3-covid19txallpop: 10] [Appendix 2.7.3-covid19txallpop: 11].

The results of a similar analysis of the spike protein identified 3 treatment-emergent amino acid substitutions (E484K, P681H, A1022T) each observed in post-baseline NP swabs from 2 participants (in the combined MOV groups) [Appendix 2.7.3-covid19txallpop: 12]. The E484K substitution has previously been observed in spike sequences from Beta and Gamma variants, while the P681H substitution is characteristic of the Alpha variant. The significance of these findings is unknown. The A1022T substitution has not been previously described. No treatment-emergent substitutions were identified in either the replicase complex proteins; including the viral polymerase or spike in OP samples tested [Appendix 2.7.3-covid19txallpop: 13].

2.2 Phase 2a Study Results

2.2.1 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: 11].

2.2.1.1 Clinical Outcomes

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

2.2.1.2 Virology Outcomes

SARS-CoV-2 RNA

Time to undetectable SARS-CoV-2 RNA (median [95% CI]) was shorter for the MOV 800 mg (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 800 mg MOV (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 RNA load (log_{10} copies/mL) showed a larger decrease in the MOV 800 mg treatment group compared with any of the other treatment groups from Days 3 to 28. Beginning at Day 3, larger decreases from baseline in mean SARS-CoV-2 viral RNA load were observed for the MOV 800 mg group compared with placebo and the MOV 200 and 400 mg groups. The largest difference between the MOV 800 mg group and placebo were 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 placebo, 200 mg MOV, and 400 mg MOV 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 or 800 mg cleared infectious virus by Day 5, whereas 1/22 (4.5%) participants in the MOV 200 mg group and 6/54 (11.1%) participants 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 mechanism of action 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 sequence data, the mean % identity of the posttreatment samples versus baseline samples was lower (99.5%) compared with that observed for the placebo participants (99.7%) indicating an increase in the number of changes after treatment [Ref. 5.3.5.1: P006MK4482: Table 9]. This represented 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 in the placebo group [Ref. 5.3.5.1: P006MK4482: Table 14.2.14.1].

The effect of the increased number of nucleotide changes after treatment was also reflected in the analysis of amino acid changes between the posttreatment and baseline samples with a mean (SD) observed for MOV-treated participants of 7.5 (10.60) compared with 4.2 (4.39)

for placebo participants [Ref. 5.3.5.1: P006MK4482: Table 14.2.13.1]. An analysis of mutations leading to amino acid changes in the RdRp gene demonstrated that the amino acid changes occurred throughout the protein sequence [Ref. 5.3.5.1: P006MK4482: Table 14.2.11.1].

2.3 Phase 2 Study Results

2.3.1 P001 (Part 1)

The efficacy results for P001 that are presented in this application are comprised of results primarily from IA2 (for dose selection, which occurred at the completion of Phase 2 after approximately 300 participants had 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. 2.7.3-covid19txallpop: 2.3.1.2].

2.3.1.1 Clinical Outcomes

No clear effect of MOV treatment was observed for the primary endpoint of time to sustained recovery in hospitalized participants in P001 [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 of deaths occurred in the MOV 200 mg, 400 mg, and 800 mg groups (n=4 [5.5%], n=8 [11.0%], and 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 placebo. In addition, 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 counted as deaths 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].

As a note, a survival status as of Day 29 of “alive” has since been obtained for 3 of the 4 participants in the MOV 400 mg group with unknown survival status at IA2 and survival status for the 1 remaining participant remains unknown. Additionally, based on a correction of the date of final follow-up for a participant in the MOV 800 mg group after IA2, vital status at Day 29 is now missing for this participant. Therefore, the number of deaths in the all-cause mortality analysis for the MOV 800 mg group has been updated to 4 (3 observed deaths and 1 imputed death). Finally, a survival status as of Day 29 of “alive” has since been obtained for the 1 participant in the placebo group with unknown survival status at IA2 [Table 2.7.3-covid19txallpop: 13].

Table 2.7.3-covid19txallpop: 13
Incidence of All-Cause Mortality Through Day 29
Modified Intent-To-Treat Population
MK-4482-001

Treatment	N	n (%)	Treatment vs. Placebo	
			Difference in Rates % (95% CI)[a]	p-Value
MK-4482 200 mg	73	4 (5.5)	4.1 (-2.3, 12.1)	0.1642
MK-4482 400 mg	73	5 (6.8)	5.5 (-1.1, 13.9)	0.0900
MK-4482 800 mg	72	4 (5.6)	4.2 (-2.3, 12.3)	0.1594
Placebo	75	1 (1.3)		
Pairwise Comparison among MK Treatment Groups			Difference in Rates % (95% CI)[a]	p-Value
MK-4482 400 mg vs. MK-4482 200 mg			1.4 (-7.4, 10.4)	0.7317
MK-4482 800 mg vs. MK-4482 200 mg			0.1 (-8.5, 8.7)	0.9840
MK-4482 800 mg vs. MK-4482 400 mg			-1.3 (-10.3, 7.6)	0.7477

[a] Differences, the corresponding confidence intervals and p-values are based on Miettinen and Nurminen method. Unknown Day 29 survival status is treated as failure.

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 and 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, 11.1.2.5].

2.3.1.2 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 also 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: 14] [Appendix 2.7.3-covid19txallpop: 15] [Appendix 2.7.3-covid19txallpop: 16]. Eleven of 200 (5.5%) of total participants in the combined MOV groups and 3 of 69 (4.3%) of total participants in the placebo group had positive viral infectivity at baseline (NP samples). No participant in the MOV groups had detectable infectious virus on Days 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 RNA mutations was observed for MOV groups compared with placebo from NP samples [Ref. 5.3.5.1: P001V01MK4482: Table 14.2-45].

A variant frequency cutoff of ≥2% was used in the primary analysis to calculate viral mutation rates in post-baseline sequences relative to baseline. An additional analysis of NGS data from Part 1 was also conducted to include only minor variants with an allele frequency between 0.4% to 10% in NP and OP samples [Ref. 5.3.5.3: 07W3MS]. This analysis showed a linear trend in the geometric mean number of minor variants observed with increasing MOV dose in NP samples at Day 3, but not at Day 5 [Ref. 5.3.5.3: 07W3MS: Table 5] [Ref. 5.3.5.3: 07W3MS: Figure 3]. In OP samples, no linear trends in the geometric mean number of minor variants with increasing MOV dose were observed at either Day 3 or Day 5 [Ref. 5.3.5.3: 07W3MS: Table 6].

A higher mean number of C to U and G to A transition mutations across the genome were observed in NP samples from MOV-treated participants compared with placebo. On Day 5, the mean number of C to U and G to A transitions in the 800 mg group were 5.9 and 1.5, compared with 3.1 and 0.1 in the placebo group [Appendix 2.7.3-covid19txallpop: 19]. Transversion mutations were less frequently observed. Results for OP samples were generally similar to results from NP samples, although the number of evaluable OP samples in some groups was small [Appendix 2.7.3-covid19txallpop: 20]. The finding of increased transitional mutations is consistent with previously reported results from animal models and mechanism of action studies.

Among the participants in the MOV group with paired baseline and post-baseline NP and OP samples, no treatment-emergent amino acid substitutions were detected in 2 or more participants in any of the replicase complex genes (nsp7-14) [Appendix 2.7.3-covid19txallpop: 21] [Appendix 2.7.3-covid19txallpop: 22].

In the spike protein, no treatment-emergent substitutions were detected in NP or OP samples from 72 participants in the MOV group, however, a deletion at position Y145, characteristic of the Alpha variant spike, was observed in NP swabs from 2 participants in the 200 mg MOV group [Appendix 2.7.3-covid19txallpop: 23] [Appendix 2.7.3-covid19txallpop: 24]. The significance of this finding is unknown.

3 COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

This section is not applicable because the current application presents efficacy results separately from 3 studies due to differences in study populations and efficacy endpoints.

4 ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS

4.1 Rationale for Dose Selection in Phase 3

An 800 mg dose of MOV administered orally Q12H for 5 days was selected after IA2 based on the virologic data from P002 (Part 1), P006, and P001, trends in the clinical efficacy in P002 (Part 1), safety data from P002 (Part 1), P006, P001, and P004, and exposure-response modeling. No clinically meaningful trends were observed in AEs, SAEs, drug-related AEs, discontinuations due to AEs, or clinical laboratory values as a function of dose or treatment.

In Part 1 of P002, consistent with the mechanism of action for MOV (viral error catastrophe), comparison of baseline and post-baseline sequences showed that the highest RNA mutation rate was in the MOV 800 mg group [Sec. 2.7.3-covid19txallpop: 2.1.2]. For participants randomized ≤5 days from symptom onset and at increased risk for severe illness from COVID-19, the percentage of participants who were hospitalized was lower in those receiving any dose of MOV versus those receiving placebo.

In P006, there was a dose-dependent reduction in the percentage of participants with positive viral RNA load and time to undetectable viral RNA load [Sec. 2.7.3-covid19txallpop: 2.2.1.2]. Larger decreases in change from baseline SARS-CoV-2 viral RNA load were observed in the MOV 800 mg group compared with lower dose groups and placebo .

PopPK and exposure-response analyses based on the data through Phase 2 (including Part 1 of P001) supported selection of MOV 800 mg dose administered Q12H for 5 days for further evaluation in the Phase 3 studies [Sec. 2.7.2-covid19txallpop: 1.5.1].

4.2 Dose-response and Exposure-response Relationships

Dose-response and exposure-response analyses support the proposed dose of 800 mg administered Q12H for 5 days. The relationship between exposures of NHC (the primary circulating metabolite of MOV) and clinical and virology endpoints has been characterized using integrated exposure-response modeling [Ref. 5.3.5.3: 08074R] [Ref. 5.3.5.3: 07YDDS]. Individual exposures for participants across the clinical program were estimated using an integrated PopPK model [Sec. 2.7.2-covid19txallpop: 2.5.2.2].

Exposure-response analysis demonstrated the relationship between probability of hospitalization or death in Part 2 of P002 and NHC exposure in terms of AUC [Sec. 2.7.2-covid19txallpop: 2.5.3.2]. Overall, most participants receiving an 800 mg dose had exposures on the plateau of the exposure-response relationship, consistent with the finding of lower hospitalization or death in participants treated with 800 mg MOV [Sec. 2.7.3-covid19txallpop: 2.1.2]. The exposure-response results support a consistent interpretation of dose- and exposure-dependency for MOV across pharmacodynamic markers from Phase 2

and Phase 3 as well, with exposures at 800 mg also falling near the top of the exposure-response curves for viral load change from baseline on Day 5 and LNS error rate. The exposure distributions of the 200 mg or 400 mg doses fall on the exposure-dependent portions of the exposure-response curves and, therefore, can be expected to be associated with reduced drug effects relative to 800 mg, supporting the choice of 800 mg [Figure 2.7.2-covid19txallpop: 3] [Ref. 5.3.5.3: 07YDDS].

From a safety perspective, AEs by AUC quartiles were generated for all MOV 800 mg COVID-19 participants in Part 1 and Part 2 of P002 as part of the Integrated Summary of Safety [Sec. 5.3.5.3.3-covid19txallpop: 2.4.2] and for all MOV 800 mg COVID-19 participants in Part 2 of P002 as a part of the exposure-response report [Ref. 5.3.5.3: 07YDDS]. In both assessments, the AE rates in the highest quartile of AUC were similar to those seen in the second and third quartiles, indicating no evidence for reduced tolerability at the highest exposures. A higher incidence of respiratory AEs associated with COVID-19 infection was observed in the lowest exposure quartile, consistent with findings from the exposure-response analysis for efficacy.

4.3 Dosing Recommendations/Adjustments

The proposed clinical dose of MOV is 800 mg administered orally Q12H for 5 days [Sec. 2.7.2-covid19txallpop: 1.5.1]. An 800 mg dose of MOV has demonstrated efficacy for reducing the risk of hospitalization or death due to COVID-19 in non-hospitalized participants from Part 2 of P002 [Sec. 2.7.3-covid19txallpop: 2.1.1]. This dose has also been supported by exposure-response analysis from the Phase 3 program (Part 2 of P002) [Sec. 2.7.2-covid19txallpop: 1.5.2]. MOV can be administered with other medications, as there is low potential for it to be a victim or perpetrator of drug-drug interactions [Sec. 2.7.2-covid19txallpop: 3.3.1]. No dose adjustment is required based on age, sex, body weight, BMI, race, ethnicity, renal impairment, or hepatic impairment [Sec. 2.7.2-covid19txallpop: 3.2].

5 PERSISTENCE OF EFFICACY AND/OR TOLERANCE EFFECT

The included clinical studies were designed to be of sufficient duration to capture the majority of important clinical efficacy outcomes to reliably demonstrate the efficacy of MOV in the treatment of a diverse population of non-hospitalized patients with COVID-19. Data through the Day 29 Visit support the efficacy of MOV.

Results from Part 2 of P002 showed that treatment with MOV was associated with a more rapid decline in SARS-CoV-2 RNA and faster elimination of infectious virus as compared with placebo. Among participants with infectious virus detected at baseline, no MOV-treated participants had infectious virus detected on Day 3 or later, whereas some participants in the placebo group had infectious virus detected up to Day 5.

6 CONCLUSIONS

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 the risk of death compared with placebo (P002 Part 2).

- Treatment with MOV was associated with improved clinical outcomes based on self-reported COVID-19 signs/symptoms and as assessed by the WHO-11 point ordinal scale compared with placebo (P002 Part 2).

- Clinically relevant markers of improvement and health care 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).

7 APPENDIX

Appendix 2.7.3-covid19txallpop: 1
Incidence of Hospitalization or Death Through Day 29 by Subgroup
Modified Intent-To-Treat Population
MK-4482-002 Part 2 Day 29 Virology DBL

	MK-4482 800 mg		Placebo		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)[a]
Time from Symptom Onset to Randomization						
≤ 3 days	25/339	(7.4)	28/335	(8.4)	-1.0	(-5.2, 3.2)
> 3 days	23/370	(6.2)	40/364	(11.0)	-4.8	(-9.0, -0.7)
Age Group						
≤ 60 years	36/591	(6.1)	52/572	(9.1)	-3.0	(-6.1, 0.0)
> 60 years	12/118	(10.2)	16/127	(12.6)	-2.4	(-10.6, 5.8)
Obesity (BMI ≥ 30)						
Yes	29/535	(5.4)	46/507	(9.1)	-3.7	(-6.9, -0.5)
No	19/174	(10.9)	22/192	(11.5)	-0.5	(-7.1, 6.2)
Diabetes Mellitus Status						
Yes	17/107	(15.9)	17/117	(14.5)	1.4	(-8.2, 11.1)
No	31/602	(5.1)	51/582	(8.8)	-3.6	(-6.6, -0.7)
Baseline COVID Severity						
Mild	19/395	(4.8)	27/376	(7.2)	-2.4	(-5.9, 1.0)
Moderate	29/311	(9.3)	40/321	(12.5)	-3.1	(-8.1, 1.8)
Severe	0/3	(0.0)	0/1	(0.0)	0.0	(-83.7, 63.1)
Unknown	0/0	(0.0)	1/1	(100.0)		

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Incidence of Hospitalization or Death Through Day 29 by Subgroup
Modified Intent-To-Treat Population
MK-4482-002 Part 2 Day 29 Virology DBL

	MK-4482 800 mg		Placebo		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)[a]
SARS-CoV-2 Baseline Nucleocapsid Antibody						
Positive	5/139	(3.6)	2/151	(1.3)	2.3	(-1.6, 7.0)
Negative	42/557	(7.5)	64/535	(12.0)	-4.4	(-8.0, -0.9)
Unknown	1/13	(7.7)	2/13	(15.4)	-7.7	(-36.9, 21.6)
Region						
North America	4/42	(9.5)	5/45	(11.1)	-1.6	(-15.6, 12.7)
Latin America	22/329	(6.7)	34/321	(10.6)	-3.9	(-8.4, 0.4)
Europe	13/229	(5.7)	18/233	(7.7)	-2.0	(-6.9, 2.6)
Asia Pacific	5/19	(26.3)	4/16	(25.0)	1.3	(-28.7, 29.9)
Africa	4/90	(4.4)	7/84	(8.3)	-3.9	(-12.4, 3.8)
Sex						
Male	32/330	(9.7)	41/355	(11.5)	-1.9	(-6.5, 2.8)
Female	16/379	(4.2)	27/344	(7.8)	-3.6	(-7.4, -0.2)
Race						
American Indian or Alaska Native	7/60	(11.7)	3/43	(7.0)	4.7	(-8.4, 16.5)
Asian	7/25	(28.0)	6/22	(27.3)	0.7	(-25.3, 26.0)
Black or Africa American	3/39	(7.7)	1/34	(2.9)	4.8	(-8.3, 18.0)
White	19/397	(4.8)	32/405	(7.9)	-3.1	(-6.6, 0.3)

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Incidence of Hospitalization or Death Through Day 29 by Subgroup
Modified Intent-To-Treat Population
MK-4482-002 Part 2 Day 29 Virology DBL

	MK-4482 800 mg		Placebo		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)[a]
Multiple	12/188	(6.4)	26/195	(13.3)	-7.0	(-13.2, -1.0)
Baseline SARS-CoV-2 Quantitative Assay Viral Load Status						
undetectable [<500 copies/mL]	0/72	(0.0)	0/86	(0.0)	0.0	(-4.3, 5.1)
low VL [500 to <=10^6 copies/mL]	10/182	(5.5)	9/180	(5.0)	0.5	(-4.4, 5.5)
high VL [>10^6 copies/mL]	38/432	(8.8)	56/417	(13.4)	-4.6	(-9.0, -0.4)
Unknown	0/23	(0.0)	3/16	(18.8)	-18.8	(-43.3, -2.5)
Baseline SARS-CoV-2 Qualitative Assay Viral Load Status(undetectable, detectable)						
Detectable	48/643	(7.5)	65/634	(10.3)	-2.8	(-6.0, 0.3)
Undetectable	0/55	(0.0)	0/53	(0.0)	0.0	(-6.8, 6.6)
Unknown	0/11	(0.0)	3/12	(25.0)	-25.0	(-53.8, 5.0)
Baseline Clade						
20J (Gamma)	0/37	(0.0)	10/50	(20.0)	-20.0	(-33.1, -9.7)
21H (Mu)	6/83	(7.2)	16/92	(17.4)	-10.2	(-20.2, -0.3)
21I (Delta)	7/55	(12.7)	7/44	(15.9)	-3.2	(-18.4, 10.9)
21J (Delta)	24/298	(8.1)	22/295	(7.5)	0.6	(-3.8, 5.0)
SARS-CoV-2 Baseline Neutralizing Antibody						
Positive	8/190	(4.2)	3/188	(1.6)	2.6	(-0.9, 6.7)
Negative	40/513	(7.8)	65/506	(12.8)	-5.0	(-8.9, -1.3)

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Incidence of Hospitalization or Death Through Day 29 by Subgroup
Modified Intent-To-Treat Population
MK-4482-002 Part 2 Day 29 Virology DBL

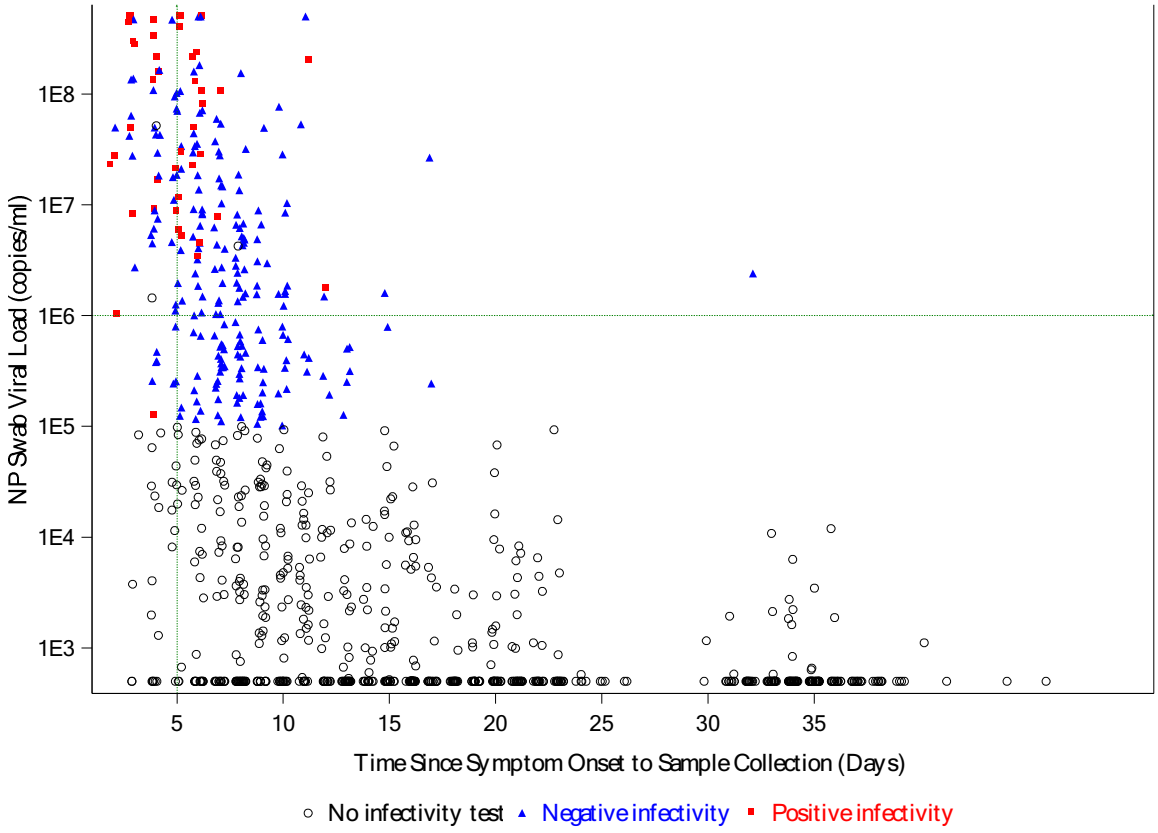
	MK-4482 800 mg		Placebo		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)[a]
Unknown	0/6	(0.0)	0/5	(0.0)	0.0	(-45.8, 41.3)

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

Source: [P002VRV03MK4482: adam-adsl; adeff1]

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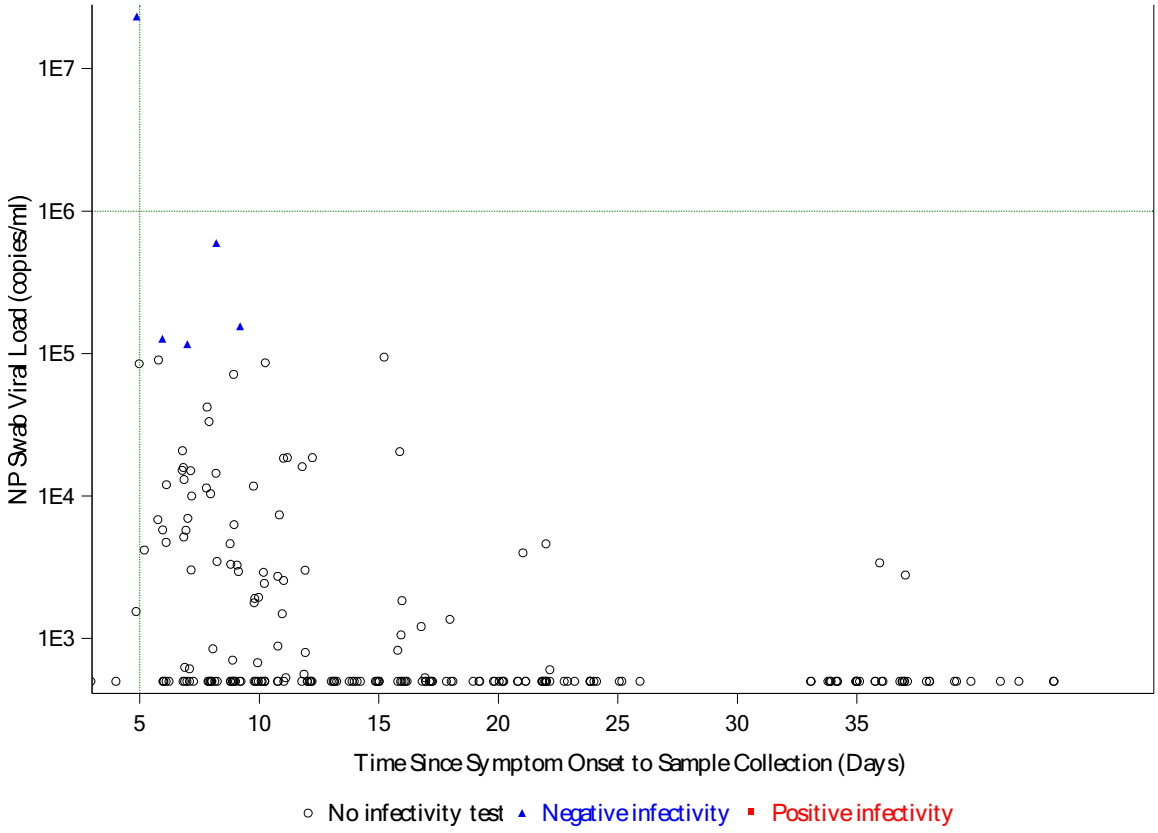
Appendix 2.7.3-covid19txallpop: 2
Plot of SARS-CoV-2 Infectivity by Viral RNA Titer and Time Since Symptom Onset
Nasopharyngeal Sample
Modified Intent-To-Treat Population with Negative Baseline Antibody
MK-4482-002 (Part 1)



SARS-CoV-2 Viral RNA titer was determined using a quantitative RT-PCR assay developed at Q2 Solutions, Morrisville, NC, USA.
Samples with viral RNA titers below 100,000 copies/ml were not evaluated for infectivity.
SARS-CoV-2 infectivity was determined by plaque assay in Vero cell cultures (LabCorp Inc, Indianapolis, IN, USA.)
Source: [P002VRV01MK4482: adam-adsl; adinf; adrna]

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Appendix 2.7.3-covid19txallpop: 3
Plot of SARS-CoV-2 Infectivity by Viral RNA Titer and Time Since Symptom Onset
Nasopharyngeal Sample
Modified Intent-To-Treat Population with Positive Baseline Antibody
MK-4482-002 (Part 1)



SARS-CoV-2 Viral RNA titer was determined using a quantitative RT-PCR assay developed at Q2 Solutions, Morrisville, NC, USA.
Samples with viral RNA titers below 100,000 copies/ml were not evaluated for infectivity.
SARS-CoV-2 infectivity was determined by plaque assay in Vero cell cultures (LabCorp Inc, Indianapolis, IN, USA.)
Source: [P002VRV01MK4482: adam-adsl; adinf; adrna]

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Appendix 2.7.3-covid19txallpop: 4
Proportion of Participants With Undetectable SARS-CoV-2 Infectivity Titers Over Time
Nasopharyngeal Sample
Modified Intent-To-Treat Population
MK-4482-002 (Part 1)

Visit	MK-4482 200 mg		MK-4482 400 mg		MK-4482 800 mg		Placebo	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)
Baseline	61/70	87.1 (77.0, 93.9)	61/76	80.3 (69.5, 88.5)	56/68	82.4 (71.2, 90.5)	62/70	88.6 (78.7, 94.9)
Day 3	67/68	98.5 (92.1, 100.0)	72/74	97.3 (90.6, 99.7)	64/66	97.0 (89.5, 99.6)	67/68	98.5 (92.1, 100.0)
EOT (Day 5)	68/68	100.0 (94.7, 100.0)	72/72	100.0 (95.0, 100.0)	63/63	100.0 (94.3, 100.0)	66/69	95.7 (87.8, 99.1)
Day 10	65/65	100.0 (94.5, 100.0)	71/71	100.0 (94.9, 100.0)	57/57	100.0 (93.7, 100.0)	61/62	98.4 (91.3, 100.0)
Day 15	66/66	100.0 (94.6, 100.0)	69/69	100.0 (94.8, 100.0)	65/65	100.0 (94.5, 100.0)	62/62	100.0 (94.2, 100.0)
Day 29	62/62	100.0 (94.2, 100.0)	68/68	100.0 (94.7, 100.0)	58/58	100.0 (93.8, 100.0)	64/64	100.0 (94.4, 100.0)

N= number of participants with baseline and post baseline SARS-CoV-2 RNA samples at the timepoint of analysis.

n= number of participants with undetectable infectious titer at each post baseline timepoint among N. Infectivity results are imputed as undetectable if the post baseline sample was not sent for infectivity testing due to SARS-CoV-2 RNA Titer being lower than 10^5 copies/ml.

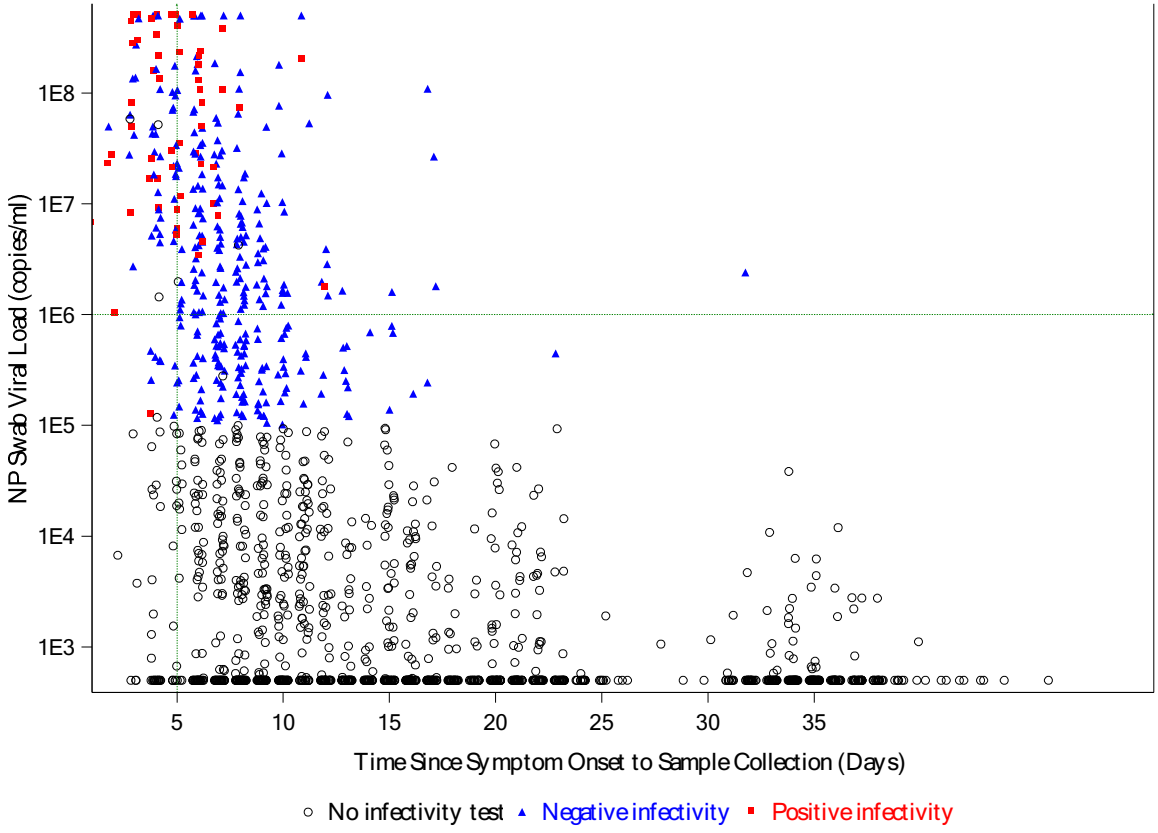
95% CI is based on Clopper-Pearson method.

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

Source: [P002VRV01MK4482: adam-adinf]

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Appendix 2.7.3-covid19txallpop: 5
Plot of SARS-CoV-2 Infectivity by Viral RNA Titer and Time Since Symptom Onset
Nasopharyngeal Sample
Modified Intent-To-Treat Population
MK-4482-002 (Part 1)



SARS-CoV-2 Viral RNA titer was determined using a quantitative RT-PCR assay developed at Q2 Solutions, Morrisville, NC, USA.
Samples with viral RNA titers below 100,000 copies/ml were not evaluated for infectivity.
SARS-CoV-2 infectivity was determined by plaque assay in Vero cell cultures (LabCorp Inc, Indianapolis, IN, USA.)
Source: [P002VRV01MK4482: adam-adsl; adinf; adrna]

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Appendix 2.7.3-covid19txallpop: 6
Proportion of Participants With Undetectable SARS-CoV-2 Infectivity Titers Over Time
Nasopharyngeal Sample
Modified Intent-To-Treat Population With Detectable SARS-CoV-2 RNA Infectivity Titers at Baseline
MK-4482-002 (Part 1)

Visit	MK-4482 200 mg		MK-4482 400 mg		MK-4482 800 mg		Placebo	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)
Baseline	0/9	0.0 (0.0, 33.6)	0/15	0.0 (0.0, 21.8)	0/12	0.0 (0.0, 26.5)	0/8	0.0 (0.0, 36.9)
Day 3	9/9	100.0 (66.4, 100.0)	12/14	85.7 (57.2, 98.2)	10/11	90.9 (58.7, 99.8)	7/8	87.5 (47.3, 99.7)
EOT (Day 5)	9/9	100.0 (66.4, 100.0)	15/15	100.0 (78.2, 100.0)	12/12	100.0 (73.5, 100.0)	6/8	75.0 (34.9, 96.8)
Day 10	9/9	100.0 (66.4, 100.0)	14/14	100.0 (76.8, 100.0)	10/10	100.0 (69.2, 100.0)	6/6	100.0 (54.1, 100.0)
Day 15	8/8	100.0 (63.1, 100.0)	14/14	100.0 (76.8, 100.0)	11/11	100.0 (71.5, 100.0)	6/6	100.0 (54.1, 100.0)
Day 29	9/9	100.0 (66.4, 100.0)	15/15	100.0 (78.2, 100.0)	10/10	100.0 (69.2, 100.0)	6/6	100.0 (54.1, 100.0)

N= number of participants with positive baseline infectivity result and with available post baseline SARS-CoV-2 RNA samples at the timepoint of analysis.

n= number of participants with undetectable infectious titer at each post baseline timepoint among N. Infectivity results are imputed as undetectable if the post baseline sample was not sent for infectivity testing due to SARS-CoV-2 RNA copies being lower than 10^5 copies/ml.

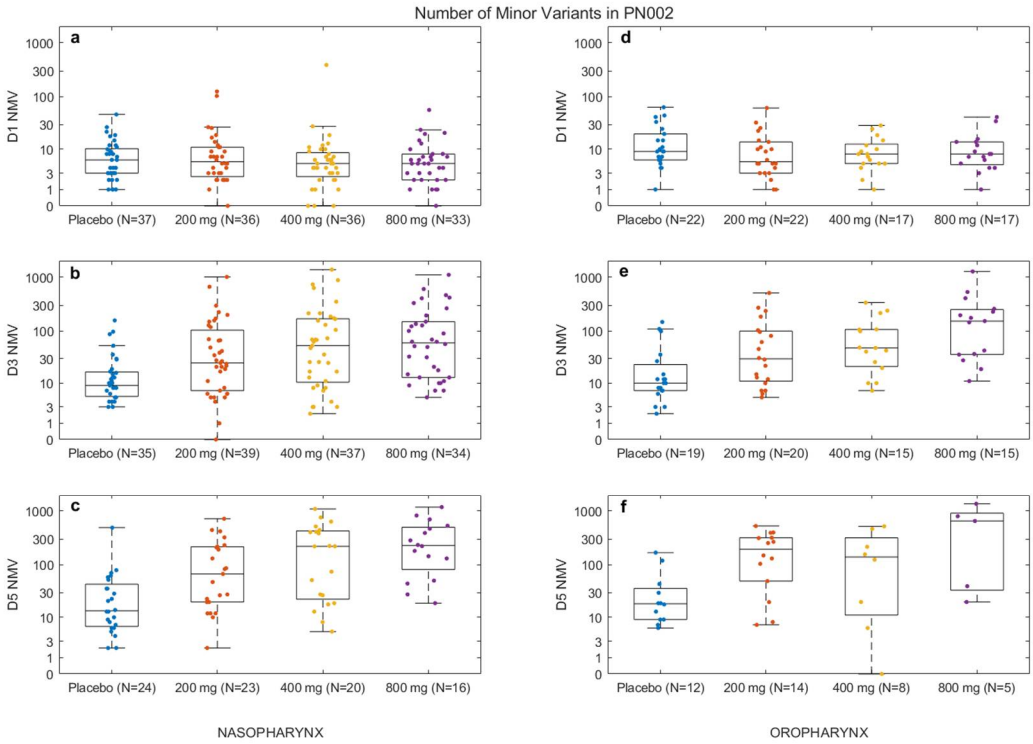
95% CI is based on Clopper-Pearson method.

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

Source: [P002VRV01MK4482: adam-adinf]

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Appendix 2.7.3-covid19txallpop: 7
Number of Minor Variants Detected in SARS-CoV-2 Genome Nasopharyngeal and Oropharyngeal Samples Intent-to-Treat Population MK-4482-002 (Part 1)



D1=Day 1; D3=Day 3; D5=Day 5; NMV=number of minor variants; NP = nasopharyngeal; OP=oropharyngeal.
Each point represents the number of minor variants in one participant. Panels (a)-(c): nasopharyngeal samples; (d)-(f): oropharyngeal samples. (a), (d): D1; (b), (e): D3; (c), (f): D5. The boxes are drawn between q_1 and q_3, which are the 25th and 75th percentile of the data, resp. The central horizontal lines correspond to the median. The lower whisker is drawn at the smallest data point above q_1-1.5(q_3-q_1). The upper whisker is drawn at the largest data point below q_3+1.5(q_3-q_1). The range between q_1-1.5(q_3-q_1) and q_3+1.5(q_3-q_1) corresponds to approximately +/–2.7σ and 99.3% coverage when the data is normally distributed.

Source: [Ref. 5.3.5.3: 07W3MS] [Ref. 5.3.5.3: 06G7VK] [Ref. 5.3.5.3: 06G7VN]

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Appendix 2.7.3-covid19txallpop: 8
Mean Number of Transition and Transversion Nucleotide Changes Observed in Post-baseline SARS-CoV-2 Sequences Relative to Baseline by Change Type
Nasopharyngeal Sample
Modified Intent-To-Treat Population
MK-4482-002 (Part 1)

Visit	Treatment	N	Transitions				Transversions								Other Nucleotide Changes
			C:U	U:C	G:A	A:G	C:A	C:G	U:A	U:G	G:U	G:C	A:C	A:U	
Day 3	MK-4482 200 mg	33	4.5	1.5	1.0	0.7	0.1	0.0	0.0	0.0	1.4	0.1	0.1	0.2	1.2
	MK-4482 400 mg	35	6.3	2.6	0.7	0.5	0.0	0.1	0.0	0.1	2.6	0.2	0.2	0.2	1.9
	MK-4482 800 mg	31	2.2	0.4	1.5	0.5	0.0	0.0	0.0	0.0	0.2	0.0	0.1	0.0	0.6
	Placebo	32	1.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.2	0.0	0.1	0.0	0.4
EOT (Day 5)	MK-4482 200 mg	19	7.3	2.1	2.1	1.1	0.0	0.1	0.0	0.0	2.6	0.2	0.2	0.5	1.5
	MK-4482 400 mg	17	6.4	1.4	4.2	2.2	0.1	0.0	0.0	0.1	0.5	0.1	0.0	0.2	0.8
	MK-4482 800 mg	14	9.0	2.5	5.7	2.6	0.0	0.0	0.0	0.1	0.9	0.0	0.0	0.0	1.1
	Placebo	20	2.6	0.2	0.2	0.3	0.1	0.0	0.0	0.0	0.5	0.1	0.1	0.1	0.6

N = number of participants with both baseline and post-baseline SARS-CoV-2 gene sequencing data at the reported visit.

Source: [P002VRV01MK4482: adam-adngsnt]

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Appendix 2.7.3-covid19txallpop: 9
Mean Number of Transition and Transversion Nucleotide Changes Observed in Post-baseline SARS-CoV-2 Sequences Relative to Baseline by Change Type
Oropharyngeal Sample
Modified Intent-To-Treat Population
MK-4482-002 (Part 1)

Visit	Treatment	N	Transitions				Transversions								Other Nucleotide Changes
			C:U	U:C	G:A	A:G	C:A	C:G	U:A	U:G	G:U	G:C	A:C	A:U	
Day 3	MK-4482 200 mg	18	1.7	0.4	0.3	0.3	0.0	0.0	0.1	0.0	0.1	0.0	0.0	0.0	0.5
	MK-4482 400 mg	14	1.4	0.1	0.5	0.1	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.2
	MK-4482 800 mg	13	2.3	0.2	1.7	0.9	0.1	0.0	0.0	0.1	0.3	0.0	0.2	0.1	0.6
	Placebo	18	1.4	0.2	0.1	0.3	0.0	0.0	0.0	0.1	0.5	0.0	0.0	0.0	0.3
EOT (Day 5)	MK-4482 200 mg	12	2.9	1.1	2.0	0.3	0.0	0.0	0.0	0.0	0.1	0.0	0.1	0.0	0.3
	MK-4482 400 mg	8	4.4	0.6	1.1	0.8	0.1	0.0	0.0	0.0	0.4	0.0	0.0	0.0	0.5
	MK-4482 800 mg	2	1.5	1.5	2.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Placebo	11	3.2	0.3	0.1	0.4	0.2	0.0	0.0	0.0	0.5	0.0	0.0	0.0	0.3

N = number of participants with both baseline and post-baseline SARS-CoV-2 gene sequencing data at the reported visit.

Source: [P002VRV01MK4482: adam-adngsnt]

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Appendix 2.7.3-covid19txallpop: 10
Participants with Treatment-Emergent Amino Acid Changes Detected in the SARS-CoV-2 Viral Replicase Complex (NSP7-NSP14) Nasopharyngeal Sample With Variant Percentage >=0.05
Modified Intent-To-Treat Population
MK-4482-002 (Part 1)

Amino Acid Variant	MK-4482 200 mg n	MK-4482 400 mg n	MK-4482 800 mg n	MK-4482 Combined n	Placebo n
Participants in population with both baseline and post-baseline SARS-CoV-2 gene sequencing data	35	36	32	103	36
NSP13					
ALA446THR	1	0	1	2	0
NSP14					
VAL466ILE	0	1	1	2	0

Every participant is counted a single time for each applicable row and column.
A 5% frequency cutoff was applied to identify treatment-emergent amino acid substitutions.
Treatment-emergent amino acid changes are reported if detected in post-baseline samples, in 2 or more MK-4482 treated participants combined and 0 in the placebo group.

Source: [P002VRV01MK4482: adam-adsl; adngsaa]

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Appendix 2.7.3-covid19txallpop: 11
Participants with Treatment-Emergent Amino Acid Changes Detected in the SARS-CoV-2 Viral Replicase Complex (NSP7-NSP14) Oropharyngeal Sample With Variant Percentage >=0.05
Modified Intent-To-Treat Population
MK-4482-002 (Part 1)

Amino Acid Variant	MK-4482 200 mg n	MK-4482 400 mg n	MK-4482 800 mg n	MK-4482 Combined n	Placebo n
No data to report.					

Every participant is counted a single time for each applicable row and column.
A 5% frequency cutoff was applied to identify treatment-emergent amino acid substitutions.
Treatment-emergent amino acid changes are reported if detected in post-baseline samples, in 2 or more MK-4482 treated participants combined and 0 in the placebo group.

Source: [P002VRV01MK4482: adam-adsl; adngsaa]

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Appendix 2.7.3-covid19txallpop: 12
Participants with Treatment-Emergent Amino Acid Changes Detected in the SARS-CoV-2 S Protein Nasopharyngeal Sample With Variant Percentage >=0.05
Modified Intent-To-Treat Population
MK-4482-002 (Part 1)

Amino Acid Variant	MK-4482 200 mg n	MK-4482 400 mg n	MK-4482 800 mg n	MK-4482 Combined n	Placebo n
Participants in population with both baseline and post-baseline SARS-CoV-2 gene sequencing data	35	36	32	103	36
ALA1022THR	1	0	1	2	0
GLU484LYS	0	1	1	2	0
PRO681HIS	2	0	0	2	0

Every participant is counted a single time for each applicable row and column.
A 5% frequency cutoff was applied to identify treatment-emergent amino acid substitutions.
Treatment-emergent amino acid changes are reported if detected in post-baseline samples, in 2 or more MK-4482 treated participants combined and 0 in the placebo group.

Source: [P002VRV01MK4482: adam-adsl; adngsaa]

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Appendix 2.7.3-covid19txallpop: 13
Participants with Treatment-Emergent Amino Acid Changes Detected in the SARS-CoV-2 S Protein Oropharyngeal Sample With Variant Percentage >=0.05
Modified Intent-To-Treat Population
MK-4482-002 (Part 1)

Amino Acid Variant	MK-4482 200 mg n	MK-4482 400 mg n	MK-4482 800 mg n	MK-4482 Combined n	Placebo n
No data to report.					
Every participant is counted a single time for each applicable row and column. A 5% frequency cutoff was applied to identify treatment-emergent amino acid substitutions. Treatment-emergent amino acid changes are reported if detected in post-baseline samples, in 2 or more MK-4482 treated participants combined and 0 in the placebo group.					

Source: [P002VRV01MK4482: adam-adsl; adngsaa]

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Appendix 2.7.3-covid19txallpop: 14
Proportion of Participants With Undetectable SARS-CoV-2 Infectivity Titers Over Time
Nasopharyngeal Sample
Modified Intent-To-Treat Population With Detectable SARS-CoV-2 RNA Infectivity Titers at Baseline
MK-4482-001 (Part 1)

Visit	MK-4482 200 mg		MK-4482 400 mg		MK-4482 800 mg		Placebo	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)
Baseline	0/6	0.0 (0.0, 45.9)	0/3	0.0 (0.0, 70.8)	0/2	0.0 (0.0, 84.2)	0/3	0.0 (0.0, 70.8)
Day 3	5/5	100.0 (47.8, 100.0)	3/3	100.0 (29.2, 100.0)	2/2	100.0 (15.8, 100.0)	1/3	33.3 (0.8, 90.6)
EOT (Day 5)	6/6	100.0 (54.1, 100.0)	3/3	100.0 (29.2, 100.0)	2/2	100.0 (15.8, 100.0)	2/3	66.7 (9.4, 99.2)
Day 10	6/6	100.0 (54.1, 100.0)	3/3	100.0 (29.2, 100.0)	1/1	100.0 (2.5, 100.0)	2/2	100.0 (15.8, 100.0)
Day 15	6/6	100.0 (54.1, 100.0)	3/3	100.0 (29.2, 100.0)	1/1	100.0 (2.5, 100.0)	2/2	100.0 (15.8, 100.0)
Day 29	2/2	100.0 (15.8, 100.0)	2/2	100.0 (15.8, 100.0)	1/1	100.0 (2.5, 100.0)	2/2	100.0 (15.8, 100.0)

N= number of participants with positive baseline infectivity result and with available post baseline SARS-CoV-2 RNA samples at the timepoint of analysis.

n= number of participants with undetectable infectious titer at each post baseline timepoint among N. Infectivity results are imputed as undetectable if the post baseline sample was not sent for infectivity testing due to SARS-CoV-2 RNA copies being lower than 10^5 copies/ml.

95% CI is based on Clopper-Pearson method.

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

Source: [P001VRV01MK4482: adam-adinf]

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Appendix 2.7.3-covid19txallpop: 15
Proportion of Participants With Undetectable SARS-CoV-2 Infectivity Titers Over Time
Nasopharyngeal Sample
Modified Intent-To-Treat Population
MK-4482-001 (Part 1)

Visit	MK-4482 200 mg		MK-4482 400 mg		MK-4482 800 mg		Placebo	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)
Baseline	60/66	90.9 (81.3, 96.6)	64/67	95.5 (87.5, 99.1)	65/67	97.0 (89.6, 99.6)	66/69	95.7 (87.8, 99.1)
Day 3	60/60	100.0 (94.0, 100.0)	64/64	100.0 (94.4, 100.0)	64/64	100.0 (94.4, 100.0)	63/65	96.9 (89.3, 99.6)
EOT (Day 5)	63/63	100.0 (94.3, 100.0)	61/61	100.0 (94.1, 100.0)	64/64	100.0 (94.4, 100.0)	59/60	98.3 (91.1, 100.0)
Day 10	59/59	100.0 (93.9, 100.0)	55/55	100.0 (93.5, 100.0)	58/58	100.0 (93.8, 100.0)	62/62	100.0 (94.2, 100.0)
Day 15	59/59	100.0 (93.9, 100.0)	52/52	100.0 (93.2, 100.0)	60/60	100.0 (94.0, 100.0)	64/64	100.0 (94.4, 100.0)
Day 29	46/46	100.0 (92.3, 100.0)	44/44	100.0 (92.0, 100.0)	56/56	100.0 (93.6, 100.0)	60/60	100.0 (94.0, 100.0)

N= number of participants with baseline and post baseline SARS-CoV-2 RNA samples at the timepoint of analysis.

n= number of participants with undetectable infectious titer at each post baseline timepoint among N. Infectivity results are imputed as undetectable if the post baseline sample was not sent for infectivity testing due to SARS-CoV-2 RNA Titer being lower than 10^5 copies/ml.

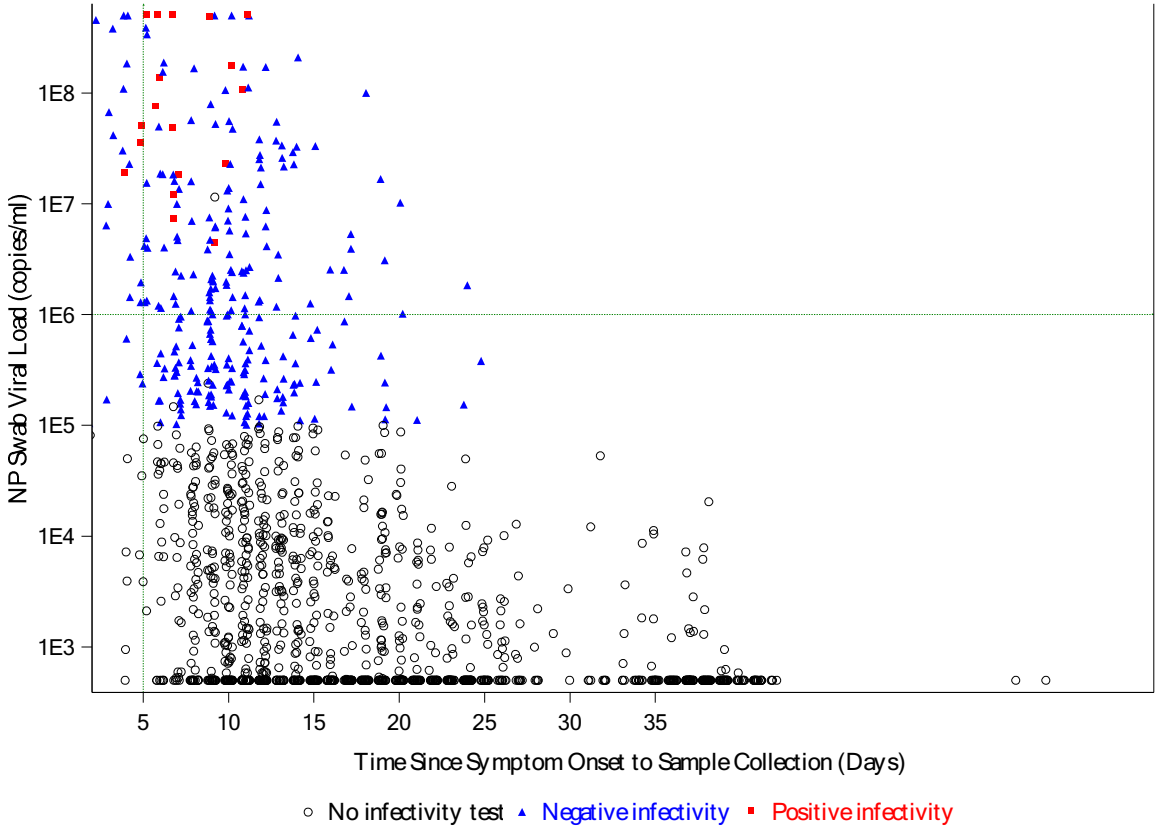
95% CI is based on Clopper-Pearson method.

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

Source: [P001VRV01MK4482: adam-adinf]

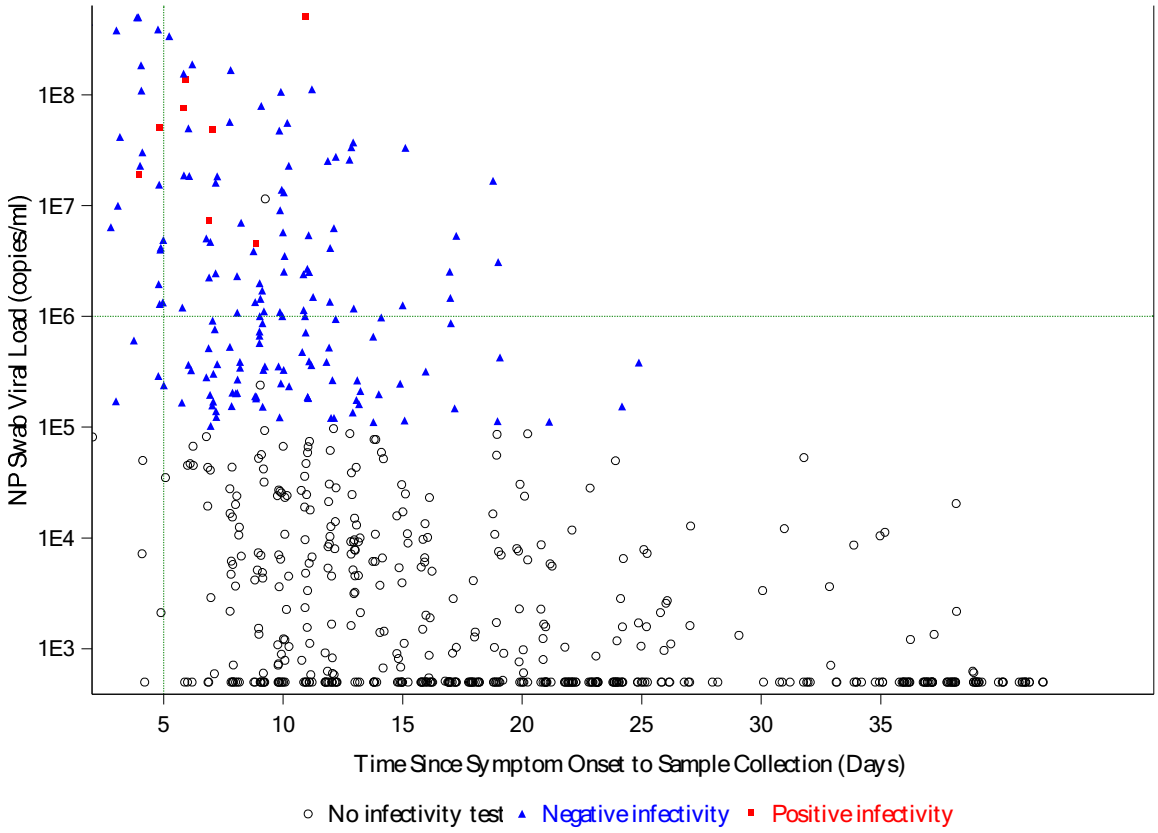
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Appendix 2.7.3-covid19txallpop: 16
Plot of SARS-CoV-2 Infectivity by Viral RNA Titer and Time Since Symptom Onset
Nasopharyngeal Sample
Modified Intent-To-Treat Population
MK-4482-001 (Part 1)



SARS-CoV-2 Viral RNA titer was determined using a quantitative RT-PCR assay developed at Q2 Solutions, Morrisville, NC, USA.
Samples with viral RNA titers below 100,000 copies/ml were not evaluated for infectivity.
SARS-CoV-2 infectivity was determined by plaque assay in Vero cell cultures (LabCorp Inc, Indianapolis, IN, USA.)
Source: [P001VRV01MK4482: adam-adsl; adinf; adrna]

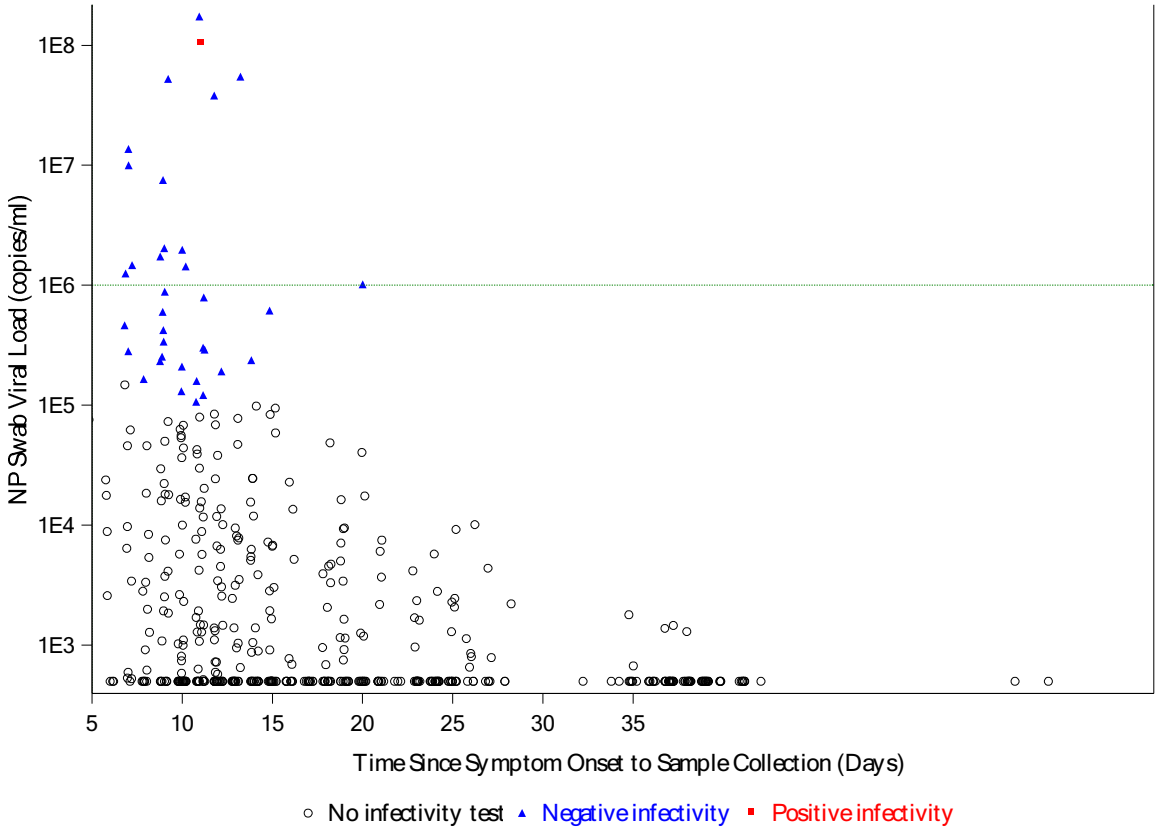
Appendix 2.7.3-covid19txallpop: 17
Plot of SARS-CoV-2 Infectivity by Viral RNA Titer and Time Since Symptom Onset
Nasopharyngeal Sample
Modified Intent-To-Treat Population with Negative Baseline Antibody
MK-4482-001 (Part 1)



SARS-CoV-2 Viral RNA titer was determined using a quantitative RT-PCR assay developed at Q2 Solutions, Morrisville, NC, USA.
Samples with viral RNA titers below 100,000 copies/ml were not evaluated for infectivity.
SARS-CoV-2 infectivity was determined by plaque assay in Vero cell cultures (LabCorp Inc, Indianapolis, IN, USA.)
Source: [P001VRV01MK4482: adam-adsl; adinf; adrna]

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Appendix 2.7.3-covid19txallpop: 18
Plot of SARS-CoV-2 Infectivity by Viral RNA Titer and Time Since Symptom Onset
Nasopharyngeal Sample
Modified Intent-To-Treat Population with Positive Baseline Antibody
MK-4482-001 (Part 1)



SARS-CoV-2 Viral RNA titer was determined using a quantitative RT-PCR assay developed at Q2 Solutions, Morrisville, NC, USA.
Samples with viral RNA titers below 100,000 copies/ml were not evaluated for infectivity.
SARS-CoV-2 infectivity was determined by plaque assay in Vero cell cultures (LabCorp Inc, Indianapolis, IN, USA.)
Source: [P001VRV01MK4482: adam-adsl; adinf; adrna]

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Appendix 2.7.3-covid19txallpop: 19
Mean Number of Transition and Transversion Nucleotide Changes Observed in Post-baseline SARS-CoV-2 Sequences Relative to Baseline by Change Type
Nasopharyngeal Sample
Modified Intent-To-Treat Population
MK-4482-001 (Part 1)

Visit	Treatment	N	Transitions				Transversions								Other Nucleotide Changes
			C:U	U:C	G:A	A:G	C:A	C:G	U:A	U:G	G:U	G:C	A:C	A:U	
Day 3	MK-4482 200 mg	19	2.9	0.4	0.4	0.5	0.2	0.0	0.1	0.1	0.6	0.1	0.1	0.1	0.6
	MK-4482 400 mg	25	4.4	1.3	1.6	1.6	0.0	0.0	0.2	0.0	0.9	0.1	0.2	0.1	1.0
	MK-4482 800 mg	18	2.1	0.2	0.8	0.7	0.0	0.0	0.0	0.0	0.3	0.0	0.1	0.0	0.5
	Placebo	22	1.1	0.1	0.1	0.2	0.0	0.0	0.0	0.0	0.4	0.0	0.0	0.1	0.5
EOT (Day 5)	MK-4482 200 mg	12	5.9	0.7	3.3	1.2	0.1	0.0	0.1	0.0	0.8	0.0	0.3	0.1	0.9
	MK-4482 400 mg	13	4.1	1.0	2.6	0.8	0.1	0.0	0.0	0.1	0.3	0.1	0.0	0.0	0.8
	MK-4482 800 mg	13	5.9	2.0	1.5	0.9	0.0	0.0	0.2	0.1	1.6	0.0	0.2	0.2	1.5
	Placebo	10	3.1	0.2	0.1	0.6	0.0	0.0	0.0	0.0	0.7	0.0	0.1	0.0	1.0

N = number of participants with both baseline and post-baseline SARS-CoV-2 gene sequencing data at the reported visit.

Source: [P001VRV01MK4482: adam-adngsnt]

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Appendix 2.7.3-covid19txallpop: 20
Mean Number of Transition and Transversion Nucleotide Changes Observed in Post-baseline SARS-CoV-2 Sequences Relative to Baseline by Change Type
Oropharyngeal Sample
Modified Intent-To-Treat Population
MK-4482-001 (Part 1)

			Transitions				Transversions								Other Nucleotide
Visit	Treatment	N	C:U	U:C	G:A	A:G	C:A	C:G	U:A	U:G	G:U	G:C	A:C	A:U	Changes
Day 3	MK-4482 200 mg	11	2.3	0.4	0.7	0.7	0.1	0.0	0.0	0.0	0.4	0.0	0.3	0.0	0.5
	MK-4482 400 mg	12	1.1	0.1	0.0	0.3	0.0	0.0	0.0	0.0	0.3	0.0	0.0	0.0	0.6
	MK-4482 800 mg	11	1.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.3
	Placebo	12	1.3	0.0	0.3	0.3	0.0	0.0	0.1	0.0	0.5	0.0	0.0	0.1	0.3
EOT (Day 5)	MK-4482 200 mg	4	2.5	0.5	1.0	0.5	0.0	0.0	0.0	0.0	0.3	0.0	0.0	0.0	0.3
	MK-4482 400 mg	8	2.3	0.3	1.1	0.9	0.1	0.0	0.0	0.0	0.1	0.1	0.0	0.0	0.3
	MK-4482 800 mg	10	2.1	0.5	0.6	0.4	0.1	0.0	0.1	0.0	1.0	0.0	0.0	0.0	0.7
	Placebo	10	2.8	0.1	0.3	0.1	0.1	0.0	0.1	0.1	0.9	0.0	0.1	0.1	0.6

N = number of participants with both baseline and post-baseline SARS-CoV-2 gene sequencing data at the reported visit.

Source: [P001VRV01MK4482: adam-adngsnt]

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Appendix 2.7.3-covid19txallpop: 21
Participants with Treatment-Emergent Amino Acid Changes Detected in the SARS-CoV-2 Viral Replicase Complex (NSP7-NSP14) Nasopharyngeal Sample With Variant Percentage >=0.05
Modified Intent-To-Treat Population
MK-4482-001 (Part 1)

Amino Acid Variant	MK-4482 200 mg n	MK-4482 400 mg n	MK-4482 800 mg n	MK-4482 Combined n	Placebo n
No data to report.					

Every participant is counted a single time for each applicable row and column.
A 5% frequency cutoff was applied to identify treatment-emergent amino acid substitutions.
Treatment-emergent amino acid changes are reported if detected in post-baseline samples, in 2 or more MK-4482 treated participants combined and 0 in the placebo group.

Source: [P001VRV01MK4482: adam-adsl; adngsaa]

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Appendix 2.7.3-covid19txallpop: 22
Participants with Treatment-Emergent Amino Acid Changes Detected in the SARS-CoV-2 Viral Replicase Complex (NSP7-NSP14) Oropharyngeal Sample With Variant Percentage >=0.05
Modified Intent-To-Treat Population
MK-4482-001 (Part 1)

Amino Acid Variant	MK-4482 200 mg n	MK-4482 400 mg n	MK-4482 800 mg n	MK-4482 Combined n	Placebo n
No data to report.					

Every participant is counted a single time for each applicable row and column.
A 5% frequency cutoff was applied to identify treatment-emergent amino acid substitutions.
Treatment-emergent amino acid changes are reported if detected in post-baseline samples, in 2 or more MK-4482 treated participants combined and 0 in the placebo group.

Source: [P001VRV01MK4482: adam-adsl; adngsaa]

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Appendix 2.7.3-covid19txallpop: 23
Participants with Treatment-Emergent Amino Acid Changes Detected in the SARS-CoV-2 S Protein Nasopharyngeal Sample With Variant Percentage >=0.05
Modified Intent-To-Treat Population
MK-4482-001 (Part 1)

Amino Acid Variant	MK-4482 200 mg n	MK-4482 400 mg n	MK-4482 800 mg n	MK-4482 Combined n	Placebo n
Participants in population with both baseline and post-baseline SARS-CoV-2 gene sequencing data	22	27	23	72	24
TYR145DEL	2	0	0	2	0

Every participant is counted a single time for each applicable row and column.
A 5% frequency cutoff was applied to identify treatment-emergent amino acid substitutions.
Treatment-emergent amino acid changes are reported if detected in post-baseline samples, in 2 or more MK-4482 treated participants combined and 0 in the placebo group.

Source: [P001VRV01MK4482: adam-adsl; adngsaa]

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Appendix 2.7.3-covid19txallpop: 24
Participants with Treatment-Emergent Amino Acid Changes Detected in the SARS-CoV-2 S Protein Oropharyngeal Sample With Variant Percentage >=0.05
Modified Intent-To-Treat Population
MK-4482-001 (Part 1)

Amino Acid Variant	MK-4482 200 mg n	MK-4482 400 mg n	MK-4482 800 mg n	MK-4482 Combined n	Placebo n
No data to report.					

Every participant is counted a single time for each applicable row and column.
A 5% frequency cutoff was applied to identify treatment-emergent amino acid substitutions.
Treatment-emergent amino acid changes are reported if detected in post-baseline samples, in 2 or more MK-4482 treated participants combined and 0 in the placebo group.

Source: [P001VRV01MK4482: adam-adsl; adngsaa]

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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
- Sex and gender
- Study intervention and study treatment and/or treatment

Abbreviation/Term	Definition
AE	Adverse event
ALT	Alanine aminotransferase
APaT	All participants as treated
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BMI	Body mass index
BP	Blood pressure
COVID-19	Coronavirus Disease 2019
CRF(s)	Case Report Form(s)
CSR	Clinical Study Report
CYP	Cytochrome P450
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
ECG	Electrocardiograms
ECI	Events of clinical interest
FDA	Food and Drug Administration
FSA	Financial sharing area
IRT	Intervention randomization system
ISS	Integrated Safety Summary
MedDRA	Medical dictionary for regulatory activities
MOV	Molnupiravir, also known as MK-4482 and EIDD-2801
NHC	N-hydroxycytidine, EIDD-1931
NHC-TP	N-hydroxycytidine-5′-triphosphate, EIDD-2601

Abbreviation/Term	Definition
NP	Nasopharyngeal
PDLC	Predefined limit of change
PK	Pharmacokinetic(s)
Q12H	Every 12 hours
QTc	QT interval corrected for heart rate
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCS	Summary of Clinical Safety
SD	Standard deviation
SMQ	Standardized MedDRA Query
SOC	System organ classes
Sp02	Oxygen saturation
sSAP	Supplemental Statistical Analysis Plan
ULN	Upper limit of normal
UK	United Kingdom
US	United States
VS	Vital Signs
WBC	White blood cell count

1 EXPOSURE TO THE INVESTIGATIONAL PRODUCT

1.1 Overall Safety Evaluation Plan and Safety Study Summaries

1.1.1 Overall Safety Evaluation Plan

Molnupiravir (also known as MK-4482 and EIDD-2801; hereafter referred to as MOV) is a novel ribonucleoside analog prodrug with broad-spectrum in vitro and in vivo antiviral activity against a range of RNA viruses, including coronaviruses.

Safety results from 8 clinical studies are presented in this Summary of Clinical Safety [Table 2.7.4-covid19txallpop: 2]. Five studies have completed. One of the 3 remaining 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. P005 and P007 remain blinded.

A total of 1468 adult participants received at least 1 dose of MOV in the studies where enrollment is completed; 944 of these participants received 1 or more doses of MOV 800 mg in a dosing regimen of Q12H for at least 5 days [Table 2.7.4-covid19txallpop: 1].

Safety was evaluated in the MOV clinical studies by collection of AEs, clinical laboratory evaluations, and physical examination (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 shown 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 Summary of Clinical Safety. This Phase 2/3 data provide the largest pool of MOV 800 mg/placebo data available for analysis from a single study population. AE and laboratory summaries from the Phase 3 data (P002 Part 2) are also provided to show the consistency between the integrated Phase 2/3 and nonintegrated Phase 3 data. 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 (see below). 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.

Protocol Number	SAP/sSAP and Protocol
P002 • Part 1 • Part 2	 • [Ref. 5.3.5.1: P002V01MK4482: 16.1.9, 16.1.1] • [Ref. 5.3.5.1: P002V03MK4482: 16.1.9, 16.1.1]
P006	[Ref. 5.3.5.1: P006MK4482: 16.1.9, 16.1.1]
P001	[Ref. 5.3.5.1: P001V01MK4482: 16.1.9, 16.1.1]
P004	[Ref. 5.3.3.1: P004MK4482: 16.1.9, 16.1.1]
P012	[Ref. 5.3.3.1: P012MK4482: 16.1.9, 16.1.1]
P008	[Ref. 5.3.3.3: P008MK4482: 16.1.9, 16.1.1]

Protocol Number	Participant Listings	Participant Narratives
P002 (Parts 1 and 2)	[Ref. 5.3.5.1: P002V01MK4482: 16.2.7] [Ref. 5.3.5.1: P002V03MK4482: 16.2.7]	[Ref. 5.3.5.1: P002V01MK4482: 16.2.7.2] [Ref. 5.3.5.1: P002V03MK4482: 16.2.7.2]
P006	[Ref. 5.3.5.1: P006MK4482: 16.2.7]	[Ref. 5.3.5.1: P006MK4482: 14.3.3]
P001	[Ref. 5.3.5.1: P001V01MK4482: 16.2.7]	[Ref. 5.3.5.1: P001V01MK4482: 16.2.7.2]
P004	[Ref. 5.3.3.1: P004MK4482: 16.2.7]	[Ref. 5.3.3.1: P004MK4482: 14.4]
P012	[Ref. 5.3.3.1: P012MK4482: 16.2.7]	[Ref. 5.3.3.1: P012MK4482: 16.2.7.2]
P008	[Ref. 5.3.3.3: P008MK4482: 16.2.7]	[Ref. 5.3.3.3: P008MK4482: 16.2.7.2]
SAP=statistical analysis plan; sSAP=supplemental statistical analysis plan.		

Table 2.7.4-covid19txallpop: 1
Number of Participants Who Received MOV (P002, P006, P001, P004, P012, and P008)

Study	**Number of Participants**	
Protocol Number (Study Phase)	**APaT (Any Dose of MOV)**	**MOV 800 mg Q12H**
P002 (Phase 2/3)	Part 2 (Phase 3): 710	Part 2 (Phase 3): 710[a]
	Part 1 (Phase 2): 225	Part 1 (Phase 2): 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 in a dosing regimen of Q12H for 5 or 5.5 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 1], [Ref. 5.3.5.1: P002V01MK4482: Table 10 1], [Ref. 5.3.5.1: P006MK4482: Table 3, 14.1.1.1], [Ref. 5.3.5.1: P001V01MK4482: Table10 1], [Ref. 5.3.3.1: P004MK4482: Table 14.1 1.1, 14.1 1.2, 14.1 1.3], [Ref. 5.3.3.1: P012MK4482: Table 10 1], and [Ref. 5.3.3.3: P008MK4482: 16.1.7].

1.1.2 Clinical Safety Study Summaries

The 8 studies contributing to clinical safety are described in [Table 2.7.4-covid19txallpop: 2].

Table 2.7.4-covid19txallpop: 2
Summary of Clinical Safety Studies of MOV

<table>
<tr><th>Study Number (Status) [CTD Location], Regions</th><th>Study Design</th><th>Number of Participants by Intervention Group (Randomized/Treated/Completed)</th><th>Study Population</th><th>Safety Endpoints</th></tr>
<tr>
<td>MK-4482-002 (MOVe OUT, P002) (ongoing)
[Ref. 5.3.5.1: P002V01MK4482]
[Ref. 5.3.5.1: P002V03MK4482]
North America
Latin America
Europe
Asia Pacific
Africa</td>
<td>Title: A Phase 2/3, Randomized, Placebo controlled, Double blind Clinical Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MK 4482 in Nonhospitalized Adults with COVID 19
Phase: 2/3
Design: randomized, placebo controlled, double blind study
Safety Assessment: AEs were assessed from the time of intervention randomization through 14 days after cessation of study intervention.</td>
<td>Part 1 (Phase 2): 1:1:1:1 MOV 200 mg, 400 mg, or 800 mg or placebo, oral Q12H × 5 days
<table>
<tr><th>Groups</th><th>R</th><th>T</th><th>C</th></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>Placebo</td><td>74</td><td>74</td><td>72</td></tr>
</table>
Part 2 (Phase 3): 1:1 MOV 800 mg or placebo, oral Q12H × 5 days
<table>
<tr><th>Groups</th><th>R</th><th>T</th><th>C</th></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>
Part 1/Part 2 combined (Phase 2/3):
<table>
<tr><th>Groups</th><th>R</th><th>T</th><th>C</th></tr>
<tr><td>MOV 800 mg</td><td>792</td><td>784</td><td>751</td></tr>
<tr><td>Placebo</td><td>791</td><td>775</td><td>744</td></tr>
</table>
</td>
<td>Males/females, ≥18 years of age with RT PCR confirmed SARS CoV 2 infection, increased risk of severe illness, nonhospitalized
Part 1 (Phase 2): symptom onset ≤7 days
<table>
<tr><th>Groups</th><th>Sex</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>Placebo</td><td>44 M/30 F</td><td>44.5 (21 82)</td></tr>
</table>
Part 2 (Phase 3): symptom onset ≤5 days
<table>
<tr><th>Groups</th><th>Sex</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>
Part 1/Part 2 combined (Phase 2/3):
<table>
<tr><th>Groups</th><th>Sex</th><th>Median Age (range) years</th></tr>
<tr><td>MOV 800 mg</td><td>367 M/425 F</td><td>43.0 (18 90)</td></tr>
<tr><td>Placebo</td><td>410 M/381 F</td><td>44.0 (18 88)</td></tr>
</table>
</td>
<td>Primary:
• AEs
• AEs leading to discontinuation of study intervention</td>
</tr>
</table>

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<table>
<tr><th>Study Number (Status) [CTD Location], Regions</th><th>Study Design</th><th>Number of Participants by Intervention Group (Randomized/Treated/Completed)</th><th>Study Population</th><th>Safety Endpoints</th></tr>
<tr>
<td>MK-4482-006 (EIDD 2801 2003, P006) (completed)
[Ref. 5.3.5.1: P006MK4482]
North America</td>
<td>Title: A Phase IIa, Randomized, Double Blind, Placebo controlled Trial to Evaluate the Safety, Tolerability, and Efficacy of EIDD 2801 to Eliminate SARS CoV 2 Viral RNA Detection in Persons with COVID 19
Phase: 2a
Design: randomized, double blind, placebo controlled study
Safety Assessment: AEs were assessed from the time of intervention randomization through 14 days after cessation of study intervention.</td>
<td>Part 1: 1:1 MOV 200 mg or placebo, oral BID × 5 days
Parts 2-5: 3:1 MOV 400 mg or 800 mg or placebo, orally BID × 5 days
Parts 6-9: 3:1 MOV 400 mg or 800 mg or placebo, orally BID × 5 day
Parts 1-9 pooled:
<table>
<tr><th>Groups[a]</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>Placebo</td><td>62</td><td>62</td><td>61</td></tr>
<tr><td colspan="4">[a] Number included in the safety population.</td></tr>
</table>
</td>
<td>Males/females, ≥18 years of age with laboratory confirmed SARS CoV 2 infection, nonhospitalized
Parts 1-9 pooled:
<table>
<tr><th>Groups</th><th>Sex</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>Placebo</td><td>28 M/34 F</td><td>39.0 (19 71)</td></tr>
</table>
</td>
<td>Primary:
• All AEs leading to early discontinuation of study intervention
• Study intervention related discontinuation of study intervention
• New Grade 3 or higher AEs
• Study intervention related new Grade 3 or higher AEs
Secondary:
• Grade 2 or higher AEs
• Study intervention related related AEs</td>
</tr>
</table>

<table>
<tr><th>Study Number (Status) [CTD Location], Regions</th><th>Study Design</th><th>Number of Participants by Intervention Group (Randomized/Treated/Completed)</th><th>Study Population</th><th>Safety Endpoints</th></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 and Africa
Asia Pacific</td>
<td>Title: Phase 2/3 Randomized, Placebo Controlled, Double Blind Clinical Study to Evaluate the Pharmacokinetics, Efficacy and Safety of MK-4482 in Hospitalized Adults With COVID 19
Phase: 2/3
Design: multicenter, efficacy, safety, pharmacokinetics, parallel assignment, double blind, placebo controlled intervention
Safety Assessment: AEs were assessed from the time of intervention randomization through 14 days after cessation of study intervention.</td>
<td>Part 1: 1:1:1:1 MOV 200 mg, 400 mg, 800 mg or placebo, oral Q12H × 5 days
<table>
<tr><th>Groups</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>Placebo</td><td>78</td><td>75</td><td>70</td></tr>
</table>
</td>
<td>Males/females, ≥18 years of age with RT PCR confirmed SARS CoV 2 infection (mild, moderate, or severe), hospitalized
Part 1:
<table>
<tr><th>Groups</th><th>Sex</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>Placebo</td><td>44 M/34 F</td><td>58.5 (31 94)</td></tr>
</table>
</td>
<td>Primary:
• AEs
• AEs leading to discontinuation of study intervention</td>
</tr>
<tr>
<td>MK-4482-004
(EIDD 2801 1001 UK, P004)
(completed)
[Ref. 5.3.3.1: P004MK4482]
United Kingdom</td>
<td>Title: A Randomized, Double blind, Placebo controlled, First in human Study Designed to Evaluate the Safety, Tolerability, and Pharmacokinetics of EIDD 2801 Following Oral Administration to Healthy Volunteers
Phase: 1
Design: randomized, double blind, placebo controlled study (Part 1 [SAD] and Part 3 [MAD]); randomized, open label, 2 period crossover, food effect (Part 2)
Safety Assessment: AEs were assessed from the time of intervention randomization</td>
<td>Part 1: 3:1 MOV 50, 100, 200, 400, 600, 800, 1200, 1600 mg or placebo, single oral dose
<table>
<tr><th>Groups</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>Placebo</td><td>16</td><td>16</td><td>16</td></tr>
</table>
</td>
<td>Males/females nonchildbearing potential, 18 60 years of age, healthy, BMI 19.0 29.9 kg/m^2, inclusive
Part 1:
<table>
<tr><th>Groups</th><th>Sex</th><th>Median Age (range) years</th></tr>
<tr><td>MOV 50 mg</td><td>4 M/2 F</td><td>55.5 (34 57)</td></tr>
<tr><td>MOV 100 mg</td><td>4 M/2 F</td><td>39.5 (23 58)</td></tr>
<tr><td>MOV 200 mg</td><td>5 M/1 F</td><td>38.5 (26 60)</td></tr>
<tr><td>MOV 400 mg</td><td>4 M/2 F</td><td>42.5 (23 57)</td></tr>
<tr><td>MOV 600 mg</td><td>4 M/2 F</td><td>36.0 (21 57)</td></tr>
<tr><td>MOV 800 mg</td><td>6 M/0 F</td><td>35.5 (23 56)</td></tr>
<tr><td>MOV 1200 mg</td><td>6 M/0 F</td><td>31.5 (24 56)</td></tr>
</table>
</td>
<td>Primary:
• Safety laboratory assessments including chemistry, hematology and urinalysis
• Physical examinations
• ECGs
• VS
• AEs</td>
</tr>
</table>

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<table>
<tr><th>Study Number (Status) [CTD Location], Regions</th><th>Study Design</th><th>Number of Participants by Intervention Group (Randomized/Treated/Completed)</th><th>Study Population</th><th>Safety Endpoints</th></tr>
<tr>
<td></td>
<td>through 14 days after cessation of study intervention.</td>
<td>
Part 2: MOV 200 mg in 2 periods, single oral dose, fed and fasted
<table>
<tr><th>Groups</th><th>R</th><th>T</th><th>C</th></tr>
<tr><td>MOV 200 mg (fed/fasted)</td><td>10</td><td>10</td><td>10</td></tr>
</table>
Part 3: 3:1 MOV 50, 100, 200, 300, 400, 600, 800 mg or placebo, oral Q12H × 5.5 days
<table>
<tr><th>Groups</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 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>Placebo</td><td>14</td><td>14</td><td>14</td></tr>
</table>
</td>
<td>
<table>
<tr><td>MOV 1600 mg</td><td>6 M/0 F</td><td>27.5 (25 46)</td></tr>
<tr><td>Placebo</td><td>14 M/2 F</td><td>38.5 (22 56)</td></tr>
</table>
Part 2:
<table>
<tr><th>Groups</th><th>Sex</th><th>Median Age (range) years</th></tr>
<tr><td>MOV 200 mg (fed/fasted)</td><td>7 M/3 F</td><td>44.0 (30 60)</td></tr>
</table>
Part 3:
<table>
<tr><th>Groups</th><th>Sex</th><th>Median Age (range) years</th></tr>
<tr><td>MOV 50 mg</td><td>5 M/1 F</td><td>31.0 (23 56)</td></tr>
<tr><td>MOV 100 mg</td><td>5 M/1 F</td><td>52.5 (20 58)</td></tr>
<tr><td>MOV 200 mg</td><td>6 M/0 F</td><td>32.5 (22 60)</td></tr>
<tr><td>MOV 300 mg</td><td>4 M/2 F</td><td>36.5 (20 58)</td></tr>
<tr><td>MOV 400 mg</td><td>5 M/1 F</td><td>38.5 (20 60)</td></tr>
<tr><td>MOV 600 mg</td><td>6 M/0 F</td><td>23.5 (20 54)</td></tr>
<tr><td>MOV 800 mg</td><td>6 M/0 F</td><td>27.5 (20 58)</td></tr>
<tr><td>Placebo</td><td>12 M/2 F</td><td>34.0 (19 59)</td></tr>
</table>
</td>
<td></td>
</tr>
</table>

<table>
<tr><th>Study Number (Status) [CTD Location], Regions</th><th>Study Design</th><th>Number of Participants by Intervention Group (Randomized/Treated/Completed)</th><th>Study Population</th><th>Safety Endpoints</th></tr>
<tr>
<td>MK-4482-012
(P012) (completed)
[Ref. 5.3.3.1: P012MK4482]
Europe</td>
<td>Title: A Multiple ascending Dose Clinical Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Molnupiravir in Healthy Participants
Phase: 1
Design: randomized, placebo controlled, multiple ascending dose, double blind, single site
Safety Assessment: AEs were assessed from the time of intervention randomization through 14 days after cessation of study intervention.</td>
<td>3:1 MOV 400, 600, 800 mg, or placebo, oral Q12H × 10.5 days
<table>
<tr><th>Groups</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>Placebo</td><td>8</td><td>8</td><td>8</td></tr>
</table>
</td>
<td>Males/females, 25 60 years of age, healthy, BMI 18 35 kg/m^2, inclusive
<table>
<tr><th>Groups</th><th>Sex</th><th>Median Age (range) years</th></tr>
<tr><td>MOV 400 mg</td><td>2 M/4F</td><td>46.0 (33 52)</td></tr>
<tr><td>MOV 600 mg</td><td>2 M/4F</td><td>47.5 (27 59)</td></tr>
<tr><td>MOV 800 mg</td><td>6 M/6F</td><td>38.0 (27 59)</td></tr>
<tr><td>Placebo</td><td>6 M/2F</td><td>50.0 (30 59)</td></tr>
</table>
</td>
<td>Primary:
• AEs
• VS
• ECGs
• Safety laboratory assessments including chemistry, hematology and urinalysis</td>
</tr>
</table>

<table>
<tr><th>Study Number (Status) [CTD Location], Regions</th><th>Study Design</th><th>Number of Participants by Intervention Group (Randomized/Treated/Completed)</th><th>Study Population</th><th>Safety Endpoints</th></tr>
<tr>
<td>MK-4482-008
(P008) (completed)
[Ref. 5.3.3.3: P008MK4482]
East Asia Pacific (Japan)</td>
<td>Title: A Single and Multiple Dose Clinical Study to Evaluate the Safety, Tolerability and Pharmacokinetics of MK-4482 in Healthy Japanese Adult Participants
Phase: 1
Design: 2 part, randomized, placebo controlled, single site double blind
Part 1: single ascending dose
Part 2: multiple dose
Safety Assessment: AEs were assessed from the time of intervention randomization through 14 days after cessation of study intervention.</td>
<td>Part 1: 3:1 MOV 200, 400 mg (fed/fasted), 1600 mg, or placebo, single oral dose; 7:2 MOV 800 mg (fed/fasted), or placebo, single oral dose
<table>
<tr><th>Groups</th><th>R</th><th>T</th><th>C</th></tr>
<tr><td>MOV 200 mg[a]</td><td>6</td><td>6</td><td>6</td></tr>
<tr><td>MOV 400 mg[b]</td><td>6</td><td>6</td><td>6</td></tr>
<tr><td>MOV 800 mg (fasted)[c]</td><td>7</td><td>7</td><td>7</td></tr>
<tr><td>MOV 800 mg (fed)[c]</td><td>7</td><td>6</td><td>6</td></tr>
<tr><td>MOV 1600 mg[a]</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>
[a] Panel A (n 8): Different participants received placebo between Period 1 and 2.
[b] Panel B (n 8)
[c] Panel C (n 9): The same participants received MK 4482 or placebo in both periods.
Part 2: 15:5 400 mg or placebo Q12H orally Q12H × 5.5 days; 15:5 800 mg or placebo orally Q12H × 5.5 days
<table>
<tr><th>Groups</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>13</td></tr>
<tr><td>Placebo</td><td>10</td><td>10</td><td>10</td></tr>
</table>
</td>
<td>Males, 20 60 years of age, healthy, Japanese, BMI 18.5 24.9 kg/m^2, inclusive
Part 1:
<table>
<tr><th>Groups</th><th>Sex</th><th>Median Age (range) years</th></tr>
<tr><td>MOV 200 mg</td><td>6 M</td><td>52.5 (21 59)</td></tr>
<tr><td>MOV 400 mg</td><td>6 M</td><td>53.0 (31 57)</td></tr>
<tr><td>MOV 800 mg (fasted)</td><td>7 M</td><td>51.0 (24 57)</td></tr>
<tr><td>MOV 800 mg (fed)</td><td>6 M</td><td>48.5 (24 57)</td></tr>
<tr><td>MOV 1600 mg</td><td>6 M</td><td>53.5 (21 59)</td></tr>
<tr><td>Placebo</td><td>8 M</td><td>51.0 (28 57)</td></tr>
</table>
Part 2:
<table>
<tr><th>Groups</th><th>Sex</th><th>Median Age (range) years</th></tr>
<tr><td>MOV 400 mg</td><td>15 M</td><td>42.0 (20 59)</td></tr>
<tr><td>MOV 800 mg (fasted)</td><td>15 M</td><td>45.0 (21 57)</td></tr>
<tr><td>Placebo</td><td>10 M</td><td>49.5 (24 59)</td></tr>
</table>
</td>
<td>Primary:
• AEs
• VS
• ECGs
• Physical examinations
• Safety laboratory assessments including chemistry, hematology and urinalysis</td>
</tr>
</table>

Study Number (Status) [CTD Location], Regions	Study Design	Number of Participants by Intervention Group (Randomized/Treated/Completed)	Study Population	Safety Endpoints
MK-4482-007 (EID 2801 2004, P007), NCT04405739, (recruitment completed) North America	**Title**: The Safety of EIDD 2801 and Its Effects on Viral Shedding of SARS CoV 2 **Phase**: 2a **Design**: randomized, double blind, placebo controlled **Safety Assessment:** AEs were assessed from the time of intervention randomization through 14 days after cessation of study intervention.	**Part 1**: 1:1:1 MOV 200, 400 mg or placebo, orally BID × 5 days **Part 2**: 2:1 MOV 400 mg or placebo, orally BID × 5 days **Part 3**: 2:1 MOV 800 mg or placebo, orally BID × 5 days **Part 4**: (optional) 2:1 MOV up to 800 mg or placebo, orally BID × 5 days	Males/females, ≥18 years of age, with PCR confirmed SARS CoV 2 and hospitalized Planned enrollment: approximately 80 participants As of [redacted] 20[redacted], 71 participants enrolled	**Primary**: • AEs and SAEs • Physical examination including VS • Safety laboratory <u>CBC w/ differential</u> •Hgb >1 g/dL or to <9 g/dL •platelet count by 50,000/µL or to <75,000/µL <u>CMP including LFTs</u> •Increased AST, ALT, amylase, or lipase to ≥3x the ULN <u>Urinalysis</u> • ECGs •Prolonged QTc to ≥500 msec.

Study Number (Status) [CTD Location], Regions	Study Design	Number of Participants by Intervention Group (Randomized/Treated/Completed)	Study Population	Safety Endpoints
MK-4482-005 (AGILE CST 2, P005), NCT04746183, (ongoing) South Africa, United Kingdom	**Title**: Randomized, Multicenter, Seamless, Adaptive, Phase I/II Platform Study to Determine the Optimal Dose, Safety, and Efficacy of EIDD 2801 for the Treatment of COVID 19 **Phase**: 1/2 **Design**: randomized, open label, controlled versus standard of care (Phase 1); placebo controlled, blinded (Phase 2) **Safety Assessment:** AEs were assessed from the time of intervention randomization through 14 days after cessation of study intervention.	**Phase 1**: MOV 300, 600, 800 mg, orally BID × 10 doses **Phase 2**: 1:1 MOV 800 mg or placebo, orally BID × 10 doses	Males/females, ≥60 years of age, or ≥50 years of age with ≥1 well controlled comorbidity, with PCR confirmed SARS CoV 2 Planned enrollment: approximately 198 participants As of [redacted], 18 participants enrolled in Phase 1 and 156 participants enrolled in Phase 2	**Primary:** • DLT using CTCAE version 5 (Grades 3 and above) over 7 days • CTCAE grading related to platelets and/or lymphocytes **Secondary:** • AEs • SAEs • Physical findings, VS, and laboratory parameters

ALT alanine aminotransferase; AST aspartate aminotransferase; BID twice daily; CBC complete blood count; CMP comprehensive metabolic panels; COVID 19 coronavirus disease 2019; CTCAE common terminology criteria for adverse events; DLT dose limiting toxicity; ECGs electrocardiograms; EIDD Emory Institute for Drug Development; Hgb hemoglobin; IA4 interim analysis 4; ID identification; LFTs liver function tests; MAD multiple ascending dose; MOV molnupiravir (MK-4482, EIDD 2801); PCR polymerase chain reaction; po oral(ly); Q12H every 12 hours RNA ribonucleic acid; SAD single ascending dose; SARS CoV 2 SARS associated coronavirus 2; UK United Kingdom; ULN upper limit of normal; VS vital signs.

Source: [Table 2.7.4 covid19txallpop: 3], [Table 2.7.4 covid19txallpop: 6], [Ref. 5.3.5.1: P002V01MK4482: Table 10 1, 14.1 5], [Ref. 5.3.5.1: P006MK4482: Table 3, 14.1.1.1], [Ref. 5.3.5.1: P001V01MK4482: Table 14.1 1, 14.1 4], [Ref. 5.3.3.1: P004MK4482: Table 14.1 1.1, 14.1 1.2, 14.1 1.3, 14.1 2.1, 14.1 2.2, 14.1 2.3], [Ref. 5.3.3.1: P012MK4482: Table 10 1, 10 2], [Ref. 5.3.3.3: P008MK4482: 16.1.7].

1.2 Overall Extent of Exposure

1.2.1 Disposition of Participants

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

The disposition of participants in P002 (Part 1 [MOV 800 mg/placebo] 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 deaths were reported for the placebo group compared with the MOV 800 mg group.

Table 2.7.4-covid19txallpop: 3
Disposition of Participants All Randomized Participants
MK-4482-002 (Part 1 and Part 2 Combined)

	MK 4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	792		791		1,583	
Status for Study Medication						
Started	784		775		1,559	
Completed	750	(95.7)	736	(95.0)	1,486	(95.3)
Discontinued	34	(4.3)	39	(5.0)	73	(4.7)
Adverse Event	13	(1.7)	21	(2.7)	34	(2.2)
Lost To Follow Up	2	(0.3)	2	(0.3)	4	(0.3)
Non Compliance With Study Drug	8	(1.0)	8	(1.0)	16	(1.0)
Physician Decision	1	(0.1)	0	(0.0)	1	(0.1)
Withdrawal By Subject	9	(1.1)	6	(0.8)	15	(1.0)
Other	1	(0.1)	2	(0.3)	3	(0.2)
Status for Day 29 Milestone[a]						
Started	784		775		1,559	
Completed	751	(95.8)	744	(96.0)	1,495	(95.9)
Discontinued	33	(4.2)	31	(4.0)	64	(4.1)
Death	1	(0.1)	9	(1.2)	10	(0.6)
Lost To Follow Up	8	(1.0)	5	(0.6)	13	(0.8)
Withdrawal By Subject	24	(3.1)	16	(2.1)	40	(2.6)
Other	0	(0.0)	1	(0.1)	1	(0.1)
Status for Trial Through LFU						
Discontinued	45	(5.7)	54	(6.8)	99	(6.3)
Death	2	(0.3)	14	(1.8)	16	(1.0)
Lost To Follow Up	11	(1.4)	7	(0.9)	18	(1.1)
Randomized By Mistake Without Study Treatment	3	(0.4)	2	(0.3)	5	(0.3)
Withdrawal By Subject	29	(3.7)	29	(3.7)	58	(3.7)
Other	0	(0.0)	2	(0.3)	2	(0.1)
Status Not Recorded	747	(94.3)	737	(93.2)	1,484	(93.7)

LFU Late Follow up Visit
Status Not Recorded Ongoing
[a] Only participants who receive at least 1 dose are included.

Source: [ISS: adam adsl]

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

The disposition of participants enrolled in the Phase 2 studies was comparable across intervention groups in each study [Table 2.7.4-covid19txallpop: 2]. A total of 810 participants (n 596 MOV all doses, n 214 placebo) were randomized in these studies. 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 in each study is shown in the CSR for that study: P002 Part 1 [Ref. 5.3.5.1: P002V01MK4482: Table 10-1], P006 [Ref. 5.3.5.1: P006MK4482: Table 14.1.1.1], and P001 Part 1 [Ref. 5.3.5.1: P001V01MK4482: Table 10-1].

1.2.1.3 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 the 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].

1.2.2 Duration of Exposure

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

The duration of exposure to study intervention in P002 (Part 1 [MOV 800 mg/placebo] and Part 2 combined) was comparable in both intervention groups [Table 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 intervention 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 [Table 5.3.5.3.3-covid19txallpop: 3].

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

Most (>89%) participants in each study intervention group took 9 to 10 doses of either MOV (200, 400, or 800 mg) or placebo in the Phase 2 studies P002 Part 1 [Ref. 5.3.5.1: P002V01MK4482: Table 14.1-7], P006 [Ref. 5.3.5.1: P006MK4482: Table 14.1.5.1.1], and P001 Part 1 [Ref. 5.3.5.1: P001V01MK4482: Table 14.1-5].

1.2.2.3 Phase 1 (P004, P008, P012)

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].

1.3 Demographic and Other Characteristics of Study Population

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

Baseline demographic and other characteristics in P002 (Part 1 [MOV 800 mg/placebo] and Part 2 combined) were generally comparable for the MOV and placebo groups in the APaT population [Table 2.7.4-covid19txallpop: 4] and the all randomized population [Table 5.3.5.3.3-covid19txallpop: 4].

This study was conducted in 23 countries with the largest proportion of participants coming from the regions of Latin America and Europe/Middle East/Africa [Ref. 5.3.5.1: P002V03MK4482: 2].

Table 2.7.4-covid19txallpop: 4
Participant Characteristics
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		1559	
Sex						
Male	364	(46.4)	400	(51.6)	764	(49.0)
Female	420	(53.6)	375	(48.4)	795	(51.0)
Age (years)						
18 to 49	513	(65.4)	497	(64.1)	1010	(64.8)
50 to 64	182	(23.2)	185	(23.9)	367	(23.5)
65 to 74	61	(7.8)	65	(8.4)	126	(8.1)
≥75	28	(3.6)	28	(3.6)	56	(3.6)
≤60	645	(82.3)	634	(81.8)	1279	(82.0)
>60	139	(17.7)	141	(18.2)	280	(18.0)
Participants with data	784		775		1559	
Mean	45.1		45.5		45.3	
SD	14.8		15.0		14.9	
Median	43.0		44.0		44.0	
Range	18 to 90		18 to 88		18 to 90	
Race						
American Indian or Alaska Native	62	(7.9)	48	(6.2)	110	(7.1)
Asian	25	(3.2)	22	(2.8)	47	(3.0)
Black or African American	44	(5.6)	37	(4.8)	81	(5.2)
White	455	(58.0)	457	(59.0)	912	(58.5)
Multiple	198	(25.3)	210	(27.1)	408	(26.2)
Unknown[a]	0	(0.0)	1	(0.1)	1	(0.1)

Participant Characteristics
All Participants as Treated Population
MK-4482-002 (Part 1 and Part 2 Combined)

	MK 4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Ethnicity						
Hispanic Or Latino	374	(47.7)	381	(49.2)	755	(48.4)
Not Hispanic Or Latino	402	(51.3)	389	(50.2)	791	(50.7)
Not Reported	6	(0.8)	3	(0.4)	9	(0.6)
Unknown[a]	2	(0.3)	2	(0.3)	4	(0.3)
Region						
Europe, the Middle East and Africa	267	(34.1)	258	(33.3)	525	(33.7)
North America	65	(8.3)	77	(9.9)	142	(9.1)
Latin America	343	(43.8)	340	(43.9)	683	(43.8)
Asia Pacific	19	(2.4)	16	(2.1)	35	(2.2)
Africa	90	(11.5)	84	(10.8)	174	(11.2)
Time from Symptom Onset to Randomization						
≤3 Days	360	(45.9)	351	(45.3)	711	(45.6)
4 5 Days	398	(50.8)	400	(51.6)	798	(51.2)
>5 Days	26	(3.3)	24	(3.1)	50	(3.2)
Participants with data	784		775		1559	
Mean	3.6		3.6		3.6	
SD	1.2		1.1		1.1	
Median	4.0		4.0		4.0	
Range	1 to 7		1 to 7		1 to 7	
Risk Factors for Severe Illness from COVID-19						
At least one risk factor	763	(97.3)	752	(97.0)	1515	(97.2)
Age >60 years	139	(17.7)	141	(18.2)	280	(18.0)
Active Cancer	14	(1.8)	16	(2.1)	30	(1.9)
Chronic Kidney Disease	41	(5.2)	46	(5.9)	87	(5.6)

Participant Characteristics
All Participants as Treated Population
MK-4482-002 (Part 1 and Part 2 Combined)

	MK 4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Chronic Obstructive Pulmonary Disease	24	(3.1)	36	(4.6)	60	(3.8)
Obesity (BMI ≥ 30)	569	(72.6)	546	(70.5)	1115	(71.5)
Serious Heart Condition	97	(12.4)	83	(10.7)	180	(11.5)
Diabetes Mellitus	115	(14.7)	135	(17.4)	250	(16.0)
Baseline COVID Severity						
Mild	425	(54.2)	414	(53.4)	839	(53.8)
Moderate	356	(45.4)	359	(46.3)	715	(45.9)
Severe	3	(0.4)	1	(0.1)	4	(0.3)
Unknown[a]	0	(0.0)	1	(0.1)	1	(0.1)

[a] Missing data, invalid sample, tests not done, or results reported as "Unknown" are categorized as Unknown. Baseline Disease Severity was Collected via IRT for participants in part 1.

Source: [ISS: adam adsl]

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

Baseline demographic and other characteristics were generally comparable across intervention groups in the Phase 2 studies. Demographics and other characteristics are described for each study in the respective CSR: P002 Part 1 [Ref. 5.3.5.1: P002V01MK4482: Table 14.1-5], P006 [Ref. 5.3.5.1: P006MK4482: Table 3, 14.1.6.1.1], and P001 Part 1 [Ref. 5.3.5.1: P001V01MK4482: 10.4].

Mean time from symptom onset to randomization was approximately 7 days for most participants in Part 1 of P001 and ≤5 days for participants in Part 1 of P002 and P006. The majority of participants in these studies had at least 1 risk factor at baseline for severe illness from COVID-19 (approximately 75% in Part 1 of P001 and P002 and 60% in P006).

1.3.3 Phase 1 (P004, P008, P012)

Baseline demographic and other characteristics were comparable across intervention groups in the Phase 1 studies. All participants in these studies were healthy participants with a higher proportion of men (>80%) compared with women. P008 enrolled healthy Japanese males only. Demographics and other characteristics are described for each study in the respective CSR: P004 [Ref. 5.3.3.1: P004MK4482: 10.2], P012 [Ref. 5.3.3.1: P012MK4482: Table 10-2], and P008 [Ref. 5.3.3.3: P008MK4482: Table 10-3, 10-4].

2 ADVERSE EVENTS

Safety was evaluated in the MOV clinical studies by collection of AEs, clinical laboratory evaluations, and physical examination (including vital signs). AEs were assessed from the time of intervention randomization through 14 days after cessation of study intervention. Note: MedDRA coded “worsening of COVID-19” to the preferred term of “COVID-19”.

2.1 Analysis of Adverse Events: Phase 2/3

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/placebo] and Part 2 combined) [Table 2.7.4-covid19txallpop: 5].

The proportion of participants who had AEs leading to death in the MOV group (n 2, 0.3%) was lower than the placebo group (n 13, 1.7%). AEs leading to death are discussed further in [Sec. 2.7.4-covidtxallpop: 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 classfied as related to study intervention [Table 2.7.4-covid19txallpop: 10]. 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 2.7.4-covid19txallpop: 5
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]

2.1.1 Common Adverse Events

2.1.1.1 Most Frequently Reported Adverse Events

The percentages of participants in P002 (Part 1 [MOV 800 mg/placebo] and Part 2 combined) with 1 or more AEs were comparable in both intervention groups (31.3% MOV, 33.4% placebo) [Table 5.3.5.3.3-covid19txallpop: 9] [Table 5.3.5.3.3-covid19txallpop: 10]. COVID-19, COVID pneumonia, and diarrhea were the most frequently reported AEs (≥2% in either group) [Table 2.7.4-covid19txallpop: 6]. COVID-19 pneumonia and cough were reported more frequently in the placebo group compared to the MOV group [Table 5.3.5.3.3-covid19txallpop: 10].

Table 2.7.4-covid19txallpop: 6
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	(%)
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)**

Confidential

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]

Confidential

2.1.1.2 Adverse Events Related to Study Intervention

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

The proportions 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 in P002 [Ref. 5.3.5.1: P002V01MK4482: 16.2.7.1.1] [Ref. 5.3.5.1: P002V03MK4482: 16.2.7.1.3].

2.1.1.2.2 Phase 3: P002 (Part 2)

AEs considered related to study intervention were reported for approximately 8% of participants in either study intervention group in P002 Part 2 [Ref. 5.3.5.1: P002V03MK4482: Table 14.3-8]. Diarrhea (1.7% MOV versus 2.1% placebo), nausea (1.4% MOV versus 0.7% placebo), and dizziness (1.0% MOV versus 0.7% placebo) were the only intervention-related AEs reported with an incidence ≥1% in either group. The proportions of participants with any AE considered related to study intervention by the investigator and SAEs were comparable in both intervention groups. Study intervention-related SAEs were not reported in the MOV group and were reported in 0.1% 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) [Ref. 5.3.5.1: P002V03MK4482: Table 14.3-9]. A complete reporting of results from P002 (Part 2) is in the CSR [Ref. 5.3.5.1: P002V03MK4482].

2.1.1.3 Study Intervention-related Adverse Events by Toxicity Grade

2.1.1.3.1 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] [Figure 5.3.5.3.3-covid19txallpop: 2]. Five participants had a Grade 3 study intervention-related AE (n 2 [0.3%] MOV, n 3 [0.4%] placebo).

2.1.1.3.2 Phase 3: P002 (Part 2)

Of the participants reporting 1 or more study intervention-related AEs, most participants in P002 Part 2 reported AEs of Grade 1 or Grade 2 [Ref. 5.3.5.1: P002V03MK4482: Table 14.3-8]. Of the 5 participants with study intervention-related AEs, 2 participants in the MOV group each had 1 AE of Grade 3 intensity (increased blood creatine phosphokinase and urticaria). Neither AE was serious and the events resolved within 1 week of onset [Ref. 5.3.5.1: P002V03MK4482: 16.1.7.2].

Table 2.7.4-covid19txallpop: 7
Participants With Drug-Related Adverse Events During Treatment and 14-Day Follow-Up Period
(Incidence ≥1% 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	(%)
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]

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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 2.7.4-covid19txallpop: 8]. 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 AEs resulting in death includes participants who died due to an AE regardless of the timing of the 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), only 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 the timing of the death occurring on or before Day 29); the remaining 4 deaths included in the safety analyses had AE onset dates within the period for AE reporting, but the deaths occurred after Day 29.

Table 2.7.4-covid19txallpop: 8
Participants With Adverse Events Resulting in Death (AE Onset 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	(%)
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)

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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]

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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 2.7.4-covid19txallpop: 9] [Figure 5.3.5.3.3-covid19txallpop: 3].

The most frequently 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 [Table 2.7.4-covid19txallpop: 10].

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 2.7.4-covid19txallpop: 9
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	(%)
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)**

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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)

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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)

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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]

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Table 2.7.4-covid19txallpop: 10
Participants With Serious Drug-Related Adverse Events During Treatment and 14-Day Follow-Up Period
(Incidence >0% in One or More Treatment Groups)
All Participants as Treated Population
MK-4482-002 (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 drug related adverse events	0	(0.0)	1	(0.1)	1	(0.1)
with no serious drug related adverse events	784	(100.0)	774	(99.9)	1,558	(99.9)
Gastrointestinal disorders	**0**	**(0.0)**	**1**	**(0.1)**	**1**	**(0.1)**
Pancreatitis	0	(0.0)	1	(0.1)	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]

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2.1.4 Other Significant Adverse Events

2.1.4.1 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 2.7.4-covid19txallpop: 11]. 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 2.7.4-covid19txallpop: 11
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	(%)
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)

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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)

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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]

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Table 2.7.4-covid19txallpop: 12
Participants With Drug-Related 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	(%)
Participants in population	784		775		1,559	
with one or more drug related adverse events leading to discontinuation	4	(0.5)	4	(0.5)	8	(0.5)
with no drug related adverse events leading to discontinuation	780	(99.5)	771	(99.5)	1,551	(99.5)
Eye disorders	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**
Vision blurred	1	(0.1)	0	(0.0)	1	(0.1)
Gastrointestinal disorders	**1**	**(0.1)**	**3**	**(0.4)**	**4**	**(0.3)**
Abdominal pain upper	0	(0.0)	2	(0.3)	2	(0.1)
Diarrhoea	0	(0.0)	3	(0.4)	3	(0.2)
Nausea	1	(0.1)	0	(0.0)	1	(0.1)
Vomiting	1	(0.1)	0	(0.0)	1	(0.1)
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)
Nervous system disorders	**2**	**(0.3)**	**0**	**(0.0)**	**2**	**(0.1)**

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Participants With Drug-Related 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	**2**	**(0.3)**	**0**	**(0.0)**	**2**	**(0.1)**
Dizziness	1	(0.1)	0	(0.0)	1	(0.1)
Headache	1	(0.1)	0	(0.0)	1	(0.1)
Psychiatric disorders	**0**	**(0.0)**	**1**	**(0.1)**	**1**	**(0.1)**
Insomnia	0	(0.0)	1	(0.1)	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]

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2.1.4.2 Events of Clinical Interest

No participants had laboratory values that met the predefined ECI criteria for potential DILI (defined as postbaseline elevated AST or ALT ≥3 x ULN and elevated total bilirubin ≥2 x ULN and alkaline phosphatase <2 x 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 postbaseline 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 postbaseline 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 the hematology consultant as hemoperfusion-related thrombocytopenia [Ref. 5.3.5.1: P002V03MK4482: 16.2.7.2].

2.1.4.3 Events of Pregnancy

No pregnancies were reported in P002 through Day 29 [Ref. 5.3.5.1: P002V01MK4482: 12.2.3.2] [Ref. 5.3.5.1: P002V03MK4482: 12.2.3.2].

2.1.4.4 Hypersensitivity Events

AEs that may indicate hypersensitivity when using the standardized MedDRA queries for "anaphylactic reaction" (narrow), "hypersensitivity" (narrow), and "angioedema" (narrow) were reported by 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 (n 1) and an SAE of shock (sepsis) (n 1) were reported in the MOV 800 mg group and 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 [Table 2.7.4-covid19txallpop: 13]. Overall, 9 (1.1%) participants in the MOV group and 5 (0.6%) participants in the placebo group reported AEs in the skin and subcutaneous SOC that were assessed by the investigator as study intervention-related [Table 5.3.5.3.3-covid19txallpop: 14]. One participant (MOV group) reported an AE of urticaria that was Grade 3 and study intervention-related as assessed by the investigator; the remaining intervention related AEs in the skin 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 in a participant in the MOV group on Day 2 was a Grade 1 intensity, assessed as study intervention-related by the investigator, not serious, 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].

Table 2.7.4-covid19txallpop: 13
Participants With Adverse Events Related to Hypersensitivity Reaction 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	(%)
Participants in population	784		775		1,559	
with one or more adverse events related to hypersensitivity/allergic reactions	14	(1.8)	6	(0.8)	20	(1.3)
with no adverse events related to hypersensitivity/allergic reactions	770	(98.2)	769	(99.2)	1,539	(98.7)
Blood and lymphatic system disorders	**0**	**(0.0)**	**1**	**(0.1)**	**1**	**(0.1)**
Immune thrombocytopenia	0	(0.0)	1	(0.1)	1	(0.1)
Immune system disorders	**0**	**(0.0)**	**1**	**(0.1)**	**1**	**(0.1)**
Hypersensitivity	0	(0.0)	1	(0.1)	1	(0.1)
Respiratory, thoracic and mediastinal disorders	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**
Bronchospasm	1	(0.1)	0	(0.0)	1	(0.1)
Skin and subcutaneous tissue disorders	**12**	**(1.5)**	**4**	**(0.5)**	**16**	**(1.0)**
Angioedema	1	(0.1)	1	(0.1)	2	(0.1)
Dermatitis	0	(0.0)	1	(0.1)	1	(0.1)
Dermatitis allergic	2	(0.3)	0	(0.0)	2	(0.1)
Eczema	1	(0.1)	0	(0.0)	1	(0.1)
Pruritus allergic	0	(0.0)	1	(0.1)	1	(0.1)
Rash	5	(0.6)	1	(0.1)	6	(0.4)
Rash macular	1	(0.1)	0	(0.0)	1	(0.1)
Rash vesicular	1	(0.1)	0	(0.0)	1	(0.1)
Urticaria	2	(0.3)	0	(0.0)	2	(0.1)
Vascular disorders	**1**	**(0.1)**	**0**	**(0.0)**	**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.
Hypersensitivity reaction is defined by Standard MedDRA Queries (narrow) for “anaphylactic reaction”, “angioedema”, and “hypersensitivity”.

Source: [ISS: adam adsl; adae]

2.2 Analysis of Adverse Events: Phase 2 (P002 Part 1, P006, P001 Part 1)

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 safety 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 per investigator [Ref. 5.3.5.1: P002V01MK4482: Table 14.3-7].

- AEs leading to study intervention-discontinuation were reported for 1.3% participants in the combined MOV group (none were study intervention-related) and 1.4% in the placebo group (1 was study intervention-related) [Ref. 5.3.5.1: P002V01MK4482: Table 14.3-11, 14.3-12].

2.2.2 P006

The AE profiles observed in P006 were generally comparable across intervention groups [Ref. 5.3.5.1: P006MK4482: 12.2.1]. 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 also 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% MOV groups combined, 6.5% placebo). [Ref. 5.3.5.1: P006MK4482: 12.2.2.1].

- SAEs were reported for 4 participants (3 in the MOV groups combined, 1 in placebo group). None were considered to be related to study intervention by 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 to be related to study intervention by the investigator [Ref. 5.3.5.1: P006MK4482: 12.3.1.3.1].

2.2.3 P001 Part 1

The overall AE 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 MOV 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 were 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 also 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% MOV groups, 16.0% placebo) [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].

- 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 14.3-9, 14.3-11].

2.3 Analysis of Adverse Events: Phase 1 (P004, P008, P012)

2.3.1 P004

MOV single doses up to 1600 mg (including the food effect panel evaluated at MOV 200 mg) and multiple doses of MOV up to 800 mg Q12H for 5.5 days were generally well tolerated in healthy adult participants [Ref. 5.3.3.1: P004MK4482: 12.1.2, 12.1.3]. No SAEs or deaths were reported in any part of the study.

The following key safety results were also observed:

- Part 1 (single dose): 17 (35.4%) participants receiving MOV and 7 (43.8%) participants receiving placebo reported at least 1 AE; Part 2 (single dose of MOV on 2 separate days): 3 (30.0%) participants reported at least 1 AE; Part 3 (multiple-dose): 18 (42.9%) participants receiving MOV and 7 (50.0%) participants receiving placebo reported at least 1 AE [Ref. 5.3.3.1: P004MK4482: 12.1.1.1, 12.1.1.3], [Ref. 5.3.3.1: P004MK4482: Table 14.3.1-1.2].

- AEs (study intervention-related) were reported for 11 (11.0%) participants receiving MOV and 5 (16.7%) receiving placebo [Ref. 5.3.3.1: P004MK4482: Table 34, 36].

- All AEs were mild to moderate in severity and resolved by the end of the study.

- One participant discontinued study intervention after receiving 3 days of 800 mg MOV Q12H due to a nonserious study intervention-related AE of rash (papulosquamous and mildly urticated rash) [Ref. 5.3.3.1: P004MK4482: 14.4].

2.3.2 P012

Daily Q12H doses of MOV 400, 600, and 800 mg for 10.5 days were generally well tolerated in healthy adult participants [Ref. 5.3.3.1: P012MK4482: 13.2]. No SAEs, deaths, discontinuations due to AEs, or ECIs were reported [Ref. 5.3.3.1: P012MK4482: 12.1].

The following key safety results were also observed:

- AEs were reported for 21 (87.5%) participants receiving MOV and 6 (75.0%) participants receiving placebo [Ref. 5.3.3.1: P012MK4482: Table 12.1].

- Study intervention-related AEs were reported by 2 participants receiving MOV (1 participant with dizziness and 1 participant with headache) and no participant in the placebo group. All AEs were mild to moderate in severity [Ref. 5.3.3.1: P012MK4482: 12.1.1].

2.3.3 P008

Single doses of MOV up to 1600 mg and multiple doses of MOV 400 and 800 mg Q12H for 5.5 days were generally well tolerated in healthy Japanese male adult participants [Ref. 5.3.3.3: P008MK4482: 12.1.1]. No SAEs, deaths or ECI were reported in any part of the study.

The following key safety results were also observed:

- In Part 1 (single dose), 2 (9.5%) participants receiving MOV reported at least 1 AE; there were no AEs reported by participants receiving placebo [Ref. 5.3.3.3: P008MK4482: Table 12.1]. In Part 2 (multiple-dose), 12 (40.0%) participants receiving MOV and 1 (10.0%) participant receiving placebo reported AEs [Ref. 5.3.3.3: P008MK4482: Table 12.2].

- Study intervention-related AEs were reported for 1 (4.8%) and 5 (16.7%) participants who received MOV in Part 1 and Part 2, respectively [Ref. 5.3.3.3: P008MK4482: Table 14.3-2, 14.3-4]. Of these, the AE term “toxic skin eruption” was the most frequently reported (3 participants in the MOV 800 mg Q12H group in Part 2). All the AEs were mild in intensity with the exception of 2 moderate AEs in 2 participants (dermatitis and toxic skin eruption) [Ref. 5.3.3.3: P008MK4482: 12.1.3.2].

- One participant discontinued study intervention after receiving 5 days of MOV 800 mg Q12H due to moderate toxic skin eruption. 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 with topical and supportive nonprescription medication and resolved before the end of the study [Ref. 5.3.3.3: P008MK4482: 12.1.2].

2.4 Blinded Safety Data From Ongoing Studies: Phases 1 and 2

2.4.1 P007

Enrollment in this study conducted in hospitalized participants with COVID-19 is complete and remains blinded. No significant safety concerns were observed based on the second interim analysis safety review committee minutes of [redacted], and the committee recommended without changes [Ref. 5.3.5.1: P007: 07VZGJ].

As of [redacted], a total of 71 participants have been enrolled. The following key blinded safety results were observed:

- SAEs were reported for 4 participants; none were considered related to study intervention by the investigator [Ref. 5.3.5.1: 07ZGPF].

- One participant had an AE leading to death (acute respiratory failure); the AE was considered serious, and not related to study intervention per investigator assessment.

- AEs leading to discontinuation of study intervention (worsening bradycardia and hypotension) were reported for 1 participant; both AEs were considered serious, and not considered by the investigator to be related to study intervention.

2.4.2 P005

This study in nonhospitalized participants with COVID-19 is ongoing. The Data Monitoring and Ethics Committee recommended continuation of the study without changes on [redacted] [Ref. 5.3.5.4: 07Y4XN].

As of [redacted], 18 participants were enrolled in Phase 1 (Part 1), and 156 participants were enrolled in Phase 2 (Part 2).

An analysis of the open-label Phase 1 data showed MOV 800 mg administered twice daily for 5 days was well tolerated [Ref. 5.4: 07ZLP9].

The following key blinded safety results from Phase 2 were observed in participants who received study intervention:

- Five participants had SAEs; 1 of which (vomiting) was considered related to study intervention by the investigator [Ref. 5.3.5.4: 07ZGLW].

- No deaths were reported.

2.5 Narratives

Narratives are provided for participant deaths and for participants with ECI, SAEs, and discontinuation of study intervention due to an AE in the individual CSRs: P002 Part 1 [Ref. 5.3.5.1: P002V01MK4482: 16.2.7.2] and Part 2 [Ref. 5.3.5.1: P002V03MK4482: 16.2.7.2], P006 [Ref. 5.3.5.1: P006MK4482: 14.3.3], P001 Part 1 [Ref. 5.3.5.1: P001V01MK4482: 16.2.7.2], and P004 [Ref. 5.3.3.1: P004MK4482: 14.4].

3 CLINICAL LABORATORY EVALUATIONS

3.1 Overview of Laboratory Events

Laboratory safety tests were collected at baseline and throughout the study.

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 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 toxicity grade in [Table 5.3.5.3.3-covid19txallpop: 25] [Table 5.3.5.3.3-covid19txallpop: 26] [Table 5.3.5.3.3-covid19txallpop: 27]. Overall, mean changes in laboratory values from baseline over time were comparable for both groups [Table 5.3.5.3.3-covid19txallpop: 28].

3.1.2 Phase 3: P002 (Part 2)

No evidence of hematologic or hepatic toxicity was observed for MOV in P002 (Part 2) [Ref. 5.3.5.1: P002V03MK4482: Table 14.4.-1].

Overall, the proportions of participants with laboratory values that met PDLC in Phase 3 data from P002 (Part 2) were comparable in both intervention groups and aligns with the Phase 2/3 integrated data from P002 as shown in [Table 5.3.5.3.3-covid19txallpop: 27]. A complete reporting of results from P002 (Part 2) is included in the CSR [Ref. 5.3.5.1: P002V03MK4482].

3.2 Hematology

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 toxicity grade in [Table 5.3.5.3.3-covid19txallpop: 25] [Table 5.3.5.3.3-covid19txallpop: 26] [Table 5.3.5.3.3-covid19txallpop: 27]. Overall mean changes in laboratory values from baseline over time were comparable for both 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 ECI are described in [Sec. 2.7.4-covid19txallpop: 2.1.4.2].

Table 2.7.4-covid19txallpop: 14
Mean Change (SD) in Selected Laboratory Values from Baseline over Time
All Participants as Treated Population
MK-4482-002 (Part 1 and Part 2 Combined)

Visit	Treatment	N	Baseline		Value		Mean Change	
			Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]
Hemoglobin (g/dL)								
Day 3	MK 4482 800 mg	609	14.27 (1.63)	[7.40, 19.60]	14.12 (1.65)	[7.30, 21.00]	0.15 (0.68)	[3.43, 2.90]
	Placebo	616	14.41 (1.56)	[8.20, 19.40]	14.24 (1.61)	[7.60, 18.90]	0.17 (0.77)	[6.10, 3.00]
EOT (Day 5)	MK 4482 800 mg	600	14.26 (1.63)	[7.40, 18.80]	14.08 (1.65)	[8.00, 19.30]	0.18 (0.91)	[7.30, 5.40]
	Placebo	611	14.43 (1.56)	[8.20, 19.40]	14.24 (1.60)	[7.90, 19.20]	0.19 (0.84)	[3.00, 3.20]
Day 10	MK 4482 800 mg	564	14.20 (1.61)	[8.40, 19.60]	13.74 (1.63)	[7.80, 21.10]	0.46 (0.90)	[3.90, 4.70]
	Placebo	570	14.42 (1.59)	[8.20, 19.40]	13.90 (1.65)	[7.30, 18.90]	0.52 (0.95)	[3.80, 3.80]
Day 15	MK 4482 800 mg	585	14.20 (1.64)	[7.40, 19.60]	13.41 (1.61)	[6.70, 20.10]	0.79 (0.91)	[6.80, 3.20]
	Placebo	573	14.46 (1.56)	[8.20, 19.40]	13.63 (1.52)	[8.10, 17.70]	0.83 (0.89)	[4.50, 2.90]
Day 29	MK 4482 800 mg	562	14.25 (1.59)	[8.40, 19.60]	13.61 (1.56)	[7.50, 20.00]	0.64 (0.93)	[6.50, 2.60]
	Placebo	572	14.46 (1.51)	[8.20, 19.40]	13.71 (1.51)	[8.80, 17.40]	0.75 (0.95)	[6.50, 2.90]

Confidential

Mean Change (SD) in Selected Laboratory Values from Baseline over Time
All Participants as Treated Population
MK-4482-002 (Part 1 and Part 2 Combined)

Visit	Treatment	N	Baseline		Value		Mean Change	
			Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]
Neutrophils (10^9/L)								
Day 3	MK 4482 800 mg	604	3.45 (1.93)	[0.45, 13.39]	3.53 (2.13)	[0.58, 18.02]	0.08 (1.69)	[8.74, 7.10]
	Placebo	615	3.46 (2.09)	[0.45, 14.18]	3.65 (2.48)	[0.49, 37.00]	0.19 (2.15)	[8.17, 35.22]
EOT (Day 5)	MK 4482 800 mg	595	3.48 (1.97)	[0.45, 13.50]	4.05 (2.47)	[0.43, 27.28]	0.57 (2.12)	[9.70, 21.41]
	Placebo	608	3.45 (2.07)	[0.45, 14.18]	3.98 (2.30)	[0.70, 15.39]	0.54 (1.93)	[8.48, 8.99]
Day 10	MK 4482 800 mg	559	3.50 (2.00)	[0.45, 14.45]	4.56 (2.48)	[0.74, 22.90]	1.07 (2.31)	[10.18, 13.00]
	Placebo	568	3.43 (2.04)	[0.45, 14.18]	4.57 (2.37)	[1.01, 17.64]	1.15 (2.37)	[9.36, 12.76]
Day 15	MK 4482 800 mg	579	3.46 (1.93)	[0.45, 13.50]	4.53 (2.26)	[0.43, 23.41]	1.07 (2.29)	[9.98, 18.87]
	Placebo	571	3.41 (2.01)	[0.45, 14.18]	4.58 (2.12)	[0.82, 16.25]	1.17 (2.42)	[8.85, 11.99]
Day 29	MK 4482 800 mg	559	3.43 (1.89)	[0.45, 13.39]	3.84 (1.83)	[0.96, 24.84]	0.41 (2.25)	[10.32, 19.66]
	Placebo	572	3.42 (2.04)	[0.45, 14.18]	3.77 (1.58)	[0.63, 12.80]	0.35 (2.31)	[11.40, 10.41]

Confidential

Mean Change (SD) in Selected Laboratory Values from Baseline over Time
All Participants as Treated Population
MK-4482-002 (Part 1 and Part 2 Combined)

Visit	Treatment	N	Baseline		Value		Mean Change	
			Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]
Platelets (10^9/L)								
Day 3	MK-4482 800 mg	601	224.30 (75.18)	[65.00, 544.00]	232.84 (79.62)	[82.00, 594.00]	8.54 (39.59)	[144.00, 200.00]
	Placebo	595	225.91 (76.81)	[69.00, 664.00]	234.63 (86.07)	[63.00, 688.00]	8.72 (43.38)	[196.00, 208.00]
EOT (Day 5)	MK-4482 800 mg	592	224.46 (75.99)	[65.00, 544.00]	267.43 (89.05)	[78.00, 682.00]	42.97 (71.47)	[167.00, 421.00]
	Placebo	598	226.36 (78.12)	[69.00, 664.00]	263.07 (100.17)	[87.00, 722.00]	36.70 (75.59)	[229.00, 438.00]
Day 10	MK-4482 800 mg	561	224.22 (75.22)	[65.00, 544.00]	320.77 (100.74)	[88.00, 886.00]	96.55 (108.04)	[210.00, 625.00]
	Placebo	561	227.66 (78.92)	[69.00, 664.00]	322.75 (104.90)	[108.00, 779.00]	95.08 (100.48)	[227.00, 441.00]
Day 15	MK-4482 800 mg	576	223.94 (75.25)	[65.00, 528.00]	307.48 (96.27)	[64.00, 804.00]	83.55 (101.83)	[227.00, 529.00]
	Placebo	556	228.41 (80.27)	[69.00, 664.00]	320.58 (100.12)	[13.00, 835.00]	92.18 (105.44)	[269.00, 630.00]
Day 29	MK-4482 800 mg	556	223.45 (74.69)	[65.00, 544.00]	256.13 (78.72)	[83.00, 1212.00]	32.68 (72.59)	[269.00, 994.00]
	Placebo	559	228.06 (79.49)	[69.00, 664.00]	257.16 (74.82)	[2.00, 779.00]	29.11 (66.93)	[341.00, 383.00]

Baseline is defined as last value obtained prior to the first dose of study treatment during treatment phase. A baseline and Treatment Value are required for a participant to be counted at a time point.

SD Standard deviation, Min Minimum, Max Maximum.

Source: [ISS: adam adlb]

Confidential

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 P002 Part 1 [Ref. 5.3.5.1: P002V01MK4482: Table 14.3-13, 14.3-16], P006 [Ref. 5.3.5.1: P006MK4482: 12.4.2.1.1], and P001 Part 1[Ref. 5.3.5.1: P001V01MK4482: Table 14.3-15]. One participant (placebo group) in P001 Part 1 had a confirmed platelet value <50,000 µL on Day 10 [Sec. 2.7.4-covid19txallpop: 2.2.3]. 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].

3.2.3 Phase 1 (P004, P012, 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) [Ref. 5.3.3.1: P004MK4482: 12.3] [Ref. 5.3.3.1: P012MK4482: 12.3.1, 12.3.2] [Ref. 5.3.3.3: P008MK4482: 12.5].

3.3 Chemistry

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 chemistry PDLC findings were low and comparable in both intervention groups [Table 5.3.5.3.3-covid19txallpop: 27]. The percentages 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 groups [Table 5.3.5.3.3-covid19txallpop: 25].

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

There were no clinically meaningful treatment- or dose-related changes in chemistry values observed in Phase 2 studies P002 Part 1 [Ref. 5.3.5.1: P002V01MK4482: Table 14.3-15], P006 [Ref. 5.3.5.1: P006MK4482: 12.4.2.1.2], and P001 Part 1 [Ref. 5.3.5.1: P001V01MK4482: Table 14.3-15, 14.3-16]. One participant (MOV 800 mg) in P001 Part 1 had postbaseline elevated AST or ALT ≥3x ULN and elevated total bilirubin ≥2x ULN and alkaline phosphatase <2x ULN (thus satisfying the criteria for potential DILI) on Day 14. The potential DILI criteria were no longer satisfied on Day 15 when alkaline phosphatase became >2x ULN. The laboratory parameters were considered to be secondary to fatal septic shock and cholestasis and not considered a DILI [Ref. 5.3.5.1: P001V01MK4482: 16.2.7.2].

3.3.3 Phase 1 (P004, P012, 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]).

3.4 Other Laboratory Values

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].

3.4.2 Phase 2 (P002 Part 1, P006, 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: P002V01MK4482: 14.3-15] [Ref. 5.3.5.1: P001V01MK4482: Table 14.3-15]. There were no treatment- or dose-related changes in any mean inflammatory values over time during P006 [Ref. 5.3.5.1: P006MK4482: 12.4.2.1.3].

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]).

4 VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

4.1 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 group showed a positive mean change in oxygen saturation beginning on Day 5, suggesting an earlier recovery for participants in the MOV group compared with the placebo group (Day 10) [Table 5.3.5.3.3-covid19txallpop: 23].

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

Vital sign 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: P002V01MK4482: 12.4] [Ref. 5.3.5.1: P001V01MK4482: 12.4]. No clinically meaningful changes in vital sign values were observed as a function of dose or treatment in P006 [Ref. 5.3.5.1: P006MK4482: 12.5.1.1.2].

4.3 Phase 1 (P004, P012, P008)

No study intervention-related clinically meaningful changes in vital sign values, ECGs (including QTc), physical examinations, or other observations 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 data 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 SAFETY IN SPECIAL GROUPS AND SITUATIONS

5.1 Intrinsic Factors

The incidence of AEs by intrinsic factors of age, sex, race, and ethnicity for participants in P002 (Part 1 [MOV 800 mg/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.

5.1.1 Age

The percentages of participants with at least 1 AE were generally comparable in the age subgroups of ≥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: 34]. Participants aged ≥65 years had higher rates of SAEs compared with participants aged <65 years in both intervention groups. As the SAEs were predominantly COVID-19 related, this likely reflects the epidemiology of COVID-19 where it has been observed that older patients are at higher risk for severe disease and adverse outcomes.

5.1.2 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].

5.1.3 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].

5.1.4 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 Extrinsic Factors

5.2.1 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 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 any of the 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 frequently 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].

5.4 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 is secreted in human milk, affect human milk production, or have effect on the breastfed infant. Breastfeeding is not recommended during treatment and for 4 days after the last dose of MOV.

5.5 Overdose

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

In Phase 2 and 3 clinical studies, 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 x MOV 800 mg). No other AEs were reported for this participant during the study [Ref. 5.3.5.1: P006MK4482: Table 12.3.1.3.4, 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 the clinical status of the patient. Hemodialysis is not expected to result in effective elimination of NHC.

5.6 Drug Abuse

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

5.7 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.

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

No studies on the effects 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.

6 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.

The estimate of patient exposure for the cumulative reporting period has been calculated from 01-NOV-2021 to 31-DEC-2021, rather than 04-NOV-2021 to 31-JAN-2022, based on the availability of monthly product distribution figures from the Company’s internal distribution data, the FSA database. MOV has been purchased and distributed as locally managed stockpile purchases (eg, government purchase or early access programs). The patient-years of treatment for MOV worldwide between 04-NOV-2021 to 31-JAN-2022

therefore could not be estimated. Cumulatively, approximately [redacted] capsules ([redacted] doses or [redacted] treatment courses) of MOV were distributed.

Postauthorization data for MOV in adults are summarized in [Sec. 2.7.4-covid19txallpop: 6.1].

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

As of 31-JAN-2022, there have been 319 postauthorization reports from spontaneous and noninterventional sources containing 515 events (460 nonserious, 55 serious) for MOV in the Company's global safety database [Appendix 2.7.4-covid19txallpop: 1]. As a case may contain more than 1 event, the total number of events is greater than the total number of reports.

Of the 319 reports received from spontaneous and noninterventional sources from 13 countries, the majority originated from Japan (approximately 78%). The preponderance of reports from Japan may be due to soliciting AEs through the Early Postmarketing Phase Vigilance and the Drug Use Results Survey (both to satisfy local Japanese regulations).

The most frequently reported AEs occurred in the SOCs of gastrointestinal disorders and skin and subcutaneous tissue disorders: diarrhea (68 cases), rash (41 cases) and nausea (27 cases). 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 55 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 Company of 14 cases reported in FDA Adverse Event Reporting System database (11 were not in the Company's global safety database) of serious events that may indicate hypersensitivity and requested a review of hypersensitivity and rash in reported to the Company's safety database in the postauthorization period. An analysis was performed using the SMQs "Anaphylactic Reaction" (narrow), "Hypersensitivity" (narrow) and "Angioedema" (narrow) terms for events reported as 31-JAN-2022, Based on this analysis, the Company Core Data Sheet was revised to add hypersensitivity 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).

Observations indicative of hypersensitivity, occurring mainly in the skin and subcutaneous tissue disorders SOC as seen in the examination of the postauthorization data, do not alter the conclusion that the overall benefit-risk balance for MOV remains positive. The Company will continue to monitor adverse event reports of MOV through routine pharmacovigilance.

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

7 CONCLUSIONS

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 Phase 1 through Phase 3 clinical studies demonstrates 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.

8 APPENDIX

Appendix 2.7.4-covid19txallpop: 1
Postauthorization Adverse Events Reported for Molnupiravir
04-NOV-2021 to 31-JAN-2022

SOC	Preferred Term	# Non-Serious Events	# Serious Events	# Events	# Cases
Cardiac disorders	Acute myocardial infarction	0	1	1	1
	Arrhythmia	0	1	1	1
	Cardiac arrest	0	1	1	1
	Palpitations	2	0	2	2
	Subtotal	**2**	**3**	**5**	**5**
Ear and labyrinth disorders	Ear discomfort	1	0	1	1
	Hypoacusis	1	0	1	1
	Tinnitus	1	0	1	1
	Vertigo	2	0	2	2
	Subtotal	**5**	**0**	**5**	**5**
Eye disorders	Eye pruritus	1	0	1	1
	Vision blurred	1	0	1	1
	Subtotal	**2**	**0**	**2**	**2**
Gastrointestinal disorders	Abdominal discomfort	3	0	3	3
	Abdominal distension	1	0	1	1
	Abdominal pain	14	1	15	15
	Abdominal pain upper	2	0	2	2
	Anaesthesia oral	1	0	1	1
	Breath odour	1	0	1	1
	Diarrhoea	66	2	68	68
	Discoloured vomit	0	1	1	1
	Dry mouth	1	0	1	1
	Dyspepsia	1	0	1	1
	Dysphagia	1	0	1	1
	Faeces discoloured	1	0	1	1
	Faeces soft	4	0	4	4
	Gastrointestinal disorder	1	0	1	1
	Gastrooesophageal reflux disease	1	0	1	1
	Lip dry	1	0	1	1
	Lip swelling	1	0	1	1
	Nausea	26	1	27	27
	Paraesthesia oral	1	0	1	1
	Vomiting	12	2	14	14
	Subtotal	**139**	**7**	**146**	**107**
	Adverse event	4	6	10	10

SOC	Preferred Term	# Non-Serious Events	# Serious Events	# Events	# Cases
General disorders and administration site conditions	Asthenia	4	0	4	4
	Chest discomfort	1	0	1	1
	Chest pain	1	0	1	1
	Chills	1	0	1	1
	Condition aggravated	2	1	3	3
	Death	0	2	2	2
	Drug ineffective	6	0	6	6
	Facial pain	1	0	1	1
	Feeling abnormal	4	2	6	6
	Feeling hot	1	0	1	1
	Feeling jittery	1	0	1	1
	Malaise	2	0	2	2
	No adverse event	9	0	9	9
	Pain	1	0	1	1
	Physical deconditioning	1	0	1	1
	Pyrexia	3	1	4	4
	Subtotal	**42**	**12**	**54**	**50**
Hepatobiliary disorders	Hepatic function abnormal	2	0	2	2
	Subtotal	**2**	**0**	**2**	**2**
Immune system disorders	Anaphylactic reaction	0	1	1	1
	Hypersensitivity	1	0	1	1
	Subtotal	**1**	**1**	**2**	**2**
Infections and infestations	Conjunctivitis	1	0	1	1
	COVID 19	8	5	13	13
	COVID 19 pneumonia	0	1	1	1
	Pneumonia	0	4	4	4
	Subtotal	**9**	**10**	**19**	**19**
Injury, poisoning and procedural complications	Accidental overdose	2	0	2	2
	Accidental underdose	3	0	3	3
	Arterial injury	0	1	1	1
	Circumstance or information capable of leading to medication error	1	0	1	1
	Contraindicated product administered	2	0	2	2
	Inappropriate schedule of product administration	3	0	3	3
	Incorrect dose administered	1	0	1	1
	Incorrect route of product administration	1	0	1	1
	Intentional dose omission	2	0	2	2
	Intentional product misuse	5	0	5	5
	Intentional product use issue	3	0	3	3
	Maternal exposure during pregnancy	20	0	20	20

SOC	Preferred Term	# Non-Serious Events	# Serious Events	# Events	# Cases
	Off label use	2	0	2	2
	Poor quality product administered	1	0	1	1
	Prescribed underdose	1	0	1	1
	Product dose omission issue	1	0	1	1
	Product use complaint	2	0	2	2
	Product use in unapproved indication	1	0	1	1
	Product use issue	5	0	5	5
	Underdose	2	0	2	2
	Wrong technique in product usage process	1	0	1	1
	Subtotal	**59**	**1**	**60**	**54**
Investigations	Ammonia increased	0	1	1	1
	Blood creatine phosphokinase increased	0	1	1	1
	Blood pressure increased	1	0	1	1
	Blood pressure systolic decreased	1	0	1	1
	Body temperature decreased	1	0	1	1
	Body temperature fluctuation	1	0	1	1
	Neutrophil count decreased	1	0	1	1
	Oxygen saturation decreased	1	2	3	3
	Platelet count decreased	2	0	2	2
	Prothrombin time shortened	1	0	1	1
	White blood cell count decreased	1	0	1	1
	Subtotal	**10**	**4**	**14**	**13**
Metabolism and nutrition disorders	Decreased appetite	9	1	10	10
	Dehydration	1	0	1	1
	Hyperkalaemia	0	1	1	1
	Subtotal	**10**	**2**	**12**	**12**
Musculoskeletal and connective tissue disorders	Muscle spasms	1	0	1	1
	Myalgia	2	0	2	2
	Pain in extremity	2	0	2	2
	Tenosynovitis	1	0	1	1
	Subtotal	**6**	**0**	**6**	**6**

SOC	Preferred Term	# Non-Serious Events	# Serious Events	# Events	# Cases
Nervous system disorders	Dizziness	18	1	19	19
	Dysgeusia	1	0	1	1
	Facial paralysis	0	1	1	1
	Headache	12	0	12	12
	Hypoaesthesia	3	0	3	3
	Paraesthesia	3	0	3	3
	Taste disorder	1	0	1	1
	Tremor	5	0	5	5
	Subtotal	**43**	**2**	**45**	**41**
Product issues	Product physical issue	1	0	1	1
	Subtotal	**1**	**0**	**1**	**1**
Psychiatric disorders	Anxiety	1	0	1	1
	Confusional state	0	1	1	1
	Hallucination	1	0	1	1
	Insomnia	2	0	2	2
	Sleep disorder	1	0	1	1
	Subtotal	**5**	**1**	**6**	**6**
Renal and urinary disorders	Anuria	0	1	1	1
	Dysuria	2	0	2	2
	Nocturia	1	0	1	1
	Pollakiuria	1	0	1	1
	Polyuria	1	0	1	1
	Renal pain	1	0	1	1
	Subtotal	**6**	**1**	**7**	**6**
Respiratory, thoracic and mediastinal disorders	Aspiration	0	1	1	1
	Cough	3	2	5	5
	Dyspnoea	0	1	1	1
	Oropharyngeal pain	2	0	2	2
	Respiratory disorder	0	1	1	1
	Sputum retention	1	0	1	1
	Throat tightness	1	0	1	1
	Tonsillar hypertrophy	1	0	1	1
	Wheezing	0	1	1	1
	Subtotal	**8**	**6**	**14**	**12**

SOC	Preferred Term	# Non-Serious Events	# Serious Events	# Events	# Cases
Skin and subcutaneous tissue disorders	Cold sweat	1	0	1	1
	Drug eruption	18	1	19	19
	Eczema	7	0	7	7
	Erythema	8	0	8	8
	Papule	1	0	1	1
	Pruritus	11	0	11	11
	Rash	42	1	43	41
	Rash erythematous	2	0	2	2
	Rash pruritic	6	0	6	6
	Stevens Johnson syndrome	0	1	1	1
	Urticaria	12	2	14	14
	Subtotal	**108**	**5**	**113**	**94**
Vascular disorders	Hypertension	1	0	1	1
	Pallor	1	0	1	1
	Subtotal	**2**	**0**	**2**	**2**
Total		**460**	**55**	**515**	**319**

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Table of All Clinical Trials

Study ID	Phase	Country/ Region	Study Title	Study design	Dosing regimen	Study population	Participant exposure
4482 001 [Ref. 5.3.5.1: P001V01MK4482]	2/3	Brazil Chile Colombia France Israel Korea, Republic of Mexico Philippines Poland Russian Federation South Africa Spain Ukraine United Kingdom United States	Efficacy, safety, and pharmacokinetic study to evaluate molnupiravir administered to hospitalized adult participants with COVID 19.	Randomized, double blind, parallel group, placebo controlled	MOV 200 mg po Q12H MOV 400 mg po Q12H MOV 800 mg po Q12H Placebo po Q12H 5 days of treatment	Males/females Age: ≥18 Participants hospitalized with COVID 19	MOV 200 mg: 73 MOV 400 mg: 73 MOV 800 mg:72 Placebo: 75
MOV= MK 4482/molnupiravir; Q12H= once every 12 hours.							

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Study ID	Phase	Country/ Region	Study Title	Study design	Dosing regimen	Study population	Participant exposure
4482 002 [Ref. 5.3.5.1: P002V01MK4482]	2/3	Brazil, Chile, Colombia, France, Germany, Israel, Russia, South Africa, Spain, Ukraine, United Kingdom, United States of America	A Phase 2/3, Randomized, Placebo Controlled, Double blind Clinical Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MK 4482 in Non hospitalized Adults with COVID 19	Randomized, placebo controlled, double blind, parallel group, active controlled	MOV 200 mg po Q12H for 5 days. MOV 400 mg po Q12H for 5 days. MOV 800 mg po Q12H for 5 days. Placebo po Q12H for 5 days.	Males/females ≥18 years of age Participants with laboratory confirmed SARS CoV 2 infection sample collection ≤7 days prior to randomization	MOV 200 mg: 74 MOV 400 mg: 77 MOV 800mg: 74 placebo: 74
MOV= MK4482/ molnupiravir; Q12H= once every 12 hours.							

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Study ID	Phase	Country/ Region	Study Title	Study Design	Dosing Regimen	Study Population	Participant Exposure
4482 002 [Ref. 5.3.5.1: P002V03MK4482]	2/3	Argentina, Brazil, Canada, Chile, Colombia, Egypt, France, Germany, Guatemala, Israel, Italy, Japan, Mexico, Philippines, Russia, South Africa, Spain, Taiwan, Ukraine, United Kingdom, United States of America	A Phase 2/3, Randomized, Placebo Controlled, Double blind Clinical Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MK 4482 in Non hospitalized Adults with COVID 19	Randomized, placebo controlled, double blind, parallel group, active controlled	MOV 800 mg po Q12H for 5 days. Placebo po Q12H for 5 days.	Males/females ≥18 years of age Participants with laboratory confirmed SARS CoV 2 infection sample collection ≤5 days prior to randomization	MOV 800 mg: 710 Placebo: 701
MOV= MK4482/molnupiravir; Q12H= once every 12 hours.							

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Study ID	Phase	Country/ Region	Study Title	Study Design	Dosing Regimen	Study Population	Participant Exposure
4482 004 (EIDD 2801 1001) [Ref. 5.3.3.1: P004MK4482]	1	UK, USA[a]	A Randomized, Double Blind, Placebo Controlled, First in Human Study Designed to Evaluate the Safety, Tolerability, and Pharmacokinetics of EIDD 2801 Following Oral Administration to Healthy Volunteers	Part 1: Double blind, placebo controlled single dose (randomized 3:1 active: placebo) Part 2: open label randomized 2 period crossover food effect study Part 3: Double blind, placebo controlled multiple dose (randomized 3:1 active: placebo)	Part 1: MOV 50, 100, 200, 400, 600, 800, 1200, 1600 mg or placebo single dose Part 2: MOV 200 mg single dose Part 3: MOV 50, 100, 200, 300, 400, 600, 800 mg or placebo Q12H × 5.5 days	Males/females (nonchildbearing potential), 18 to 60 years of age, healthy participants	Part 1: MOV 50 mg: 6 MOV 100 mg: 6 MOV 200 mg: 6 MOV 400 mg: 6 MOV 600 mg: 6 MOV 800 mg: 6 MOV 1200 mg: 6 MOV 1600 mg: 6 Placebo: 16 Part 2: MOV 200 mg: 10 Part 3: MOV 50 mg: 6 MOV 100 mg: 6 MOV 200 mg: 6 MOV 300 mg: 6 MOV 400 mg: 6 MOV 600 mg: 6 MOV 800 mg: 6 Placebo: 14
[a] One site in the UK enrolled all participants. No sites in the US enrolled participants.							

Study ID	Phase	Country/ Region	Study Title	Study Design	Dosing Regimen	Study Population	Participant Exposure
4482 006 (EIDD 2801 2003) [Ref. 5.3.5.1: P006MK4482]	2a	USA	A Phase IIa, Randomized, Double Blind, Placebo Controlled Trial to Evaluate the Safety, Tolerability, and Efficacy of EIDD 2801 to Eliminate SARS CoV 2 Viral RNA Detection in Persons with COVID 19	Randomized, double blind, placebo controlled	Part 1: 1:1 MOV 200 mg or placebo BID x 5 days Parts 2 to 9: 3:1 MOV up to 800 mg or placebo BID x 5 days	Males/females, ≥18 years of age with laboratory confirmed SARS CoV 2	Part 1: MOV 200 mg: 23 Placebo: 23 Parts 2 to 9: MOV 400 mg: 62 MOV 800 mg: 55 Placebo: 39

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Study ID	Phase	Country/ Region	Study Title	Study Design	Dosing Regimen	Study Population	Participant Exposure
4482 008 [Ref. 5.3.3.3: P008MK4482]	1	Japan	A Single and Multiple Dose Clinical Study to Evaluate the Safety, Tolerability and Pharmacokinetics of MK 4482 in Healthy Japanese Adult Participants	2 part, randomized, placebo controlled, single site, double blind	Part 1 MK 4482 200 1600 mg or placebo po once Part 2 MK 4482 400 800 mg or placebo po every 12 hours for 5.5 days	Males Age: 20 59 healthy participants	Part 1 MK 4482 200 mg: 6 MK 4482 400 mg: 6 MK 4482 800 mg: 7 MK 4482 800 mg (fed): 6 MK 4482 1600 mg: 6 Placebo: 8 Part 2 MK 4482 400 mg:15 MK 4482 800 mg: 15 Placebo: 10

Study ID	Phase	Country/ Region	Study Title	Study Design	Dosing Regimen	Study Population	Participant Exposure
4482 012 [Ref. 5.3.3.1: P012MK4482]	1	Belgium/ Europe	A Multiple Ascending Dose Clinical Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Molnupiravir in Healthy Participants	Single center, safety, tolerability, multiple ascending dose, double blind, placebo controlled intervention	Molnupiravir (MK 4482) 400 mg, 600 mg or 800 mg Q12H for 10.5 days Placebo Q12H for 10.5 days	Males/females Age: 27 59 Healthy participants	Molnupiravir: 400 mg: 6 600 mg: 6 800 mg: 12 Placebo: 8
Q12H=Every 12 hours							

2 SYNOPSIS

SPONSOR: Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co., Inc., NJ, USA (MSD)

COMPOUND NAME: Molnupiravir (MOV; MK-4482)

PROTOCOL TITLE: A Phase 2/3, Randomized, Placebo-Controlled, Double-Blind Clinical Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MK-4482 in Hospitalized Adults with COVID-19

STUDY IDENTIFIERS:

IND: 147734	EudraCT: 2020-003367-26	WHO: N/A	NCT: 04575584

STUDY PHASE: 2/3

INDICATION: Treatment of COVID-19

STUDY CENTERS: This study was conducted at 86 centers in 15 countries.

STUDY STATUS: This study is ongoing; this report is based on interim analysis 2 (IA2) data for Part 1 (Phase 2).

First Patient, First Visit	Last Patient, Last Visit	Data Cut-off or Database Lock Date
19-OCT-2020	[redacted]-[redacted]-20[redacted]	11-MAR-2021

NOTE: Patient = Participant

METHODOLOGY: This is a Phase 2/3, randomized, placebo-controlled, double-blind, multisite study to evaluate the efficacy, safety, and pharmacokinetics (PK) of molnupiravir (MOV or MK-4482) administered to hospitalized participants ≥18 years of age with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection with signs/symptoms attributable to coronavirus disease 2019 (COVID-19).

The study was to be conducted in 2 parts: Part 1 (Phase 2 - Dose Ranging) and Part 2 (Phase 3 - Evaluation of Selected Dose). In Part 1, 304 participants with an initial onset of signs/symptoms attributable to COVID-19 ≤10 days prior to the day of randomization and ≥1 sign/symptom attributable to COVID-19 present at randomization were enrolled. Participants were randomized in a 1:1:1:1 ratio into 1 of 4 intervention groups: MOV 200 mg, MOV 400 mg, MOV 800 mg, or placebo. Intervention randomization was stratified according to time from symptom onset prior to the day of randomization (≤5 days, >5 days), age (≤60 years, >60 years), and remdesivir use for treatment of the index diagnosis of COVID-19 prior to or at the time of randomization (yes, no). Sponsor-designated standard of care treatment of COVID-19, which included remdesivir, systemic corticosteroids, and convalescent plasma, was permitted.

Participants received assigned study intervention by oral administration for 5 days once every 12 hours (Q12H), and were followed for 28 days after randomization (through Day 29) for the primary endpoint. Events of clinical interest (ECI) included transaminase elevations suggestive of drug-induced liver injury (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] ≥3x upper limit of normal [ULN], total bilirubin ≥2x ULN, and alkaline phosphatase < 2x ULN), platelet count of <50,000/µL, and amylase or lipase values >3x ULN.

This report is based on IA2, which was conducted after all Part 1 participants completed Day 29. Data from IA2 indicated that MOV is unlikely to demonstrate a clinical benefit in a clinical study enrolling hospitalized participants, who generally have a long duration of symptoms (>5 days) prior to study entry; therefore, this study will not proceed to Part 2 (Phase 3). Part 1 participants will continue to be followed until Month 7. Data for participants in Part 1 through the 7-month follow-up period will be provided in a separate report.

The study interventions administered in Part 1 are presented in the following table.

Intervention Groups and Duration

Intervention Group Name	Dose Frequency	Route of Administration	Treatment Period
MOV 200 mg	Q12H	Oral	5 days (10 doses total)
MOV 400 mg	Q12H	Oral	5 days (10 doses total)
MOV 800 mg	Q12H	Oral	5 days (10 doses total)
Placebo	Q12H	Oral	5 days (10 doses total)
MOV molnupiravir; Q12H once every 12 hours			

ELIGIBILITY CRITERIA:

Male or female participants ≥ 18 years of age with laboratory-confirmed SARS-CoV-2 infection with sample collection ≤10 days prior to randomization who met the following key inclusion criteria were eligible to participate in the study:

- Had initial onset of signs/symptoms attributable to COVID-19 for ≤10 days prior to the day of randomization and ≥1 sign/symptom attributable to COVID-19 present at randomization.
- Required medical care in the hospital for ongoing clinical manifestations of COVID-19 (not only for public health or quarantine purposes).
- Had mild, moderate, or severe COVID-19 as defined in Appendix 9 of the protocol.

OBJECTIVES AND ENDPOINTS:

Primary Objectives	Primary Endpoints
- To evaluate the efficacy of MOV compared to placebo as assessed by the rate of sustained recovery from randomization through Day 29.	- Time-to-sustained recovery
- To evaluate the safety and tolerability of MOV compared to placebo.	- Adverse events - Adverse events leading to discontinuation of study intervention
Secondary Objectives	Secondary Endpoints
- To evaluate the efficacy of MOV compared to placebo as assessed by the percentage of participants who die through Day 29.	- All-cause mortality
- To evaluate the efficacy of MOV compared to placebo as assessed by the odds of a more favorable response on selected ordinal outcome scales at Day 3, EOT, Day 10, Day 15, and Day 29.	- Pulmonary score - Pulmonary+ score
- To evaluate the efficacy of MOV compared to placebo as assessed by the odds of a more favorable response in the clinical risk of mortality category from the National Early Warning Score at EOT.	- National Early Warning Score
- To evaluate the efficacy of MOV compared to placebo as assessed by the odds of a more favorable response on the WHO 11-point ordinal scale on Day 3, EOT, Day 10, Day 15, and Day 29.	- WHO 11-point scale score

NUMBER OF PARTICIPANTS (planned and analyzed): The planned enrollment total for Part 1 was approximately 300 participants. A total of 304 participants were randomized as follows: 75 participants (MOV 200 mg), 75 participants (MOV 400 mg), 76 participants (MOV 800 mg), 78 participants (placebo).

STATISTICAL ANALYSIS METHODS: The primary population for efficacy analyses was the modified intent-to-treat (MITT) population, which consisted of all randomized participants who received at least 1 dose of study intervention. Participants were included in the intervention group to which they were randomized. The primary efficacy analysis compared MOV 200 mg, MOV 400 mg, and MOV 800 mg, and placebo with respect to time-to-sustained recovery by Day 29 using a stratified log-rank test. The sustained recovery

rate ratio was estimated using the stratified Cox proportional hazards regression model. No formal hypothesis testing was performed in Part 1 of the study.

The change from baseline in SARS-CoV-2 RNA titer, calculated as $\log_{10}$ (post) minus $\log_{10}$ (baseline), as measured by quantitative reverse transcriptase polymerase chain reaction (RT-PCR) of samples from nasopharyngeal (NP) and oropharyngeal (OP) swabs was summarized separately by intervention group and time point. Treatment differences in change in SARS-CoV-2 RNA titer from baseline over time were estimated using longitudinal models.

Safety analyses were based on the All Participants as Treated (APaT) population, which included 293 randomized participants who received at least 1 dose of study intervention. Participants were included in the intervention group corresponding to the study treatment they actually received.

RESULTS:

Disposition, Demographics and Baseline Characteristics

Number of participants randomized /treated/discontinued:

- MOV 200 mg: 75 randomized/ 73 treated/ 3 discontinued study intervention/ 62 followed through Day 29.
- MOV 400 mg: 75 randomized/ 73 treated/ 7 discontinued study intervention/ 60 followed through Day 29.
- MOV 800 mg: 76 randomized/ 72 treated/ 3 discontinued study intervention/ 66 followed through Day 29.
- Placebo group: 78 randomized/ 75 treated/ 3 discontinued study intervention/ 70 followed through Day 29.

Overall Mean Age (range): 57.0 years (19 to 94 years)

Sex: 172 (56.6%) male, 132 (43.4%) female

Ethnicity: 184 (60.5%) not Hispanic or Latino, 114 (37.5%) Hispanic or Latino, 4 (1.3%) not reported, 2 (0.7%) unknown.

Race: 6 (2.0%) American Indian or Alaska Native, 23 (7.6%) Asian, 18 (5.9%) black or African-American, 27 (8.9%) other/multiple, 1 (0.3%) Native Hawaiian or Other Pacific Islander, 227 (74.7%) white, 2 (0.7%) unknown

Efficacy:

- The observed rate of sustained recovery through Day 29 was high overall and similar in the MOV groups compared with placebo.
- There was a higher number of deaths in participants in each MOV group compared with placebo.
- Improvement in outcomes over time, as assessed by the Pulmonary ordinal scale, Pulmonary+ ordinal scale, National Early Warning score (NEWS), and World Health

Organization (WHO) 11-point scale, were similar in the MOV groups compared with placebo.

- Similar decreases from baseline in mean SARS-CoV-2 RNA titers in NP and OP samples, as assessed by quantitative PCR, were observed in the MOV groups compared with placebo at all timepoints.
- The proportion of participants with undetectable SARS-CoV-2 RNA in NP and OP samples over time, as assessed by a qualitative PCR assay, was generally similar across all intervention groups.
- Consistent with the mechanism of action of MOV (viral error catastrophe), an increased SARS-CoV-2 mutation rate was observed by Day 3 or Day 5 in NP swabs in participants receiving any dose of MOV compared with placebo.

Safety:

- The overall safety profiles observed were generally comparable for MOV at all doses studied and placebo. No trends in incidence of adverse events (AEs) by MOV dose were observed.
- Study intervention-related serious adverse events (SAEs) and discontinuation of study intervention due to an AE were infrequent and the proportions of participants experiencing these AEs were comparable across intervention groups.
- The most frequently reported AEs (>5%) in any of the MOV intervention groups were COVID-19, AST/ALT elevations, constipation, bacterial pneumonia, hyperglycemia, and respiratory failure.
- The most frequently reported AEs (>5%) in the placebo group were constipation, COVID-19, COVID-19 pneumonia, ALT increased, and respiratory failure.
- A total of 16 participants had AEs resulting in death by Day 15. A higher number of AEs resulting in death were reported in the MOV groups compared with the placebo group. None of the deaths were considered to be related to study intervention per investigator assessment.
- No evidence of hematologic, pancreatic, or hepatic toxicity was observed for MOV.

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Adverse Event Summary
During Treatment and 14-Day Follow-Up Period
All Participants as Treated Population
MK-4482-001 IA2

	MK 4482 200 mg		MK 4482 400 mg		MK 4482 800 mg		MK 4482 Combined		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	73		73		72		218		75		293	
with one or more adverse events	40	(54.8)	36	(49.3)	45	(62.5)	121	(55.5)	46	(61.3)	167	(57.0)
with no adverse event	33	(45.2)	37	(50.7)	27	(37.5)	97	(44.5)	29	(38.7)	126	(43.0)
with drug related[a] adverse events	8	(11.0)	6	(8.2)	10	(13.9)	24	(11.0)	16	(21.3)	40	(13.7)
with serious adverse events	11	(15.1)	9	(12.3)	13	(18.1)	33	(15.1)	12	(16.0)	45	(15.4)
with serious drug related adverse events	1	(1.4)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.3)
who died	6	(8.2)	4	(5.5)	4	(5.6)	14	(6.4)	2	(2.7)	16	(5.5)
discontinued drug due to an adverse event	0	(0.0)	1	(1.4)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.3)
discontinued drug due to a drug related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)	1	(1.4)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.3)
discontinued drug due to a serious drug related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the drug.

Source: [P001V01MK4482: adam adsl; adae]

CONCLUSIONS:

Results from IA2 in hospitalized participants randomized ≤10 days of COVID-19 symptom onset indicate:

- No clear effect of MOV treatment on sustained recovery was observed.
- All MOV doses studied were generally well tolerated.

PUBLICATION(S): As of the date of this report, there are no publications based on this study.

REPORT DATE: [redacted]

2 SYNOPSIS

SPONSOR: Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co., Inc., NJ, USA (MSD)

COMPOUND NAME: Molnupiravir (MOV; MK-4482)

PROTOCOL TITLE: A Phase 2/3, Randomized, Placebo-Controlled, Double-Blind Clinical Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MK-4482 in Non-Hospitalized Adults with COVID-19

STUDY IDENTIFIERS:

IND: 147734	EudraCT: 2020-003368-24	WHO: N/A	NCT: 04575597

STUDY PHASE: 2/3

INDICATION: Treatment of COVID-19

STUDY CENTERS: This study was conducted at 82 study sites in 12 countries.

STUDY STATUS: This study is ongoing; this report is based on interim analysis 2 (IA2) data for Part 1 (Phase 2).

First Patient, First Visit	Last Patient, Last Visit	Data Cut-off
19-OCT-2020	N/A	[redacted]-20[redacted]

NOTE: Patient = Participant

METHODOLOGY: This is a Phase 2/3, randomized, placebo-controlled, double-blind, multi-site study to evaluate the efficacy, safety, and pharmacokinetics (PK) of molnupiravir (MOV, MK-4482, or EIDD-2801) administered to non-hospitalized participants ≥18 years of age with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection with signs/symptoms attributable to coronavirus disease 2019 (COVID-19).

This study is conducted in 2 parts: Part 1 (Phase 2 Dose ranging) and Part 2 (Phase 3 Evaluation of selected dose). In Part 1 of the study, 302 participants with an initial onset of signs/symptoms attributable to COVID-19 ≤7 days prior to the day of randomization and ≥1 sign/symptom attributable to COVID-19 present at randomization were enrolled. Participants were randomized 1:1:1:1 into 1 of 4 intervention groups: MOV 200 mg, MOV 400 mg, MOV 800 mg, or placebo. Randomization was stratified by time from symptom onset (≤5 days, >5 days) and by increased risk of severe illness from COVID-19 (yes, no).

Participants received assigned study intervention by oral administration for 5 days, once every 12 hours (Q12H), and were followed for 28 days after randomization (through Day 29) for the primary endpoint. Events of clinical interest (ECI) included liver transaminase

elevations suggestive of drug-induced liver injury, platelet count of <50,000/µL, and amylase or lipase values >3X the upper limit of normal.

This report is based on IA2 data, which was conducted after all Part 1 participants completed Day 29. Dose selection for Part 2 was based on analyses of data from this study in combination with the totality of data available across the MOV clinical program. Data related to dose selection as well as data for participants in Part 1 through the 7-month follow-up period and for Part 2 of the study will be provided in separate reports.

The study interventions administered in Part 1 are presented in the following table.

Intervention Groups and Duration

Intervention Group Name	Dose Frequency	Route of Administration	Treatment Period
Part 1			
MOV 200 mg	Q12H	Oral	5 days (10 doses total)
MOV 400 mg	Q12H	Oral	5 days (10 doses total)
MOV 800 mg	Q12H	Oral	5 days (10 doses total)
Placebo	Q12H	Oral	5 days (10 doses total)

MOV molnupiravir; Q12H once every 12 hours

ELIGIBILITY CRITERIA: Male or female participants ≥18 years of age with laboratory-confirmed SARS-CoV-2 infection with sample collection ≤7 days prior to randomization who met the following key inclusion criteria were eligible to participate in the study:

- Had initial onset of signs/symptoms attributable to COVID-19 ≤7 days prior to the day of randomization and at least 1 sign/symptom attributable to COVID-19 on the day of randomization.
- Had mild or moderate COVID-19 as defined in Appendix 9 of the protocol; participants with mild COVID-19 must have had at least 1 characteristic or underlying medical condition associated with an increased risk of severe illness from COVID-19 as defined in Appendix 10 of the protocol.

OBJECTIVES AND ENDPOINTS:

Primary Objective(s)	Primary Endpoint(s)
▪ To evaluate efficacy of MOV compared to placebo as assessed by the percentage of participants who are hospitalized and/or die from randomization through Day 29	▪ Hospitalization or death
▪ To evaluate the safety and tolerability of MOV compared to placebo	▪ Adverse events (AEs)

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	▪ AEs leading to discontinuation of study intervention
Secondary Objective(s)	**Secondary Endpoint(s)**
▪ To evaluate the efficacy of MOV compared to placebo as assessed by time to sustained resolution or improvement, and time to progression of each targeted self-reported sign/symptom of COVID-19 from randomization through Day 29	▪ COVID-19 signs/symptoms
▪ To evaluate the efficacy of MOV compared to placebo as assessed by the odds of a more favorable response on the World Health Organization (WHO) 11-point ordinal scale on Day 3, End-of-Treatment (EOT), Day 10, Day 15, and Day 29	▪ WHO 11-point scale score

NUMBER OF PARTICIPANTS (planned and analyzed): The planned enrollment total for Part 1 was approximately 300 participants. A total of 302 participants were randomized as follows: 75 participants (MOV 200 mg), 77 participants (MOV 400 mg), 76 participants (MOV 800 mg), and 74 participants (placebo).

STATISTICAL ANALYSIS METHODS: The primary population for efficacy analyses was the modified intent-to-treat population which consisted of all randomized participants who received at least 1 dose of study intervention; participants were included in the intervention group to which they were randomized. The primary efficacy analysis compared the efficacy of MOV 200 mg, 400 mg, and 800 mg with respect to the percentage of participants with either hospitalization (≥24 hours of acute care in a hospital or similar acute care facility, including emergency rooms or facilities created to address hospitalization needs during the COVID-19 pandemic) or death by Day 29 using the stratified Miettinen and Nurminen method. No formal hypothesis testing was conducted in Part 1 of the study.

The change from baseline in SARS-CoV-2 RNA titer, calculated as $\log_{10}$ (post) minus $\log_{10}$ (baseline) as measured by quantitative real-time polymerase chain reaction of samples from nasopharyngeal (NP) and oropharyngeal (OP) swabs was summarized separately by intervention group and time point. Treatment differences in change in SARS-CoV-2 RNA titer from baseline over time were estimated using longitudinal models.

Safety analyses were based on the all-participants-as-treated population which included randomized participants who received at least 1 dose of study intervention; participants were included in the intervention group corresponding to the study treatment they actually received.

RESULTS:

Disposition, Demographics and Baseline Characteristics

Number of participants randomized/treated/discontinued

- MOV 200 mg: 75 randomized/ 74 treated/ 69 completed Day 29/ 5 discontinued.
- MOV 400 mg: 77 randomized/ 77 treated/ 73 completed Day 29/ 4 discontinued.
- MOV 800 mg: 76 randomized/ 74 treated/ 70 completed Day 29/ 4 discontinued.
- Placebo: 74 randomized/ 74 treated, 71 completed Day 29/ 3 discontinued.

Overall Mean Age (range): 49.2 years

Sex: 159 (52.6%) male, 143 (47.4%) female

Ethnicity: 182 (60.3%) not Hispanic or Latino, 115 (38.1%) Hispanic or Latino, 5 (1.6%) missing

Race: 216 (71.5%) white, 51 (16.9%) multiple, 22 (7.3%) black or African American, 11 (3.6%) American Indian or Alaska Native, 1 (0.3%) Asian, and 1 (0.3%) unknown

Efficacy:

- Overall, the number of hospitalization events were low and similar in all intervention groups, but fewer participants in the MOV groups were hospitalized through Day 29 compared with participants in the placebo group. No participants died in the study through Day 29.
- No clear evidence of a treatment effect was observed for time to sustained resolution/improvement or time to progression of each of the 15 self-reported COVID-19 signs and symptoms.
- No clear evidence of treatment effect was observed between intervention groups as assessed by the odds of a more favorable response on the WHO-11 point ordinal scale.
- Mean SARS-CoV-2 RNA titer decreased comparably over time across intervention groups in both NP and OP samples.
- A higher proportion of participants in the MOV 400 mg and MOV 800 mg groups with detectable SARS-CoV-2 RNA NP samples at baseline had undetectable RNA results compared with placebo at Days 5 (EOT), 10, 15, and 29.
- Consistent with MOV's proposed mechanism of action, higher mutation rates were observed at Day 5 in viral sequences from post-baseline NP samples in the MOV intervention groups compared with placebo. The highest RNA mutation rate was observed in the MOV 800 mg intervention group.

Safety:

Overall, the safety profiles of MOV (all doses) and placebo were comparable. No trends were observed for AEs, including changes in clinical laboratory values, as a function of dose or treatment.

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- The most frequently reported AEs (≥5% in any group) were COVID-19 pneumonia in the MOV 800 mg group and diarrhea and COVID-19 in the placebo group.
- The proportion of participants with AEs considered related to study intervention as determined by the investigator was comparable across all intervention groups.
- No drug-related SAEs were reported during the treatment and 14-day follow-up periods.
- Discontinuation of study intervention due to an AE was infrequent and the proportion of participants experiencing this was comparable across intervention groups.
- One death was reported (placebo group on Day 36).
- No participants had laboratory values that met the predefined criteria for an ECI.
- No evidence of hematologic, pancreatic, or hepatic toxicity was observed for MOV.

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Adverse Event Summary
During Treatment and 14-Day Follow-Up Period
All Participants as Treated Population
MK-4482-002 IA2

	MK 4482 200 mg		MK 4482 400 mg		MK 4482 800 mg		MK 4482 Combined		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	74		77		74		225		74		299	
with one or more adverse events	25	(33.8)	19	(24.7)	29	(39.2)	73	(32.4)	28	(37.8)	101	(33.8)
with no adverse event	49	(66.2)	58	(75.3)	45	(60.8)	152	(67.6)	46	(62.2)	198	(66.2)
with drug related[a] adverse events	4	(5.4)	6	(7.8)	4	(5.4)	14	(6.2)	5	(6.8)	19	(6.4)
with serious adverse events	1	(1.4)	3	(3.9)	4	(5.4)	8	(3.6)	4	(5.4)	12	(4.0)
with serious drug related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.3)
discontinued drug due to an adverse event	0	(0.0)	0	(0.0)	3	(4.1)	3	(1.3)	1	(1.4)	4	(1.3)
discontinued drug due to a drug related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.3)
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)	2	(2.7)	2	(0.9)	0	(0.0)	2	(0.7)
discontinued drug due to a serious drug related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the drug.

Source: [P002V01MK4482: adam adsl; adae]

CONCLUSIONS

Results from IA2 in non-hospitalized participants with laboratory-confirmed COVID-19 indicate:

- Fewer participants in the MOV intervention groups were hospitalized or died through Day 29 compared with the placebo group.
- All MOV doses studied were generally well tolerated.

PUBLICATION(S): As of the date of this report, there are no publications based on this study.

REPORT DATE: [redacted]-[redacted]-20[redacted]

2 SYNOPSIS

SPONSOR: Merck, Sharp & Dohme Corp., Whitehouse Station, NJ USA (MSD)

COMPOUND NAME: Molnupiravir (MOV; MK-4482)

PROTOCOL TITLE: A Phase 2/3, Randomized, Placebo-Controlled, Double-Blind Clinical Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MK-4482 in Non-Hospitalized Adults with COVID-19

STUDY IDENTIFIERS:

IND: 147734	EudraCT: 2020-003368-24	WHO: N/A	NCT: 04575597

STUDY PHASE: 2/3

INDICATION: Treatment of COVID-19

STUDY CENTERS: This study was conducted at 166 centers in 23 countries.

STUDY STATUS: This study is ongoing (safety follow-up); this report is based on results from all randomized participants in Part 2. Demographic, efficacy, and virologic response data from the combined interim analysis (IA) IA3/IA4 are also included.

First Patient, First Visit	Last Patient, Last Visit	Data Cutoff
Part 2 (Phase 3): 06-MAY-2021	N/A	[redacted]

NOTE: Patient = Participant

METHODOLOGY: This is a Phase 2/3, randomized, placebo-controlled, double-blind, multi-site study to evaluate the efficacy, safety, and pharmacokinetics (PK) of molnupiravir (MOV, MK-4482) administered to non-hospitalized participants ≥18 years of age with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection with signs/symptoms attributable to coronavirus disease 2019 (COVID-19). SARS-CoV-2 vaccines were prohibited any time prior to randomization and through Day 29.

This study is being conducted in 2 parts: Part 1 (Phase 2 dose ranging) and Part 2 (Phase 3 evaluation of selected dose). The results from Part 1 are reported in a separate Clinical Study Report. In Part 2, approximately 1550 participants were to be randomized 1:1 to receive 5 days of MOV 800 mg or placebo Q12H. Randomization was stratified by time from symptom onset to day of randomization (≤3 days or >3 [4-5] days). Participants were followed for 29 days for the evaluation of efficacy, safety and virology, and for 7 months for the evaluation of safety.

The results of protocol-defined interim analyses (IA3/IA4), conducted when 50% (n 775) of the planned enrollment completed the Day 29 visit, showed that MOV met the protocol-defined criterion (one sided p-value boundary <0.0092) for demonstration of superiority to placebo for the primary efficacy endpoint. The external Data Monitoring Committee (eDMC) concluded that MK-4482 demonstrated clinical efficacy at this timepoint and based on the recommendation of the eDMC, the study was closed to further enrollment.

This report includes the results for the 1433 participants enrolled in Part 2 of the study (775 at the time of IA3/IA4 [randomized by [redacted]] and an additional 658 enrolled after IA3/IA4 [randomized after [redacted]]) through Day 29. Demographic, efficacy, and virologic response data from the combined IA3/IA4 are also included. Virologic response data for all randomized participants in Part 2 will be presented separately. Results from the 7-month follow-up will be reported in a subsequent report.

The study interventions administered in Part 2 are presented in the following table.

Intervention Group Name	Dose Frequency	Route of Administration	Treatment Period
MOV 800 mg	Q12H	Oral	5 days (10 doses total)
Placebo	Q12H	Oral	5 days (10 doses total)
MOV= molnupiravir; Q12H= once every 12 hours.			

ELIGIBILITY CRITERIA: Male or female participants ≥18 years of age with laboratory-confirmed SARS-CoV-2 infection with sample collection ≤5 days prior to the day of randomization who met the following key inclusion criteria were eligible to participate in Part 2 of the study:

- Had initial onset of signs/symptoms attributable to COVID-19 ≤5 days prior to the day of randomization and at least 1 sign/symptom attributable to COVID-19 on the day of randomization.
- Had mild or moderate COVID-19 as defined in Appendix 9 of the protocol and at least 1 characteristic or underlying medical condition associated with an increased risk of severe illness from COVID-19 as defined in Appendix 10 of the protocol.

OBJECTIVES AND ENDPOINTS:

Primary Objectives	**Primary Endpoints**
▪ To evaluate the efficacy of MK-4482 compared to placebo as assessed by the percentage of participants who are hospitalized and/or die from randomization through Day 29.	▪ Hospitalization or death
▪ To evaluate the safety and tolerability of MK-4482 compared to placebo.	▪ Adverse events ▪ Adverse events leading to discontinuation of study intervention
Secondary Objectives	**Secondary Endpoints**
▪ To evaluate the efficacy of MK-4482 compared to placebo as assessed by time to sustained resolution or improvement, and time to progression of each targeted self-reported sign/symptom of COVID-19 from randomization through Day 29.	▪ COVID-19 signs/symptoms
▪ To evaluate the efficacy of MK-4482 compared to placebo as assessed by the odds of a more favorable response on the WHO 11-point ordinal scale on Day 3, EOT, Day 10, Day 15, and Day 29.	▪ WHO 11-point scale score

NUMBER OF PARTICIPANTS (planned and analyzed): The planned enrollment total for Part 2 was approximately 1550 participants. However, based on the combined IA3/IA4 efficacy results, the study was stopped early and 1433 participants were randomized (716 participants MOV 800 mg and 717 participants placebo) and comprise the full Part 2 population.

STATISTICAL AND ANALYTICAL METHODS: The primary population for efficacy analyses was the modified intent-to-treat population which consisted of all randomized participants who received at least 1 dose of study intervention and were not hospitalized prior to administration of the first dose of study intervention; participants were included in the intervention group to which they were randomized. The primary efficacy analysis compared the efficacy of MOV 800 mg and placebo with respect to the percentage of participants with either hospitalization (≥24 hours of acute care in a hospital or similar acute care facility, including emergency rooms or facilities created to address hospitalization needs during the

COVID-19 pandemic) or death by Day 29 using the stratified Miettinen and Nurminen method.

At the IA3/IA4 timepoint, the prespecified statistical criterion for success was met (one-sided p-value 0.0012, one sided p-value boundary <0.0092) and the study's formal evaluation of efficacy was considered complete. Summaries of efficacy for all randomized participants in Part 2 through Day 29 are therefore considered to be supportive of the analyses reported at the IA3/IA4 timepoint.

Safety analyses were based on the all-participants-as-treated population which included all randomized participants in the study who received at least 1 dose of study intervention; participants were included in the intervention group corresponding to the study treatment they actually received.

RESULTS:

Participant Disposition (All Randomized Participants):

- MOV 800 mg: 716 randomized/ 710 treated/ 680 completed treatment/ 680 completed follow-up through Day 29
- Placebo: 717 randomized/ 701 treated/ 665 completed treatment/ 672 completed follow-up through Day 29

Demographics and Baseline Characteristics (All Randomized Participants):

- **Overall Median Age (range):** 43.0 years (18 to 90 years)
- **Sex:** 698 (48.7%) male, 735 (51.3%) female
- **Ethnicity:** 713 (49.8%) not Hispanic or Latino, 711 (49.6%) Hispanic or Latino, 5 (0.3%) not reported, 4 (0.3%) unknown/missing
- **Race:** 49 (3.4%) Asian, 104 (7.3%) American Indian or Alaska Native, 75 (5.2%) Black or African American, 392 (27.4%) Multiple, and 813 (56.7%) White

Efficacy:

Combined IA3/IA4 (Primary Basis of Statistical Inference)

- MOV 800 mg Q12H demonstrated superiority to placebo in reducing the risk of hospitalization or death through Day 29 at the combined IA3/IA4 timepoint. Treatment with MOV resulted in a 6.8 percentage point reduction (95% CI: -11.3, -2.4; p 0.0012) in the incidence of hospitalization or death through Day 29 compared with placebo (approximately 50% relative risk reduction).

All Randomized Participants

- The primary efficacy endpoint results for all randomized participants support the benefit observed for MOV compared with placebo in reducing the incidence of hospitalization or death through Day 29. Treatment with MOV resulted in a 3.0 percentage point 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).

- The secondary efficacy endpoint results for all randomized participants in Part 2 showed that MOV 800 mg Q12H was associated with improved clinical outcomes through Day 29 based on self-reported COVID-19 signs/symptoms and as assessed by the WHO-11 point ordinal scale.
    - For most COVID-19 signs/symptoms, sustained improvement or resolution was more likely and progression was less likely for participants in the MOV group compared with the placebo group.
    - 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.

Safety (All Randomized Participants):

- Overall, the safety profile of MOV 800 mg Q12H was comparable to placebo. No specific safety findings associated with MOV treatment were observed.
- The most frequently reported (≥5% in any group) adverse events (AEs) were COVID-19 and COVID-19 pneumonia, both reported at a higher rate in the placebo group.
  Note: Worsening COVID-19 is coded as COVID-19 in MedDRA version 24.1.
- No drug-related serious adverse events (SAEs) were reported in the MOV group. The proportion of participants with AEs, SAEs, and AEs considered related to study intervention as determined by the investigator was comparable in both intervention groups.
- Discontinuation of study intervention due to an AE was infrequent and comparable across intervention groups.
- A lower incidence of AEs leading to death was reported in the MOV group. Of the 14 AEs leading to death, 2 were reported in the MOV group and none was related to study intervention.
- No participants had laboratory values that met the predefined event of clinical interest criteria for potential drug-induced liver injury; 2 participants (1 MOV, 1 placebo) had laboratory values that met the predefined event of clinical interest criteria for post-baseline platelet value <50,000/µL, and neither was considered by the investigator to be related to study intervention.
- The proportions of participants with laboratory values that met the pre-defined limit of change criteria were low and comparable for both intervention groups.
- No evidence of hematologic or hepatic toxicity was observed for MOV.

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Analysis of Adverse Event Summary
During Treatment and 14-Day Follow-Up Period
All Participants as Treated Population
MK-4482-002 Part 2 Day 29 DBL

	MK 4482 800 mg		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[a]
Participants in population	710		701		
with one or more adverse events	216	(30.4)	231	(33.0)	2.5 (7.4, 2.3)
with no adverse event	494	(69.6)	470	(67.0)	2.5 (2.3, 7.4)
with drug related[b] adverse events	57	(8.0)	59	(8.4)	0.4 (3.3, 2.5)
with serious adverse events	49	(6.9)	67	(9.6)	2.7 (5.6, 0.2)
with serious drug related adverse events	0	(0.0)	1	(0.1)	0.1 (0.8, 0.4)
who died	2	(0.3)	12	(1.7)	1.4 (2.7, 0.5)
discontinued drug due to an adverse event	10	(1.4)	20	(2.9)	1.4 (3.1, 0.1)
discontinued drug due to a drug related adverse event	4	(0.6)	3	(0.4)	0.1 (0.8, 1.1)
discontinued drug due to a serious adverse event	5	(0.7)	13	(1.9)	1.2 (2.5, 0.0)
discontinued drug due to a serious drug related adverse event	0	(0.0)	0	(0.0)	0.0 (0.5, 0.5)

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

Source: [P002V03MK4482: adam adsl; adae]

CONCLUSIONS:

Based on the results of this study, the following conclusions may be made in non-hospitalized adult patients with mild or moderate laboratory-confirmed COVID-19:

- MOV is superior to placebo in reducing the risk of hospitalization or death through Day 29.
- MOV is generally well tolerated.

PUBLICATION(S):

Caraco Y, Crofoot GE, Moncada PA, Nikolaevna Galustyan A, Badibanga Musungaie D, Payne B, et al. Phase 2/3 Trial of Molnupiravir for Treatment of COVID-19 in Nonhospitalized Adults. N Engl J Med Evid. 2021 Dec 16.

Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. N Engl J Med. 2021 Dec 16.

REPORT DATE: [redacted]

2. SYNOPSIS

Title of study: A Randomized, Double-blind, Placebo-controlled, First-in-human Study Designed to Evaluate the Safety, Tolerability, and Pharmacokinetics of EIDD-2801 Following Oral Administration to Healthy Volunteers

Investigational product: EIDD-2801

Sponsor: Ridgeback Biotherapeutics, 3480 Main Highway, Unit 402, Miami, FL 33133, United States

Investigator: Dr Jim Bush, MBChB, PhD, MRCS, FFPM

Publications: None

Period of study: 10 April 2020 (date of first informed consent) to 24 August 2020 (date of final poststudy observation)

Phase of development: Clinical Phase 1

Objectives:

Primary Objectives

The primary objective of Part 1 of the study was to determine the safety and tolerability of single ascending doses of EIDD-2801.

The primary objective of Part 2 of the study was to assess the effect of food on the pharmacokinetics (PK) on EIDD-2801 and EIDD-1931 following a single oral dose.

The primary objective of Part 3 of the study was to determine the safety and tolerability of multiple ascending doses of EIDD-2801.

Secondary Objectives

The secondary objectives of Part 1 and Part 3 of the study were to define the PK of EIDD-2801 and EIDD-1931 in plasma and urine following single and multiple doses administered to healthy volunteers.

The secondary objective of Part 2 of the study was to determine the safety and tolerability of single doses of EIDD-2801.

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Exploratory Objectives

The exploratory objectives of Part 1[1] and Part 3 were to collect data to assess the relationship between EIDD-2801/EIDD-1931 concentrations and QT interval corrected for heart rate.

Methodology:

The study was composed of 3 parts; Part 1 was the single-ascending-dose study, Part 2 was the food-effect study, and Part 3 was the multiple-ascending-dose study.

Part 1: There were 8 dose-escalation cohorts, each of which comprised 8 subjects. Subjects were randomized to receive a single oral dose of either EIDD-2801 or placebo on Day 1 in a 3:1 ratio; 6 subjects received EIDD-2801 and 2 subjects received placebo. Subjects in the first 6 cohorts received a powder-in-bottle (PIB) formulation of either 50 to 800 mg EIDD-2801 or placebo and subjects in the final 2 cohorts received a capsule formulation of either 1200 or 1600 mg EIDD-2801 or placebo. Subjects were followed for 14 days postdose. Cohort 1 was divided into 2 groups; safety data for the first group of 2 subjects (sentinel group) were reviewed 24 hours postdose to ensure that no halting criteria had been met. Safety and tolerability data up to 72 hours postdose were reviewed prior to each dose escalation; PK data were used for dose-escalation decisions as they became available.

Part 2: Subjects were randomized to a treatment sequence in a 1:1 ratio: 200 mg EIDD-2801 (capsule formulation) in the fed state followed by 200 mg EIDD-2801 (capsule formulation) in the fasted state or vice versa. There was a 14-day washout period between doses. Subjects were followed for 14 days post final dose.

Part 3: There were 7 dose-escalation cohorts, each of which comprised 8 subjects. Subjects were randomized to receive either 50 to 800 mg EIDD-2801 or placebo (capsule formulation) in a 3:1 ratio. Doses were administered twice daily (BID) on Days 1 through 5, inclusive, and a single final dose was administered on the morning of Day 6. Subjects were followed for 14 days post final dose.

Number of subjects (planned and analyzed):

It was planned for 64 subjects in Part 1, 10 subjects in Part 2, and 56 subjects in Part 3 to be enrolled into this study. Sixty-four subjects in Part 1, 10 subjects in Part 2, and 56 subjects in Part 3 were randomized, dosed, completed the study, and were included in the safety population. All subjects who received at least 1 dose of EIDD-2801 (48 in Part 1, 10 in Part 2, and 42 in Part 3) were included in the PK population.

[1] Cohorts 7 and 8 only.

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Diagnosis and main criteria for inclusion and exclusion:

Healthy male and female subjects, of any ethnic origin, aged between 18 and 60 years, inclusive, and with a body mass index between 18 and 30 kg/m^2, inclusive, were selected.

Investigational product, dose and mode of administration, batch/lot number:

Part 1: 50, 100, 200, 400, 600, or 800 mg EIDD-2801 (PIB formulation) or 1200 or 1600 mg EIDD-2801 (capsule formulation).

Part 2: 200 mg EIDD-2801 (capsule formulation).

Part 3: 50, 100, 200, 300, 400, 600, or 800 mg EIDD-2801 (capsule formulation).

Capsules were provided as [redacted]- (batch/lot number [redacted]), [redacted] (batch/lot number [redacted]), and 200-mg (batch/lot number [redacted]) strengths. Powder-in-bottle was provided from batch/lot number [redacted].

Reference therapy, dose and mode of administration, batch number:

Matching placebo was supplied as either PIB (batch/lot number [redacted]) or capsules (batch/lot number [redacted]).

Duration of treatment:

Part 1: Subjects received a single dose of EIDD-2801 or placebo.

Part 2: Subjects received 2 single doses of EIDD-2801.

Part 3: Subjects received multiple BID doses of EIDD-2801 or placebo for 5 days, inclusive, followed by a single final dose for a total of 11 doses.

Criteria for evaluation:

Pharmacokinetics:

Blood and urine samples were collected for the analysis of plasma and urinary concentrations of EIDD-2801 and EIDD-1931.

Pharmacokinetic Parameters Determined from the Plasma Concentrations of EIDD-2801 (Where Possible) and EIDD-1931 for Protocol EIDD-2801-1001-UK

Parameter	Definition
AUC_{last}	area under the plasma concentration-time curve, from time 0 to the last measurable non-zero concentration
$AUC_{0\text{-}inf}$	area under the plasma concentration-time curve from time 0 extrapolated to infinity (Part 1; Part 2; and Part 3 [Day 1])
AUC_{τ}	area under the plasma concentration-time curve during a dosing interval[b] (Part 3)
$\%AUC_{extrap}$	percentage of $AUC_{0\text{-}inf}$ that is due to extrapolation from the last quantifiable concentration to infinity (Part 1; Part 2; and Part 3 [Day 1])
$\%AUC_{\tau,extrap}$	percentage of AUC_{τ} that is due to extrapolation from the last quantifiable concentration to the end of the dosing interval (Part 3 only)
C_{max}	maximum observed concentration
t_{max}	time of the maximum observed concentration
t_{last}	time of the last quantifiable concentration
λ_z	apparent terminal elimination rate constant
$t_{1/2}$	apparent terminal elimination half-life
CL/F	apparent clearance following an extravascular dose (EIDD-2801 only)
V_z/F	apparent volume of distribution during the terminal phase following and extravascular dose (EIDD-2801 only)
C_{trough}	plasma concentration at the end of the dosing interval (Part 3 only)
MR_{AUC}	EIDD-1931:EIDD-2801 ratio based on $AUC_{0\text{-}inf}$ (Parts 1, 2, and 3 [Day 1]) or AUC_{τ} (Part 3 [Day 6])
MR_{Cmax}	EIDD-1931:EIDD-2801 ratio based on C_{max}
$RA_{AUC\tau}$	observed accumulation ratio based on AUC_{τ} (Part 3)
RA_{Cmax}	observed accumulation ratio based on C_{max} (Part 3)

Pharmacokinetic Parameters Determined from the Urine Concentrations of EIDD-2801 and EIDD-1931 for Protocol EIDD-2801-1001-UK

Parameter	Definition
$Ae_{t1\text{-}t2}$	amount of the dose administered recovered in urine over the time interval t1 to t2 (calculated by interval and cumulatively)
$Fe_{t1\text{-}t2}$	percentage of the dose administered recovered in urine over the time interval t1 to t2 (calculated by interval and cumulatively)
CL_R	renal clearance

Safety:

Safety assessments included adverse events (AEs), vital signs, 12-lead electrocardiogram (ECG), clinical laboratory evaluations, and physical examinations.

Statistical methods:

Pharmacokinetics:

Plasma and urine concentrations were listed and plasma concentrations were summarized using descriptive statistics. Pharmacokinetic parameters (where available) were listed and, with the exception of diagnostic regression-related PK parameters, were summarized using descriptive statistics.

Part 1: A statistical analysis was conducted to investigate the dose proportionality of the PIB formulation for PK parameters ($AUC_{0\text{-}inf}$, AUC_{last}, and C_{max}) of EIDD-1931.

Additionally, a statistical analysis was also conducted to investigate the dose-proportionality of the capsule formulation for the PK parameters ($AUC_{0\text{-}inf}$, AUC_{last}, and C_{max}) of EIDD-1931 by combining the Day 1 data in Part 3 with similar data from cohorts in Part 1 where the capsule formulation was administered.

Part 2: A statistical analysis was conducted to investigate the effect of food by comparing treatments 200 mg EIDD-2801 (fed) to 200 mg EIDD-2801 (fasted) for PK parameters ($AUC_{0\text{-}inf}$, AUC_{last}, and C_{max}) of EIDD-1931.

The natural log (ln)-transformed PK parameters were analyzed using a mixed model. The model included planned treatment sequence, period, and actual treatment as fixed effects, and subject within planned treatment sequence as a random effect.

The least squares mean (LSM) for each treatment, difference in LSMs between the fed and fasted treatments, and corresponding 90% confidence intervals (CIs) were calculated for each PK parameter. These values were then back-transformed to give the geometric least squares mean (GLSM), ratio of GLSMs, and corresponding 90% CI. Additionally, the pooled estimate (across all treatments) of the within-subject coefficient of variation (CV) was calculated, and residual plots were produced to assess the adequacy of the model(s) fitted.

A statistical analysis using the Wilcoxon signed-rank test was conducted to investigate the effect of food on the PK by comparing the fed treatment to the fasted treatment for t_{max}. The median for each treatment, Hodges-Lehmann estimate of the median difference between the fed and fasted treatments, and corresponding 90% CIs were calculated.

Part 3: A statistical analysis was conducted to investigate the dose proportionality for PK parameters (AUC_{τ} and C_{max}) of EIDD-1931 on Day 6.

The PK parameters detailed above were analyzed using a power model that had the following form:

$$\text{parameter} = \text{intercept} \times \text{dose}^{\text{slope}} + \text{random error}$$

Using the natural log (ln) transformation, the power model was expressed as a linear regression equation:

$$\ln(\text{parameter}) = \text{intercept} + \text{slope} \times \ln(\text{dose}) + \text{random error}$$

A pooled estimate (across all doses) of slope, corresponding 90% CI, and between-subject CV was calculated for each PK parameter. Plots of individual values, power-model line (90% CI), and dose proportionality-line (the power-model line with slope of 1) were presented for each parameter. Additionally, plots of individual values and geometric means were created for each corresponding parameter normalized by dose. The lack-of-fit test was conducted for the statistical assessment of linearity assumption and thus appropriateness of the power model. The lack-of-fit model was the same as the power model fitted, but with dose included as additional fixed effect. The statistical assessment ruled the linearity

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assumption acceptable if the diagnostic plots appeared reasonable and the lack-of-fit p-value >0.05 (dose effect was not significant at the 0.05 level of significance).

It was concluded that the PK parameter was dose proportional for the dose range studied if the assumption of linearity was ruled acceptable and the 90% CI for the slope spanned 1.

For parameters where the 90% CI of the slope did not span 1, additional between treatment pairwise comparisons based on ln-transformed dose-normalized PK parameters were performed using an analysis of variance (ANOVA) model, which included dose as a factor. For each PK parameter separately, the LSM for each dose, difference in LSMs between each dose, and corresponding 90% CIs were calculated; these values were back-transformed to give the GLSM, ratio of GLSMs, and corresponding 90% CI.

Safety:

All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 and were assigned a severity grade using the Division of Microbiology and Infectious Diseases (DMID) toxicity scale (March 2014). Treatment-emergent AEs (TEAEs) were summarized by treatment, severity, and relationship to the study drug, and by system organ class, preferred term, treatment, and day of onset (Part 3).

Clinical laboratory evaluations, vital signs, and ECG parameters (including changes from baseline) were listed, summarized using descriptive statistics, and presented graphically as appropriate. Shift tables were presented for chemistry and hematology parameters. Any values outside of the reference ranges were listed by treatment and timepoint. An outlier analysis was performed for QT interval corrected for heart rate using Fridericia's formula.

Summary - Conclusions:

- EIDD-2801 was quantifiable in plasma following administration of EIDD-2801 at higher doses; however, plasma concentrations were close to the lower limit of quantification. The geometric mean MR_{Cmax} (where measurable) ranged from 329 to 610 and <0.02% of the dose administered was excreted unchanged as EIDD-2801 in urine.
- EIDD-1931 appeared rapidly in plasma following EIDD-2801 dosing, with a median t_{max} between 0.500 and 1.5. hours for the PIB formulation and 1.00 to 6.00 hours for the capsule formulation.
- At lower doses (typically <800 mg), the elimination of EIDD-1931 was monophasic with a geometric mean $t_{1/2}$ of approximately 1 hour. A second, slower elimination phase was quantifiable at higher doses, with a geometric mean $t_{1/2}$ of 4.59 (range of 1.47 to 7.58 hours) following administration of a single 1600-mg dose of EIDD-2801 and 7.08 hours (range of 1.49 to 19.1 hours) on Day 6 following multiple administrations of 800 mg EIDD-2801 BID.
- Administration of EIDD-2801 capsule formulation provided similar systemic exposure to EIDD-1931 (based on $AUC_{0\text{-}inf}$ and AUC_{last}) as the PIB formulation at the same dose. However, C_{max} was up to 24% lower and t_{max} was up to 0.75 hours later following administration of the capsule formulation, indicating that the rate of

absorption for the capsule formulation was slightly lower, but the extent of absorption was similar.

- Administration of EIDD-2801 capsule formulation in the fed state delayed median t_{max} for EIDD-1931 by 2 hours and reduced C_{max} by 35.6% when compared to administration in the fasted state. However, $AUC_{0\text{-}inf}$ and AUC_{last} were similar (within 5%), which indicated that the rate, but not the extent, of absorption was lower in the fed state.
- Increases in $AUC_{0\text{-}inf}$ and AUC_{last} for EIDD-1931 following administration of single doses of EIDD-2801 and AUC_{τ} following administration of multiple doses of EIDD-2801 were slightly supraproportional, particularly at higher doses. However, the increases in C_{max} were generally dose proportional.
- There was no evidence of accumulation, which was consistent with the dosing interval and the majority of $t_{1/2}$ estimates up to doses of 800 mg EIDD-2801 BID. The longer secondary elimination phases observed for some subjects at 800 mg EIDD-2801 BID did not result in consistently higher accumulation ratios as this phase represented only a small amount of the overall AUC_{τ}.
- Between-subject variability in systemic exposure to EIDD-1931 was generally low (<25%) to moderate (25% to 40%), but between-subject variability in urinary excretion parameters was generally high (>40%).
- The amount of EIDD-1931 that was excreted in urine was small and represented between 0.820% and 6.70% (geometric mean $Fe_{0\text{-}24}$) of the dose administered following single doses of between 50 and 1600 mg EIDD-2801 and between 0.854% and 3.61% (geometric mean $Fe_{0\text{-}12}$) following multiple doses of between 50 and 800 mg EIDD-2801 BID. There was a trend for the percentage of EIDD-1931 excreted in urine and CL_R to increase with increasing dose at doses >200 mg.
- Overall, single doses of up to 1600 mg EIDD-2801 or multiple doses of up to 800 mg EIDD-2801 BID were generally safe and well tolerated, with fewer subjects reporting TEAEs following administration of EIDD-2801 than placebo. The majority of TEAEs were mild (Grade 1) in severity and not considered by the investigator to be treatment-related.
- There were no dose-related trends or clinically significant findings in clinical laboratory, vital signs, or 12-lead ECG data.

2. SYNOPSIS

Name of Sponsor/Company: Ridgeback Biotherapeutics LP **Name of Finished Product:** Molnupiravir **Name of Active Ingredient:** NHC-TP (N-hydroxycytidine triphosphate) (also known as EIDD-1931)	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Title of Study: A Phase IIa, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Safety, Tolerability, and Efficacy of EIDD-2801 to Eliminate SARS-CoV-2 Viral RNA Detection in Persons with COVID-19		
Study center(s): Ten study centers in the United States enrolled participants in this study.		
Publications (reference): Painter WP, Sheahan T, Baric R, et al. Reduction in infectious SARS-CoV-2 in treatment study of COVID-19 with molnupiravir. Abstract presented at: Virtual Conference on Retroviruses and Opportunistic Infections. March 6-10, 2021. Abstract 777.		
Studied period (years): Date first participant enrolled: 19 June 2020 Date last participant completed: 21 February 2021		**Phase of development:** IIa

Objectives:

Primary:

- Primary Efficacy Objective: To determine if molnupiravir reduces the time to viral RNA negativity. Viral RNA negativity was determined by reverse transcription polymerase chain reaction (RT-PCR) of nasopharyngeal (NP) swabs.
- Primary Safety Objective: To determine the safety and tolerability of molnupiravir including:
  1) any adverse events (AEs) leading to early discontinuation of treatment,
  2) study drug-related discontinuation of treatment,
  3) new grade 3 or higher AEs (not already present at Baseline), and
  4) study drug-related new grade 3 or higher AEs.

Secondary:

- To determine if molnupiravir reduces the time (days) to negativity of infectious virus isolation in NP swabs from severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)-infected adults. Infectious virus isolation was determined by isolation in Vero cell line culture.
- To compare the incidence of grade 2 or higher AEs and drug-related AEs between treatment arms.
- To determine if molnupiravir reduces the shedding of SARS-CoV-2 RNA in NP swabs compared to placebo as measured by median change in RNA at Treatment Days 3, 5, 7, 14, and 28 as determined by quantitative RT-PCR.
- To determine if molnupiravir increases viral RNA mutation rate. RNA mutation rate was measured by next-generation sequencing.
- To determine if molnupiravir changes the severity and duration of self-reported symptoms of coronavirus disease 2019 (COVID-19).
- To determine if molnupiravir treatment reduces the proportion of participants who are hospitalized for COVID-19-related illness by Day 28.
- To characterize the pharmacokinetics of molnupiravir/EIDD-1931 in participants with COVID-19 following

administration of study regimen.

- To determine the relationship between drug exposure and viral elimination dynamics including time to clearance.

Exploratory:

- To determine if molnupiravir prevents the composite endpoint of hospitalization, oxygen desaturation, oxygen requirement, mechanical ventilation, or death by 28 days after study entry. Hospitalization was defined as ≥24 hours of acute care. Oxygen desaturation was measured using pulse oximetry. Oxygen requirement was measured using the World Health Organization (WHO) ordinal scale (see Appendix 1 of the study protocol, provided in [16.1.1].
- To determine the comparability between site-collected NP and available oropharyngeal (OP) swabs and available self-collected nasal mid-turbinate swabs for the quantification of SARS-CoV-2 RNA or quantitative culture. Note: this analysis was not performed for this report.
- To determine comparability between viral RNA detection and virus isolation from site-collected NP swabs.

Methodology:

This was a Phase IIa, double-blind, placebo-controlled, randomized trial designed to compare the safety, tolerability, and antiviral activity of escalating doses of molnupiravir vs placebo as measured by viral RNA detection, evaluation of AEs, and other safety assessments, in symptomatic adult outpatients with COVID-19. The study was a multicenter trial conducted in the US.

Up to approximately 172 fully evaluable participants were planned for enrollment into multiple study parts. If participants in a dose group dropped out or otherwise had missing or unevaluable primary or key secondary virology endpoint data, additional participants were enrolled to ensure adequate data at each dose level. The total number of participants to be enrolled was not to exceed 204.

In Part 1 of this study, up to approximately 44 participants were randomized 1:1 to receive molnupiravir 200 mg twice daily (BID) (Arm A) or placebo BID (Arm B) orally for 5 days. Enrollment in Part 1 could be interrupted to initiate enrollment in a different cohort, and Part 1 enrollment could resume at a later time point. The study continued to enroll the following (optional) study parts:

- In Parts 2-4, up to approximately16 participants per part were randomized 3:1 into Arms C and D (Part 2), Arms E and F (Part 3), and Arms G and H (Part 4) to receive treatment as follows: molnupiravir up to 800 mg or placebo orally BID for 5 days.
- In Parts 5-9, up to approximately 16 participants per part were randomized 3:1 into Arms I and J (Part 5), Arms K and L (Part 6), Arms M and N (Part 7), Arms O and P (Part 8), and Arms Q and R (Part 9) to receive treatment as follows: molnupiravir up to 800 mg or placebo orally BID for 5 days.

The dose of molnupiravir evaluated in Part 1 was 200 mg BID. The doses selected for subsequent study parts could be the same, higher, or lower than the dose(s) studied in previous study parts, and could not exceed 800 mg BID. Doses were chosen based on emerging virology and safety data from this and other ongoing studies. Selected doses were communicated in an official memo/protocol clarification letter.

All planned study part sizes were approximate. Study parts could be combined for randomization purposes if the same dose was planned for more than one part. Study parts enrolling at the same dose level could be enrolled simultaneously.

All participants were followed for 5 days on treatment and an additional 23 days off treatment at a series of in-clinic and in-home visits. Participants who did not start study treatment were replaced.

Number of participants (planned and analyzed):

Planned: 172

Analyzed: 202

Diagnosis and main criteria for inclusion:

Participants were required to meet all of the following inclusion criteria to be enrolled in the study:

1. Able to provide informed consent prior to initiation of any study procedures.
2. ≥18 years of age at Screening.
3. Study treatment was expected to begin within ≤168 hours from first symptom onset.
4. Ability to swallow pills.
5. Documentation of confirmed active SARS-CoV-2 infection, as determined by a molecular or non-molecular ("rapid") test conducted at any clinic or laboratory that had a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent from a sample collected ≤96 hours prior to study entry.
6. Was experiencing at least 1 of the following SARS-CoV-2 infection symptoms at the time of enrollment: fever (could be subjective including feeling feverish or having chills) OR signs/symptoms of respiratory illness (including but not limited to upper respiratory congestion, loss of sense of smell or taste, sore throat OR lower respiratory illness – cough, shortness of breath).
7. Agreed to not participate in another interventional clinical trial for the treatment of SARS-CoV-2 during the study period (28 days) unless hospitalized.
8. Agreed to not obtain investigational medications outside of the molnupiravir study.
9. Agreed to the sampling detailed in the Schedule of Events and to comply with study requirements including contraception requirements.
10. A female participant was eligible to participate if she was not pregnant or breastfeeding and at least one of the following conditions applied:

    - Was not a woman of childbearing potential (WOCBP)

      OR

    - Was a WOCBP and using a contraceptive method that is highly effective (a low user dependency method OR a user-dependent method in combination with a barrier method), or was abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 2 of the study protocol during the intervention period and for at least 50 days after the last dose of study intervention. The investigator evaluated the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.
    - A WOCBP must have had a negative highly sensitive pregnancy test (serum or urine) within 24 hours before the first dose of study intervention.
    - Additional requirements for pregnancy testing during and after study intervention were provided in the study protocol.
    - The investigator was responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
    - Contraceptive use by women was to be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
    - Given the elevated risk of venous thrombotic events in patients hospitalized with COVID-19 (Benson et al, 2020; Spratt et al, 2020), estrogen-containing contraceptives could not be started to fulfill the contraceptive requirement of this study at any time during participant's participation. If contraceptives were interrupted as standard of care management of COVID-19 patients and resumed at a later time point, such as at hospital discharge, then abstinence was practiced for the defined period of back-up contraception per the contraceptive product labeling. After this period, contraceptive use had to adhere to the guidance in Appendix 2 of the study protocol.
11. Male participants were eligible to participate if they agreed to the following during the intervention period and for at least 100 days after the last dose of study intervention:

    - Refrained from donating sperm

      PLUS either:

- Were abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agreed to remain abstinent.

  OR

- Had to agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 2 of the study protocol]) as detailed below:
  - Agreed to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who was not pregnant. Note: Men with a pregnant or breastfeeding partner had to agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.
  - Contraceptive use by men was to be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Participants were not enrolled in the study if they met any of the following exclusion criteria:

1. Need for hospitalization or immediate medical attention in the clinical opinion of the study investigator.
2. Hemoglobin <10 g/dL in men and <9 g/dL in women.
3. Platelet count <100,000/ µL or received a platelet transfusion within 5 days prior to enrollment.
4. Was on dialysis or has an estimated glomerular filtration rate <30 mL/min/1.73 m^2.
5. Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) >3× the upper limit of normal.
6. History of or current hospitalization for COVID-19. NOTE: Individuals hospitalized and then discharged, even if only hospitalized for 1 day, were excluded.
7. History of kidney disease as evidenced by estimated creatinine clearance value <30 mL/min.
8. History of significant liver disease in the opinion of the site investigator or active hepatitis B or active hepatitis C. Human immunodeficiency virus that was advanced (CD4 <200/mm^3) and/or on treatment with nucleos(t)ide analogues.
9. Use of therapeutic interventions with possible anti-SARS-CoV-2 activity within 30 days prior to study entry, (eg, remdesivir, lopinavir/ritonavir fixed-dose combination, ribavirin, chloroquine, hydroxychloroquine, and convalescent plasma), or participation in a clinical trial involving any of these drugs whether for treatment or prophylaxis.
10. Receipt of a SARS-CoV-2 vaccination prior to study entry.
11. Known allergy/sensitivity or any hypersensitivity to components of molnupiravir or its formulation.
12. Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.
13. History of recent (within the past 3 months) hemorrhagic cerebrovascular accident or major bleed.
14. Presence of a condition, that in the opinion of the investigator, would place the participant at increased risk from study participation.

Test product, dose and mode of administration, batch number:

Molnupiravir (100 mg and 200 mg) and matching placebo were supplied as dry filled capsules for oral administration. Doses administered in this study were 200 mg, 400 mg, or 800 mg BID.

Batch numbers of molnupiravir used during this study were: [redacted], [redacted], [redacted], [redacted], and [redacted]

Duration of treatment:

Molnupiravir or matching placebo was administered BID on Days 1 to 5 of the study, for a total of 10 doses for each participant.

Reference therapy, dose and mode of administration, batch number:

Placebo capsules matching molnupiravir capsules were administered orally BID.

Batch number of placebo used during this study were [redacted] and [redacted].

Criteria for evaluation:

Efficacy:

- SARS-CoV-2 RNA samples were collected via NP, OP, and nasal mid-turbinate swabs and analyzed by RT-PCR assay for viral load.
- SARS-CoV-2 infectious virus was collected via NP swabs. Vero E6 cell monolayers were infected with an aliquot from the sample for 1 hour. Culture medium was analyzed for viral load at 2 and 5 days post infection by RT-PCR.
- SARS CoV-2 samples collected via NP swab were analyzed for SARS-CoV-2 viral sequencing.
- Blood samples were collected for analysis of SARS-CoV-2 antibodies.
- COVID-19-related outpatient medical visits and hospitalizations were recorded.
- Oxygen saturation was recorded.
- Investigators rated the severity of each participant's illness using the WHO Ordinal Scale for Clinical Improvement.
- Participants kept a daily diary of COVID-19 symptoms.
- For participants who discontinued prematurely from the study for reasons other than withdrawal of consent, follow-up vital status information was recorded, when possible.

Safety:

- AEs were recorded.
- Vital signs were recorded.
- Clinical laboratory tests (hematology, clinical chemistry, inflammatory biomarkers) were performed.

Pharmacokinetics:.

- Blood samples for analysis of molnupiravir and EIDD-1931 plasma concentrations were collected on Day 5 pre-dose and at 1 and 2 hours post-dose.

Statistical Methods:

Efficacy

Treatment comparisons between each active dose group and placebo group in SARS-CoV-2 RNA change from Baseline were analyzed using a mixed model for repeated measures (MMRM) with restricted maximum likelihood estimation and an unstructured covariance matrix. The statistical model was fitted with terms for treatment group, visit, treatment by visit interaction, Baseline SARS-CoV-2 RNA, Baseline SARS-CoV-2 RNA by visit interaction, days from COVID-19 symptom onset, and days from COVID-19 symptom onset by visit interaction. The estimated treatment difference for "Active – Placebo" at each visit was displayed in the summary of statistical analysis together with the 95% confidence interval and the associated p-value. Least squares means and estimated treatment differences for each visit were also presented with the standard error. The time to response in undetectable SARS-CoV-2 RNA was summarized using the Kaplan-Meier (KM) method. The median time to response and the cumulative probability of response by visit along with the 95% confidence intervals were provided by treatment group. P-values for between group comparisons were provided using log-rank test.

The number and percentage of participants with SARS-CoV-2 RNA ≤ the lower limit of quantification (LLOQ), or SARS-CoV-2 RNA reduction of ≥1, 2, or 3 $\log_{10}$ from Baseline were presented for each treatment group by visit. P values for between-group comparisons were provided using the Fisher exact test.

Infectious Virus:

The number and percentage of participants with negative infectious SARS-CoV-2 virus isolation in NP swabs based on RT-PCR of Vero cell culture supernatants were summarized for each treatment group by visit. P-values for between-group comparisons were provided using the Fisher exact test. Dose response assessment was performed using the Exact Cochran-Armitage trend test.

SARS-CoV-2 RNA Sequencing:

Comparisons of RNA dependent RNA polymerase (RdRp) gene sequences were obtained using next-generation sequencing. Amino acid mutations and nucleotide changes based on the detection of changes that occurred at ≥1% were flagged by participant and visit.

Baseline changes were defined based on comparison with the Wuhan reference sequence (Genbank reference: NC_045512). Treatment-emergent amino acid mutations were defined as mutations that were not present at Baseline. The number and percentage of participants with treatment-emergent mutations at each amino acid position and with treatment-emergent nucleotide changes at each nucleotide position were summarized by treatment group. The between-treatment group comparisons were performed using a 2-sample T-test based on the average number of treatment-emergent mutations and the average number of treatment-emergent nucleotide changes.

The results of mutation analysis of SARS-CoV-2 RdRp nucleotide sequences compared with the reference SARS-CoV-2 RdRp were summarized by treatment and study visit. The results of mutation analysis of the post Baseline vs the Baseline SARS-CoV-2 RdRp nucleotide sequences were summarized by treatment. The data were presented separately based on the detection of changes occurring at ≥1%, ≥3%, or ≥10%.

Participant Diaries:

Participant diary data were listed and individual symptom scores were summarized by treatment and visit. The worst severity of all individual symptoms was summarized by treatment and visit.

The following time to response endpoints were derived and summarized using the KM method.

- Time to COVID-19symptom resolution (overall)
- Time to participant reported general physical health of 3 or 4 (very good or excellent)
- Time to participant reported returned to (pre-COVID-19) health
- Time to resolution of upper respiratory tract symptoms
- Time to resolution of common symptoms (based on the 13 or 12 symptoms)
- Time to resolution of cough

WHO Ordinal Scale for Clinical Improvement

Results of the WHO Ordinal Scale for Clinical Improvement were listed and summarized as a continuous score by treatment and visit.

COVID-19-Related Medical Visits

The number and percentage of participants who had a COVID-19-related medical visit during the study were presented for each treatment group.

The number and percentage of participants who were hospitalized during the study were also summarized by treatment group.

SARS-CoV-2 Antibodies

SARS-CoV-2 antibodies were summarized by treatment and visit for each test (total immunoglobulin [Ig], IgA, IgM, IgG, and composite [ie, any of the previous 4]).

The composite antibody test result was derived based on individual test results as follows:

- Serum antibody positive, defined as testing positive for any of the following: IgG, IgM, IgA, total Ig, or composite (any 1 of the 4)
- Serum antibody negative, defined as testing negative for all evaluable antibody types measured: total Ig, IgG, IgM, IgA

<u>Pharmacokinetics</u>

Plasma molnupiravir/EIDD-1931 concentrations were determined by validated analytical procedures. Plasma concentration data were summarized descriptively by planned time point.

Safety data including AEs, clinical laboratory data, and vital signs were summarized using descriptive statistics and listed individually for each participant.

<u>Extent of Exposure</u>

Exposure duration in number of days was summarized. The number and percentage of participants with the number of doses received in the following categories were summarized for the Safety population:

- ≥1 and <5 doses
- ≥5 and ≤9 doses
- ≥10 Doses

Safety

Safety data including AEs, clinical laboratory data, and vital signs were summarized using descriptive statistics and listed individually for each participant.

Adverse Events

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA®) Version 23.0. Any events reported after the initiation of study treatment and up to 14 days after the last dose of study treatment were defined as treatment-emergent adverse events (TEAEs). AEs started more than 14 days after the last dose of study treatment were considered post treatment and were summarized separately.

AE summaries included only TEAEs. AEs were categorized by TEAE, serious TEAE (SAE), AEs resulting in death, and AEs leading to discontinuation. These categories were further summarized by the causal relationship to study drug (AEs reported as related and possibly related were grouped together as related; AEs reported as unlikely and not related were grouped together as not related).

Clinical Laboratory Tests

Individual data listings of laboratory results were presented by study part, treatment, participant, and time point. Values outside of the laboratory's reference range and lab toxicity grade were included in the laboratory listings.

Quantitative values and change from Baseline in quantitative values were summarized by planned nominal time and treatment for each quantitative laboratory analyte.

Laboratory abnormalities were graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1, if applicable.

Any graded abnormality that occurred following the initiation of study drug and represented at least a 1-grade increase from the Baseline assessment was defined as treatment-emergent. The number and percentage of participants experiencing treatment-emergent graded laboratory abnormalities were summarized. Laboratory abnormality shifts from Baseline to worst post-Baseline assessments were also summarized for the treatment emergent abnormality.

Vital Signs

Vital sign results were listed by participant and time point. Vital signs were summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) over time in terms of absolute values and changes from Baseline at each scheduled time point for the Safety Population.

SUMMARY - CONCLUSIONS:

Disposition and Demographics:

A total of 240 patients were screened for this study, 36 failed the screening process and were not enrolled, and 204 were enrolled. Two participants withdrew from the study before taking any double-blind study drug. Therefore, a total of 202 participants were randomized into the study and received at least 1 dose of double-blind study drug and 195 of those completed the study. The reasons that 7 participants did not complete the study included AE (n=2 randomized to molnupiravir and n=1 randomized to placebo), lost to follow-up (n=1 randomized to molnupiravir), physician decision (the investigator discontinued the participant because of lack of study drug compliance; n=1 randomized to molnupiravir), and withdrawal by subject (n=2 randomized to molnupiravir).

On average, participants in the molnupiravir 200-mg group were slightly younger, with a mean age of 36.5 years, compared with mean ages of 42.4, 42.2, and 39.7 years in the molnupiravir 400-mg, molnupiravir 800-mg, and placebo groups, respectively. The molnupiravir 800-mg group had the lowest mean viral load at Baseline at 5.80 $\log_{10}$ copies/mL, compared with viral loads of 6.69, 6.38, and 6.11 $\log_{10}$ copies/mL in the molnupiravir 200-mg, molnupiravir 400-mg, and placebo groups, respectively. The molnupiravir 800-mg group also had a higher proportion of Hispanic participants (60.0%) compared with the other treatment groups (range: 30.4% to 37.1%), while the molnupiravir 200-mg group had a higher proportion of black participants (13%) compared with the other treatment groups (range: 3.2% to 5.5%). Other demographic and Baseline characteristics were generally comparable across treatment groups.

Efficacy Results

A tabular summary of key efficacy results is provided in the following table.

	Molnupiravir 200 mg (N=23)	Molnupiravir 400 mg (N=61)	Molnupiravir 800 mg (N=53)	All Molnupiravir (N=137)	Placebo (N=61)
Primary Endpoint: Time to Undetectable SARS-CoV-2 RNA (days)					
Number (%) with response	21 (91.3)	48 (78.7)	49 (92.5)	118 (86.1)	49 (80.3)
Number (%) censored	2 (8.7)	13 (21.3)	4 (7.5)	19 (13.9)	12 (19.7)
Median time to response (95% CI)	22.0 (15.0, 28.0)	27.0 (15.0, 28.0)	14.0 (13.0, 14.0)	15.0 (14.0, 20.0)	15.0 (15.0, 27.0)
Log rank p-value	0.5551	0.7270	0.0128	0.4216	
Proportion of Participants with Undetectable SARS-CoV-2 RNA by Study Day					
Day 3					
Number (%) undetectable	2/23 (8.7)	6/60 (10.0)	11/53 (20.8)	19/136 (14.0)	6/61 (9.8)
p-value (Fisher exact test)	>.9999	>.9999	0.1199	0.4941	
Day 5					
Number (%) undetectable	5/23 (21.7)	15/59 (25.4)	16/53 (30.2)	36/135 (26.7)	8/61 (13.1)
p-value (Fisher exact test)	0.3304	0.1067	0.0373	0.0419	
Day 7					
Number (%) undetectable	4/23 (17.4)	16/58 (27.6)	22/52 (42.3)	42/133 (31.6)	17/61 (27.9)
p-value (Fisher exact test)	0.4051	>.9999	0.1173	0.7370	
Day 14					
Number (%) undetectable	12/23 (52.2)	31/59 (52.5)	38/51 (74.5)	81/133 (60.9)	40/61 (65.6)
p-value (Fisher exact test)	0.3166	0.1936	0.4095	0.6324	
Day 28 (EOS)					
Number (%) undetectable	21/23 (91.3)	45/55 (81.8)	46/48 (95.8)	112/126 (88.9)	46/56 (82.1)
p-value (Fisher exact test)	0.4924	>.9999	0.0343	0.2389	
Summary of SARS-CoV-2 Infectious Virus Results					
Day 1					
Number (%) positive participants	11/22 (50.0)	18/43 (41.9)	20/52 (38.5)	49/117 (41.9)	25/53 (47.2)
p-value (Fisher exact test)	>.9999	0.6816	0.4320	0.6167	
Day 3					
Number (%) positive participants	4/22 (18.2)	5/43 (11.6)	1/53 (1.9)	10/118 (8.5)	9/54 (16.7)
p-value (Fisher exact test)	>.9999	0.5691	0.0161	0.1225	
p-value (Exact Cochran-Armitage trend test)					0.0095
Day 5					
Number (%) positive participants	1/22 (4.5)	0/42 (0.0)	0/53 (0.0)	1/117 (0.9)	6/54 (11.1)
p-value (Fisher exact test)	0.6658	0.0335	0.0270	0.0043	
p-value (Exact Cochran-Armitage trend test)					0.0025
Day 7					
Number (%) positive participants	1/21 (4.8)	0/47 (0.0)	0/52 (0.0)	1/120 (0.8)	2/56 (3.6)
p-value (Fisher exact test)	>.9999	0.4990	0.4960	0.2379	
p-value (Exact Cochran-Armitage trend test)					0.092
MMRM Analysis of Change from Baseline in SARS-CoV-2 Viral Load					
Day 3	N=23	N=58	N=51	N=132	N=56
LSM Difference	0.064	-0.094	-0.203	-0.078	
p-value	0.7806	0.5891	0.2392	0.6108	
Day 5	N=23	N=56	N=52	N=131	N=57
LSM Difference	-0.150	-0.434	-0.547	-0.377	
p-value	0.5663	0.0300	0.0062	0.0347	
Day 7	N=23	N=51	N=49	N=123	N=56
LSM Difference	-0.076	-0.311	-0.534	-0.307	
p-value	0.7667	0.1168	0.0060	0.0896	
Day 14	N=23	N=53	N=48	N-124	N=54
LSM Difference	-0.019	0.026	-0.175	-0.056	
p-value	0.8932	0.8355	0.1258	0.6214	
Day 28 (EOS)	N=23	N=52	N=47	N=122	N=52
LSM Difference	-0.035	0.058	-0.044	-0.007	
p-value	0.5948	0.4147	0.4438	0.8911	

Abbreviations: CI = confidence interval; EOS = end of study; LSM = least squares mean; MMRM = mixed model for repeated measures; SARS CoV-2 = severe acute respiratory syndrome coronavirus-2.
Sources: Table 14.2.9.1, Table 14.2.4.1, Table 14.2.5.1.1, and Table 14.2.6.1.1

Primary Efficacy Endpoint

Time to clearance of viral RNA in NP swabs was the primary endpoint of this study and was shorter in participants receiving 800 mg molnupiravir (median: 14 days) compared with those administered placebo (log-rank p = 0.0128).

The proportion of participants who achieved undetectable SARS-CoV-2 RNA at each time point was also greater in the molnupiravir 800-mg group compared with the placebo group (p=0.0373 on Day 5 and p=0.0343 on Day 28).

Other Efficacy Endpoints

Analysis of Infectious Virus

The proportion of participants with positive cultures decreased faster for participants treated with molnupiravir 800-mg compared with participants treated with placebo, molnupiravir 200-mg, or molnupiravir 400-mg.

At Baseline, the proportion of participants with positive SARS-CoV-2 infectivity results varied across treatment groups, with higher proportions of participants in the molnupiravir 200-mg group (50.0%) and placebo group (47.2%) testing positive compared with the 400-mg group (41.9%) and 800-mg group (38.5%). On Day 3, the proportions of participants with positive infectivity results had decreased to 1/53 (1.9%) in the molnupiravir 800-mg group compared with 9/54 (16.7%), 4/22 (18.2%), and 5/43 (11.6%) in the placebo, molnupiravir 200-mg, and molnupiravir 400-mg groups, respectively (p = 0.0161 for the comparison between molnupiravir 800 mg vs placebo; and p=0.0095 for the dose-response effect).

On Day 5, none of the participants in the molnupiravir 400-mg or 800-mg groups had positive results compared with 11.1% of participants in the placebo group and 4.5% of participants in the molnupiravir 200 mg group (p = 0.0335 and p = 0.0270 for the differences between the molnupiravir 400-mg and 800-mg groups, respectively, vs placebo; and p = 0.0025 for the dose-response relationship)..

By Day 7 (the last date of testing), the number of participants with culturable virus in the molnupiravir 400-mg and 800-mg groups remained 0, with 1 participant in the molnupiravir 200-mg group and 2 participants in the placebo group providing positive results.

Change from Baseline in SARS-CoV-2 RNA

Analysis of change from Baseline in SARS-CoV-2 viral load (log_{10} copies/mL) using an MMRM also showed a larger decrease in the molnupiravir 800-mg treatment group compared with any of the other treatment groups from Days 3 to 28 (p=0.0062 and p=0.0060 for the differences between the molnupiravir 800-mg and placebo groups on Days 5 and 7, respectively).

Sequencing of SARS-CoV-2 RdRp Genome

Analysis of SARS-CoV-2 RdRp nucleotide changes occurring in the RdRp region at levels ≥1% of the individual participant's viral population compared with the Wuhan consensus sequence indicated an increased mutation rate in participants receiving molnupiravir compared with those receiving placebo. Among the molnupiravir-treated participants with paired sequence data, the mean % identity of the posttreatment samples vs Baseline samples was lower (99.54%) compared with that observed for the placebo participants (99.73%), indicating an increase in the number of changes following treatment. Furthermore, these changes occurred across the entire RdRp region, regardless of treatment. Comparison of RdRp sequences from Baseline and Day 5 (end of treatment) samples supports the mechanism of action of viral error catastrophe.

Additional Virology Analyses

Treatment with molnupiravir did not prevent the development of antibodies to SARS-CoV-2. By Day 28 of the study, nearly all participants in all groups had positive antibody status, and more participants in the molnupiravir groups had SARS-CoV-2 antibodies than participants in the placebo group (100.0%, 100.0%, 98.1%, and 96.5% of participants in the molnupiravir 200-mg, 400-mg, and 800-mg, and placebo groups, respectively).

Examination of subgroups showed an important effect of Baseline antibody status on response to molnupiravir. On Day 3, the decrease from Baseline in viral load was approximately 3-fold greater among participants with negative antibody status in the molnupiravir treatment groups, whereas the decrease from Baseline in viral load in the placebo group was similar regardless of composite antibody status at Baseline. On Day 5, the difference between viral load reduction among antibody negative participants in the molnupiravir-treated groups compared with placebo was maintained. The reduction in viral load in molnupiravir-treated groups prior to development of antibody response is indicative of direct antiviral effect.

Furthermore, analysis of time to undetectable SARS-CoV-2 RNA by Baseline antibody status showed a markedly faster median time to viral negativity in the molnupiravir-treated group compared with the placebo-treated group for

the subset of participants who did not have antibodies to SARS-CoV-2 at Baseline (14 days in the molnupiravir 800-mg groups vs 27, 22, and 26 days for the placebo, molnupiravir 200-mg, and molnupiravir 400-mg groups, respectively). In addition, the overall proportion of participants who achieved viral negativity during the study was greater in the molnupiravir-treated group compared with the placebo-treated group for the subset of participants who did not have antibodies to SARS-CoV-2 at Baseline.

Analysis of Clinical Endpoints

Changes over time in WHO Ordinal Scale were similar in the molnupiravir- and placebo-treated groups. All participants were rated as 1 or 2 (ie, ambulatory) on this scale of 0-8 points.

There were no clinically important differences between treatment groups in the proportion of participants who met the composite endpoint or the proportion of participants who were hospitalized during the study in this population. A total of 4 participants met the composite endpoint during the study: 2 in the molnupiravir 400-mg group, 1 in the molnupiravir 800-mg group, and 1 in the placebo group.

Analysis of the agreement between SARS-CoV-2 RNA and infectivity results indicated a very low level of agreement between the 2 assays. Although infectivity results were negative for every sample that had a negative SARS-CoV-2 RNA result, infectivity results were positive for 45.1% of samples that had a positive SARS-CoV-2 RNA result at Baseline and for 15.6% of all samples that had a positive SARS-CoV-2 RNA result through Day 7 of the study.

Pharmacokinetic Results

The plasma concentration values observed in this study in participants with COVID-19 were similar to those reported previously in healthy volunteers. Geometric mean plasma concentrations of EIDD-1931, the active antiviral nucleoside metabolite of molnupiravir, in samples taken at 1 hour postdose on Day 5 were approximately 551, 1440, and 1604 ng/mL in the molnupiravir 200-mg, 400-mg, and 800-mg groups, respectively. Geometric mean plasma concentrations of EIDD-1931 in samples taken close to the estimated time of maximum concentration (ie, at approximately 2 hours postdose) increased with dose and were approximately 794, 1618, and 2404 ng/mL in the molnupiravir 200-mg, 400-mg, and 800-mg groups, respectively.

Safety Results

Most participants in each treatment group took the prescribed number of doses of study drug (ie, 10 doses) (range: 90.9% to 100.0% of participants).

The overall incidence of AEs was lowest in the molnupiravir 800-mg group (20.0% of participants experienced ≥1 AE in the molnupiravir 800-mg group) compared with the placebo, molnupiravir 200-mg and molnupiravir 400-mg groups (incidences of 9.0%, 47.8%, and 32.3%, respectively). The incidence of AEs related to study drug and the incidence of AEs ≥Grade 2 (moderate or severe) were also lowest in the molnupiravir 800 mg group.

The only AE reported in more than 5% of participants in either the placebo or combined molnupiravir treatment group was insomnia, which was reported by 6.5% of participants in the placebo group and 2.9% of participants in the combined molnupiravir group. AEs reported in more than 3% of participants in either the placebo group or the combined molnupiravir treatment groups were headache (4.3% of participants in the combined molnupiravir group and 4.8% of participants in the placebo group), alanine aminotransferase increased (2.9% of participants in the combined molnupiravir group and 3.2% of participants in the placebo group), and abdominal pain (0.7% of participants in the combined molnupiravir group and 3.2% of participants in the placebo group). All other AEs were reported by fewer than 3% of participants in the placebo and the combined molnupiravir groups.

A total of 4 SAEs were reported during this study: hypoxia in a participant who took 2 doses of placebo, oxygen saturation decreased in a participant who took 8 doses of molnupiravir 400-mg, cerebrovascular accident in a participant who took 9 doses of molnupiravir 400 mg, and acute respiratory failure in a participant who took 2 doses of molnupiravir 800-mg. The SAE in the placebo group resulted in the participant's death 31 days after discontinuation from the study. Three of the SAEs resulted in discontinuation of the participant from study treatment and from the study (1 in the molnupiravir 400-mg group, 1 in the molnupiravir 800-mg group, and 1 in the placebo group). None of the SAEs were considered to be related to study drug.

There were no treatment- or dose-related trends in mean hematology data over time during the study. Mean change from Baseline values in platelet count showed increases for all groups at all post Baseline time points. The incidence of shifts in platelets from Grade 0 at Baseline to ≥1 post-Baseline was higher in the placebo-treated group than in the molnupiravir-treated groups.

One participant in the molnupiravir 400-mg group had a treatment-emergent Grade 3 ALT result on Day 5. The participant had Grade 1 AST and ALT values at Screening, and normal values on Days 1, 14, and 28. Bilirubin

remained within the normal range throughout the study. No AE for this event was reported. No possible explanation for the event was found in the medical history, concomitant medications, or other electronic case report forms.

TEAEs related to laboratory tests (including liver function tests) were reported in similar proportions of participants from the placebo and molnupiravir treatment groups.

Mean changes from Baseline in oxygen saturation were small during the study, and similar across treatment groups. Mean values remained at or above 97.5% in all groups at all time points. Mean changes in other vital signs over time were generally small and similar among treatment groups and mean values remained within normal ranges at all time points.

Oxygen saturation below 94% was reported for 6 participants (1 in the placebo group, 3 in the molnupiravir 400-mg group, and 2 in the molnupiravir 800-mg group). Three of the participants discontinued the study due to SAEs related to low oxygen saturation and the other 3 participants completed the study with oxygen saturation ≥96%.

Conclusions

Study-EIDD-2801-2003 met the objectives of showing an antiviral effect of molnupiravir and demonstrating the safety of molnupiravir in an adult outpatient population with mild to moderate COVID-19 disease. The one participant in the molnupiravir 800-mg group who had an SAE (FO-002) entered the study with severe disease per NIH criteria (oxygen saturation <94%), had 3 risk factors for developing severe COVID-19 disease, and took only 2 doses of molnupiravir. All efficacy and safety data accumulated during this study and analysis of the risk-to-benefit relationship for both safety and efficacy show that the molnupiravir 800-mg dose most quickly and effectively decreased levels of SARS-CoV-2 in patients with COVID-19 with no change in tolerability compared with lower doses. All virology data were consistent, regardless of whether virology endpoints were measured by SARS-CoV-2 RNA (RT-PCR) or culture of infectious virus. The proportion of participants who achieved nondetectable virus was higher in the molnupiravir 800-mg group. Molnupiravir did not inhibit the production of antibodies to SARS-CoV-2.

The proposed mechanism of action of molnupiravir was supported by the results of next-generation sequencing analysis of SARS-CoV-2 RdRp. Furthermore, the faster reduction in viral load in the molnupiravir-treated groups compared with placebo among participants who did not have antibodies to SARS-CoV-2 at Baseline is indicative of a direct antiviral effect.

The tolerability and safety of all molnupiravir dose levels were comparable to placebo in all categories assessed. Overall, safety findings were identified in a smaller proportion of participants treated with molnupiravir compared with participants treated with placebo.

The results of this study support continued development of molnupiravir at the 800-mg dose level.

2 SYNOPSIS

SPONSOR: Merck, Sharp & Dohme Corp., Whitehouse Station, NJ USA (MSD)

COMPOUND NAME: MK-4482

PROTOCOL TITLE: A Single and Multiple Dose Clinical Study to Evaluate the Safety, Tolerability and Pharmacokinetics of MK-4482 in Healthy Japanese Adult Participants

STUDY IDENTIFIERS:

IND: N/A	EudraCT: N/A

STUDY PHASE: 1

INDICATION: Treatment and prevention of coronavirus disease caused by severe acute respiratory syndrome coronavirus 2

STUDY CENTERS: This study was conducted at 1 center in 1 country.

STUDY STATUS: This study is complete.

First Patient, First Visit	Last Patient, Last Visit	Date of Last Contact	Final Database Lock Date
09-APR-2021	[redacted]-2021	21-SEP-2021	[redacted]-20[redacted]

NOTE: Patient = Participant

METHODOLOGY: This was a 2-part, randomized, placebo-controlled, single-site, double-blind study of MK-4482 (molnupiravir) in healthy Japanese adult male participants. The trial consisted of 2 parts (Part 1: single oral dose administration of MK-4482 final market image capsules or placebo under fasted and fed states [high-fat meal]; Part 2: multiple oral dose administration of MK-4482 final market image capsules or placebo). The study design is depicted in [Table 2-1] and [Table 2-2].

In Part 1, participants were randomized to one of 3 Panels (A, B, and C) and received a single oral dose of MK-4482 200 mg, 400 mg or 800 mg (N 6 per panel), respectively, or placebo (N 2 per panel) in a blinded fashion in the fasted state in Period 1. In Period 2, Panel A participants received a single oral dose of MK-4482 1600 mg (N 6) or placebo (N 2) and Panel C participants received a single oral dose of MK-4482 800 mg (N 6) or placebo (N 2) following consumption of high-fat breakfast.

In Part 2, participants were randomized to Panels E and F and received multiple oral doses of 400- or 800-mg MK-4482 (N 15 per panel), respectively, or placebo (N 5 per panel) Q12H for 5.5 days (total of 11 doses per participant) in a blinded fashion. The first and last dose of study interventions (on Day 1 am and Day 6 am, respectively) were administered in the fasted condition.

In both Part 1 and Part 2, plasma and peripheral blood mononuclear cells (PBMC) samples were collected for assessment of N-hydroxycytidine (NHC) and N-hydroxycytidine triphosphate (NHC-TP), respectively.

Participants in both of Part 1 and Part 2 were followed for safety throughout the study, until approximately 14 days following administration of the last dose of study intervention. In addition, the participants were verbally contacted to confirm contraceptive requirements 90 days (within + 1 week) after the last study intervention.

Table 2-1
Study Design (Part 1-1)

Panel	N (MK-4482:placebo)	Period 1			Period 2
A[a]	6:2	MK-4482 200 mg or placebo			MK-4482 1600 mg or placebo
B	6:2		MK-4482 400 mg or placebo		
C[b]	7:2 [c]			MK-4482 800 mg or placebo	MK-4482 800 mg or placebo with food

a Different participants received placebo between Period 1 and 2.
b The assigned intervention for Periods 1 (fasted) and 2 (fed) were the same, such that the same participants received MK 4482 or placebo in both treatment periods.
c One (1) participant was replaced because the participant discontinued study intervention in Period 1. A total of 9 participants were enrolled in Panel C. The replacement participant participated in Period 1 and 2.

Table 2-2
Study Design (Part 2)

Panel	N (MK-4482:placebo)	Treatment Period	
E	15:5	MK-4482 400 mg or placebo Q12H for 5.5 days	
F	15:5		MK-4482 800 mg or placebo Q12H for 5.5 days

Q12H: every 12 hours

Clinical investigator study sites were advised to follow local and national guidance regarding the pandemic and to share any mitigation plans for study participant management with the Institutional Review Board (IRB)/ Ethics Committee (EC) and the Sponsor. Study sites were

also advised to remain in contact with study participants to monitor for safety concerns, help ensure participants adhered to their study intervention schedule, and to keep participants informed of changes to the study and other study activities.

This study was conducted during the COVID-19 pandemic. The Sponsor continued to follow its Standard Operating Procedures (SOP) for study conduct, monitoring, and oversight during the pandemic and employed a risk-based approach to assess and mitigate impact on study conduct.

ELIGIBILITY CRITERIA: Healthy Japanese male participants, aged between 20 and 60 years (inclusive) and body mass index (BMI) between $\geq$ 18.5 and $\leq$ 24.9 kg/m^2 at screening.

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OBJECTIVES AND ENDPOINTS:

Primary Objective(s)	**Primary Endpoint(s)**
Part 1 • To evaluate the safety and tolerability of single oral doses of MK-4482	• Adverse events, vital signs, laboratory safety tests, 12-lead electrocardiograms, physical examinations
• To evaluate the pharmacokinetic profile of N-hydroxycytidine in plasma following a single oral dose of MK-4482 • Estimation: The pharmacokinetic profile of N-hydroxycytidine following a single oral dose of MK-4482 final market image capsules will be estimated.	• Cmax, Tmax, t1/2, AUC0-12, AUC0-last and AUC0-inf
Part 2 • To evaluate the safety and tolerability of multiple oral doses of MK-4482	• Adverse events, vital signs, laboratory safety tests, 12-lead electrocardiograms, physical examinations
• To evaluate the pharmacokinetic profile of N-hydroxycytidine in plasma following multiple oral doses of MK-4482 • Estimation: The pharmacokinetic profile of N-hydroxycytidine following multiple oral doses of MK-4482 final market image capsules will be estimated.	• Ctrough, Cmax, Tmax, t1/2*, AUC0-τ, AR for Cmax and AUC0-τ (following first dose and last dose) *Following last dose only
Secondary Objective(s)	**Secondary Endpoint(s)**
Part 1 • To evaluate the effect of a high-fat meal on the comparative bioavailability of N-hydroxycytidine following a single oral dose of MK-4482	• AUC0-inf (AUC0-12 if AUC0-inf is unavailable for at least one participant) and Cmax
• To evaluate the pharmacokinetic profile of N-hydroxycytidine triphosphate in peripheral blood mononuclear cells following a single oral dose of MK-4482	• Cmax, Tmax, t1/2, AUC0-12, AUC0-last and AUC0-inf
Part 2 • To evaluate the pharmacokinetic profile of N-hydroxycytidine triphosphate in peripheral blood mononuclear cells following multiple oral doses of MK-4482	• Ctrough, Cmax, Tmax, t1/2*, AUC0-τ, AR for Cmax and AUC0-τ (following first dose and last dose) *Following last dose only

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NUMBER OF PARTICIPANTS (planned and analyzed): The planned enrollment total was 72 participants. As of final database lock for this report, 65 participants were randomized (8 each in Panel A and Panel B, 9 in Panel C, and 20 each in Panel E and Panel F). A total of 65 participants completed the study.

In Period 1 of Part 1, 1 participant withdrew consent for personal reasons after receiving a single dose of MK-4482 800 mg in the fasted state and completed subsequent follow-up procedures. This participant was replaced.

In Part 2, 1 participant withdrew consent for personal reasons after receiving 2 doses of MK-4482 800 mg and completed subsequent follow-up procedures. Another participant discontinued study intervention for an AE (toxic skin eruption) after receiving 10 doses of MK-4482 800 mg and completed subsequent follow-up procedures. These participants were not replaced.

STATISTICAL AND ANALYTICAL METHODS: This study was conducted during the COVID-19 pandemic and there were no changes in the planned analyses of the study due to the COVID-19 pandemic.

The All Participants as Treated (APaT) Population consisted of all participants who received at least one dose of treatment. This population was used for assessments of safety.

The Per-Protocol Population consisted of the subset of participants who complied with the protocol sufficiently to ensure that generated data would be likely to exhibit the effects of treatment, according to the underlying scientific model. All participants in APaT were included in the Per-Protocol (PP) Population since all of the participants were compliant with the study procedure and had available data from at least one treatment. This population was used for assessments of PK.

Part 1

Safety

Summary statistics and plots were generated for raw laboratory safety tests, ECGs, and resting and orthostatic vital signs as well as for change from baseline. Depending on the safety parameter, the difference from baseline was computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline).

Pharmacokinetics

Model-based PK summary (NHC in plasma and NHC-TP in PBMC):

PK parameter values for NHC in plasma and NHC-TP in PBMC were natural log-transformed and evaluated with separate linear mixed effects models containing a fixed effect for treatment and a random effect for participant. Kenward and Roger's method was used to calculate the denominator degrees of freedom for the fixed effect. Ninety-five percent confidence intervals for the least squares means for each treatment (considering food

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condition) was constructed on the natural log scale and referenced a t-distribution. Exponentiating the least-squares means and lower and upper limits of these confidence intervals yielded estimates for the population geometric means and confidence intervals about the geometric means on the original scale.

The PK parameters assessed for model-based PK summary were:

- Cmax, AUC0-12, AUC0-last and AUC0-inf for NHC in plasma
- Cmax, AUC0-12, AUC0-last and AUC0-inf for NHC-TP in PBMC

Assessment of Dose Proportionality (NHC in plasma):

An exploratory assessment of dose proportionality of NHC Cmax, AUC0-12 and AUC0-inf in the fasted state was conducted. Separately for each PK parameter, a linear mixed effects model with ln(dose) as a fixed covariate and participant as a random effect was used to obtain the slope estimate associated with ln(dose). A least squares estimate and 95% confidence interval for the slope associated with ln(dose) was obtained from the model. A plot of the observed PK data versus dose on the raw scale was provided, along with an estimated regression line and a 95% Schéffe confidence band.

Food effect (NHC in plasma):

The effect of food on NHC exposures was estimated by obtaining the geometric mean ratio (fed/fasted) and 90% confidence interval for Cmax and AUC0-inf at the dose level administered in both the fasted and fed state, based on the linear mixed effects model described above.

Part 2

Safety

Summary statistics and plots were generated for raw laboratory safety tests, ECGs, and/or resting and orthostatic vital signs as well as for change from baseline. Depending on the safety parameter, the difference from baseline was either computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline).

Pharmacokinetics

Model-Based Pharmacokinetic Summary (NHC in plasma and NHC-TP in PBMC):

PK parameter values (Cmax and AUC0-τ) for NHC in plasma and NHC-TP in PBMC were natural log transformed and evaluated with separate linear mixed effects models containing fixed effects for treatment, day (Day 1, Day 6), and treatment-by-day interaction and a random effect for participant. Ninety-five percent confidence intervals for the least squares means by treatment and day were constructed on the natural log scale and referenced the t-distribution. Exponentiating the least-squares means and lower and upper limits of these confidence intervals yielded estimates for the population geometric means and confidence intervals about the geometric means on the original scale for each treatment and day.

Similarly, the least squares mean differences (Day 6 Day 1) and 90% confidence intervals from the models were back-transformed to obtain the geometric mean accumulation ratios (Day 6 / Day 1) and 90% confidence intervals for Cmax and AUC0-τ.

RESULTS:

Participant Disposition:

- Part 1: 25 randomized, 25 completed study, and 1 discontinued study intervention.
- Part 2: 40 randomized, 40 completed study, and 2 discontinued study intervention.

Demographics and Baseline Characteristics:

- **Overall Median Age (range):** 51.0 years (21 to 59 years) in Part 1, 45.0 years (20 to 59 years) in Part 2
- **Sex:** 25 (100.0%) males in Part 1, 40 (100.0%) males in Part 2
- **Race:** 25 (100.0%) Asian in Part 1, 40 (100.0%) Asian in Part 2

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Table 2-3
Participant Characteristics
(Part 1, All Participants as Treated)

	Placebo		MK 4482 200 mg		MK 4482 400 mg		MK 4482 800 mg (fasted)		MK 4482 800 mg (fed)		MK 4482 1600 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	8		6		6		7		6		6		25	
Sex														
Male	8	(100.0)	6	(100.0)	6	(100.0)	7	(100.0)	6	(100.0)	6	(100.0)	25	(100.0)
Age (Years)														
20 to 29	1	(12.5)	1	(16.7)	0	(0.0)	1	(14.3)	1	(16.7)	1	(16.7)	3	(12.0)
30 to 39	0	(0.0)	0	(0.0)	1	(16.7)	1	(14.3)	1	(16.7)	0	(0.0)	2	(8.0)
40 to 49	2	(25.0)	0	(0.0)	1	(16.7)	1	(14.3)	1	(16.7)	1	(16.7)	4	(16.0)
> 50	5	(62.5)	5	(83.3)	4	(66.7)	4	(57.1)	3	(50.0)	4	(66.7)	16	(64.0)
Mean	48.9		49.0		49.3		45.1		43.3		47.5		47.3	
SD	8.8		14.1		9.3		12.7		12.9		14.7		11.4	
Median	51.0		52.5		53.0		51.0		48.5		53.5		51.0	
Range	28 to 57		21 to 59		31 to 57		24 to 57		24 to 57		21 to 59		21 to 59	
Race														
Asian	8	(100.0)	6	(100.0)	6	(100.0)	7	(100.0)	6	(100.0)	6	(100.0)	25	(100.0)
Race by Ethnicity														
Not Hispanic Or Latino	8	(100.0)	6	(100.0)	6	(100.0)	7	(100.0)	6	(100.0)	6	(100.0)	25	(100.0)
Asian	8	(100.0)	6	(100.0)	6	(100.0)	7	(100.0)	6	(100.0)	6	(100.0)	25	(100.0)
Weight (kg)														
Participants with data	10		6		6		7		6		6		41	
Mean	63.0		62.9		62.3		65.6		64.8		62.1		63.4	
SD	5.9		6.8		5.5		3.9		3.4		5.8		5.2	

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Participant Characteristics
(Part 1, All Participants as Treated)

	Placebo		MK 4482 200 mg		MK 4482 400 mg		MK 4482 800 mg (fasted)		MK 4482 800 mg (fed)		MK 4482 1600 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Median	65.6		61.9		63.0		66.3		64.9		62.0		65.4	
Range	53.0 to 71.3		54.8 to 71.3		55.8 to 69.0		59.3 to 71.0		59.3 to 68.4		54.8 to 69.4		53.0 to 71.3	
Height (cm)														
Participants with data	10		6		6		7		6		6		41	
Mean	169.1		169.5		167.8		170.9		170.0		168.8		169.4	
SD	2.9		4.9		3.1		2.8		1.8		4.6		3.4	
Median	168.0		169.5		168.0		170.0		169.5		168.0		169.0	
Range	166.0 to 175.0		163.0 to 176.0		163.0 to 171.0		168.0 to 176.0		168.0 to 173.0		163.0 to 176.0		163.0 to 176.0	
BMI (kg/m2)														
Participants with data	10		6		6		7		6		6		41	
Mean	22.2		22.1		21.8		22.3		22.2		22.0		22.1	
SD	2.0		1.8		1.8		1.6		1.8		1.7		1.7	
Median	22.9		22.6		21.9		22.4		22.3		22.6		22.7	
Range	19.0 to 24.0		19.8 to 23.9		19.4 to 24.1		19.2 to 24.3		19.2 to 24.3		19.8 to 24.0		19.0 to 24.3	

SD Standard deviation

Source: [P008MK4482: adam adsl]

Table 2-4
Participant Characteristics
(Part 2, All Participants as Treated)

	Placebo		MK 4482 400 mg		MK 4482 800 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	10		15		15		40	
Sex								
Male	10	(100.0)	15	(100.0)	15	(100.0)	40	(100.0)
Age (Years)								
20 to 29	1	(10.0)	4	(26.7)	2	(13.3)	7	(17.5)
30 to 39	3	(30.0)	3	(20.0)	3	(20.0)	9	(22.5)
40 to 49	1	(10.0)	3	(20.0)	4	(26.7)	8	(20.0)
> 50	5	(50.0)	5	(33.3)	6	(40.0)	16	(40.0)
Mean	45.3		39.9		43.3		42.5	
SD	11.6		12.7		12.3		12.2	
Median	49.5		42.0		45.0		45.0	
Range	24 to 59		20 to 59		21 to 57		20 to 59	
Race								
Asian	10	(100.0)	15	(100.0)	15	(100.0)	40	(100.0)
Race by Ethnicity								
Not Hispanic Or Latino	10	(100.0)	15	(100.0)	15	(100.0)	40	(100.0)
Asian	10	(100.0)	15	(100.0)	15	(100.0)	40	(100.0)
Weight (kg)								
Participants with data	10		15		15		40	
Mean	61.6		63.8		61.9		62.5	
SD	4.0		6.1		4.5		5.0	
Median	61.8		64.7		60.2		61.8	

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Participant Characteristics
(Part 2, All Participants as Treated)

	Placebo		MK 4482 400 mg		MK 4482 800 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Range	54.4 to 67.7		55.7 to 74.3		56.0 to 69.6		54.4 to 74.3	
Height (cm)								
Participants with data	10		15		15		40	
Mean	169.3		169.9		167.4		168.8	
SD	5.4		5.4		3.5		4.8	
Median	169.0		170.0		167.0		169.0	
Range	162.0 to 179.0		157.0 to 176.0		161.0 to 174.0		157.0 to 179.0	
BMI (kg/m2)								
Participants with data	10		15		15		40	
Mean	21.7		22.1		22.1		22.0	
SD	1.4		1.7		1.5		1.5	
Median	21.8		22.7		21.6		22.0	
Range	19.3 to 24.1		19.6 to 24.7		19.4 to 24.6		19.3 to 24.7	

SD Standard deviation

Source: [P008MK4482: adam adsl]

Safety: All 65 participants were included in the assessment of safety and tolerability. AE summaries for each part are shown in [Table 2-5], [Table 2-6]; the number (%) of participants with specific AEs presented by system organ class are shown in [Table 2-7], [Table 2-8].

- Single doses of MK-4482 up to 1600 mg and multiple doses of MK-4482 400 mg and 800 mg Q12H for 5.5 days were generally well tolerated in healthy Japanese male adult participants.

- In Part 1 (single dose), 2 participants out of 25 (8.0%) reported 3 AEs. In Part 2 (multiple dose), 13 participants out of 40 (32.5%) reported 15 AEs. There were no serious adverse events (SAEs) or events of clinical interest (ECIs).

- Drug-related AEs were reported for 1 and 5 participants who received MK-4482 in Part 1 and Part 2, respectively. Of these, toxic skin eruption was the most frequently reported (3 participants in the MK-4482 800 mg group in Part 2). There were no drug-related AEs in both of the placebo groups in Part 1 and Part 2.

- All the AEs were mild in intensity except 2 events: 1 moderate dermatitis reported in 1 participant who received a single dose of MK-4482 200 mg in Period 1 of Part 1, and 1 moderate toxic skin eruption reported in 1 participant who received multiple doses of MK-4482 800 mg Q12H for 5 days in Part 2. The participant who reported moderate dermatitis also received a single dose of MK-4482 1600 mg in Period 2 of Part 1 without recurrence of dermatitis.

- In Part 1, the reported AEs in the MK-4482 group were dermatitis, increased lipase and increased amylase (1 participant each). There were no AEs in the placebo group. In Part 2, the most frequently reported AE (≥3 participants) in the total MK-4482 group was toxic skin eruption (3 participants). In the placebo group in Part 2, only decreased haemoglobin (1 participant) was reported.

- There was 1 AE (moderate toxic skin eruption) resulting in discontinuation of study intervention in Panel F (multiple doses of MK-4482 800 mg Q12H for 5.5 days). The toxic skin eruption occurred on Day 4 pm before dosing of study intervention and resolved on Day 14 following treatment with betamethasone butyrate propionate and fexofenadine hydrochloride. The participant received 10 doses of MK-4482 800 mg and discontinued study intervention after the Day 5 pm dosing.

- No clinically meaningful trends were observed for changes in clinical laboratory values, vital signs, or 12-lead ECGs as a function of dose or treatment.

Table 2-5
Adverse Event Summary
Part 1, All Participants as Treated

	Placebo		MK 4482 200 mg		MK 4482 400 mg		MK 4482 800 mg (fasted)		MK 4482 800 mg (fed)		MK 4482 1600 mg		Total MK 4482 group		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	8		6		6		7		6		6		21		25	
with one or more adverse events	0	(0.0)	1	(16.7)	1	(16.7)	0	(0.0)	0	(0.0)	0	(0.0)	2	(9.5)	2	(8.0)
with no adverse event	8	(100.0)	5	(83.3)	5	(83.3)	7	(100.0)	6	(100.0)	6	(100.0)	19	(90.5)	23	(92.0)
with drug relateda adverse events	0	(0.0)	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	1	(4.0)
with serious adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
with serious drug related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a drug related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious drug related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the drug.

Source: [P008MK4482: adam adsl; adae]

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Table 2-6
Adverse Event Summary
Part 2, All Participants as Treated

	Placebo		MK 4482 400 mg		MK 4482 800 mg		Total MK 4482 group		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	10		15		15		30		40	
with one or more adverse events	1	(10.0)	4	(26.7)	8	(53.3)	12	(40.0)	13	(32.5)
with no adverse event	9	(90.0)	11	(73.3)	7	(46.7)	18	(60.0)	27	(67.5)
with drug relateda adverse events	0	(0.0)	1	(6.7)	4	(26.7)	5	(16.7)	5	(12.5)
with serious adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
with serious drug related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	0	(0.0)	0	(0.0)	1	(6.7)	1	(3.3)	1	(2.5)
discontinued drug due to a drug related adverse event	0	(0.0)	0	(0.0)	1	(6.7)	1	(3.3)	1	(2.5)
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious drug related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the drug.

Source: [P008MK4482: adam adsl; adae]

Table 2-7
Participants With Adverse Events
(Incidence > 0% in One or More Treatment Groups)
(Part 1, All Participants as Treated)

	Placebo		MK 4482 200 mg		MK 4482 400 mg		MK 4482 800 mg (fasted)		MK 4482 800 mg (fed)		MK 4482 1600 mg		Total MK 4482 group		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	8		6		6		7		6		6		21		25	
with one or more adverse events	0	(0.0)	1	(16.7)	1	(16.7)	0	(0.0)	0	(0.0)	0	(0.0)	2	(9.5)	2	(8.0)
with no adverse events	8	(100.0)	5	(83.3)	5	(83.3)	7	(100.0)	6	(100.0)	6	(100.0)	19	(90.5)	23	(92.0)
Investigations	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(16.7)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(4.8)**	**1**	**(4.0)**
Amylase increased	0	(0.0)	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	1	(4.0)
Lipase increased	0	(0.0)	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	1	(4.0)
Skin and subcutaneous tissue disorders	**0**	**(0.0)**	**1**	**(16.7)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(4.8)**	**1**	**(4.0)**
Dermatitis	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	1	(4.0)

Every participant is counted a single time for each applicable row and column.
MedDRA version 24.1.

Source: [P008MK4482: adam adsl; adae]

Table 2-8
Participants With Adverse Events
(Incidence > 0% in One or More Treatment Groups)
(Part 2, All Participants as Treated)

	Placebo		MK 4482 400 mg		MK 4482 800 mg		Total MK 4482 group		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	10		15		15		30		40	
with one or more adverse events	1	(10.0)	4	(26.7)	8	(53.3)	12	(40.0)	13	(32.5)
with no adverse events	9	(90.0)	11	(73.3)	7	(46.7)	18	(60.0)	27	(67.5)
Cardiac disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(6.7)**	**1**	**(3.3)**	**1**	**(2.5)**
Postural orthostatic tachycardia syndrome	0	(0.0)	0	(0.0)	1	(6.7)	1	(3.3)	1	(2.5)
Gastrointestinal disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(6.7)**	**1**	**(3.3)**	**1**	**(2.5)**
Stomatitis	0	(0.0)	0	(0.0)	1	(6.7)	1	(3.3)	1	(2.5)
Investigations	**1**	**(10.0)**	**1**	**(6.7)**	**3**	**(20.0)**	**4**	**(13.3)**	**5**	**(12.5)**
Alanine aminotransferase increased	0	(0.0)	0	(0.0)	1	(6.7)	1	(3.3)	1	(2.5)
Amylase increased	0	(0.0)	1	(6.7)	0	(0.0)	1	(3.3)	1	(2.5)
Blood creatine phosphokinase increased	0	(0.0)	0	(0.0)	2	(13.3)	2	(6.7)	2	(5.0)
Haemoglobin decreased	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.5)
Nervous system disorders	**0**	**(0.0)**	**1**	**(6.7)**	**0**	**(0.0)**	**1**	**(3.3)**	**1**	**(2.5)**
Dizziness postural	0	(0.0)	1	(6.7)	0	(0.0)	1	(3.3)	1	(2.5)
Skin and subcutaneous tissue disorders	**0**	**(0.0)**	**0**	**(0.0)**	**5**	**(33.3)**	**5**	**(16.7)**	**5**	**(12.5)**
Dyshidrotic eczema	0	(0.0)	0	(0.0)	1	(6.7)	1	(3.3)	1	(2.5)
Eczema nummular	0	(0.0)	0	(0.0)	1	(6.7)	1	(3.3)	1	(2.5)
Toxic skin eruption	0	(0.0)	0	(0.0)	3	(20.0)	3	(10.0)	3	(7.5)
Vascular disorders	**0**	**(0.0)**	**2**	**(13.3)**	**0**	**(0.0)**	**2**	**(6.7)**	**2**	**(5.0)**

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Participants With Adverse Events
(Incidence > 0% in One or More Treatment Groups)
(Part 2, All Participants as Treated)

	Placebo		MK 4482 400 mg		MK 4482 800 mg		Total MK 4482 group		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Vascular disorders	**0**	**(0.0)**	**2**	**(13.3)**	**0**	**(0.0)**	**2**	**(6.7)**	**2**	**(5.0)**
Orthostatic hypotension	0	(0.0)	2	(13.3)	0	(0.0)	2	(6.7)	2	(5.0)

Every participant is counted a single time for each applicable row and column.
MedDRA version 24.1.

Source: [P008MK4482: adam adsl; adae]

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Pharmacokinetics:

Part 1

- Following single oral dose administration of MK-4482 final market image capsules in the fasted state to healthy Japanese male participants, NHC appeared rapidly in plasma and reached Cmax with a median Tmax between 1.00 and 2.00 hours. AUC0-inf and Cmax of plasma NHC increased approximately in a dose proportional manner across the dose levels of 200 to 1600 mg. Administration of MK-4482 final market image capsules in the fed state delayed median Tmax for NHC by 1.5 hours and reduced Cmax by 24% when compared to administration in the fasted state. However, AUC0-inf was comparable, which indicates that the rate, but not the extent, of absorption is slightly lower in the fed state [Table 2-9].

- Following single oral dose administration of MK-4482 final market image capsules in the fasted state to healthy Japanese male participants, NHC-TP PBMC concentrations reached Cmax with a median Tmax between 3.00 and 8.00 hours, and NHC-TP was eliminated with a geometric mean (GM) apparent terminal t1/2 of 13.1 to 17.9 hours. AUC and Cmax for NHC-TP in PBMC generally increased with dose following single oral dose administration of MK-4482 200 to 1600 mg in the fasted state [Table 2-10].

Part 2

- Following multiple oral dose administration of MK-4482 every 12 hours (Q12H) for 5.5 days, the GM apparent terminal t1/2 of plasma NHC was 11.5 hours and 10.2 hours after the last dose of 400 mg and 800 mg, respectively. No meaningful accumulation of NHC was observed following multiple oral dose administration of MK-4482 Q12H for 5.5 days, indicating that the terminal phase does not contribute meaningfully to accumulation after multiple dose administration [Table 2-11], [Table 2-12].

- Following multiple oral dose administration of MK-4482 Q12H for 5.5 days to healthy Japanese male participants, NHC-TP PMBC concentrations reached Cmax with a median Tmax between 3.00 and 5.00 hours, and NHC-TP was eliminated with a GM apparent terminal t1/2 of approximately 16.4 to 19.2 hours on Day 6. The GM and corresponding 90% CI for accumulation ratio (Day 6/Day 1) at 400 mg was 2.49 (2.19, 2.83) and 2.33 (1.89, 2.89) for AUC0-12 and Cmax, respectively. The GM and corresponding 90% CI for accumulation ratio (Day 6/Day 1) at 800 mg was 2.65 (2.31, 3.03) and 2.42 (1.93, 3.02) for AUC0-12 and Cmax, respectively. These results are consistent with the t1/2 of NHC-TP and Q12H dosing [Table 2-13], [Table 2-14].

Table 2-9
Summary Statistics for NHC Pharmacokinetics in Plasma Following Single Oral Dose Administration of MK-4482 in Healthy Japanese Male Participants Part 1 Per-Protocol

PK Parameter	MK 4482 200 mg	MK 4482 400 mg	MK 4482 800 mg (fasted)	MK 4482 800 mg (fed)	MK 4482 1600 mg	rMSE
N	6	6	7	6	6	
AUC0 inf (h•ng/mL)†	2280 (2000, 2600)	6410 (5550, 7410)	12400 (10900, 14200)	13700 (12000, 15800)	25300 (22200, 28900)	0.078
AUC0 last (h•ng/mL)†	2280 (1990, 2600)	6390 (5520, 7390)	12400 (10800, 14200)	13700 (11900, 15700)	25300 (22100, 28900)	0.078
AUC0 12 (h•ng/mL)†	2270 (1990, 2600)	6350 (5490, 7350)	12300 (10800, 14100)	13600 (11900, 15600)	25100 (22000, 28700)	0.079
Cmax (ng/mL)†	1240 (984, 1560)	3160 (2450, 4090)	4750 (3750, 6030)	3610 (2830, 4600)	7650 (6070, 9640)	0.113
Tmax (h)‡	1.00 (0.50, 5.00)	1.00 (1.00, 1.50)	1.50 (0.52, 2.50)	3.00 (2.00, 3.00)	2.00 (1.00, 2.00)	
t1/2 (h)§	1.28 (13.9)	8.37 (15.1)	3.95 (113.3)	3.74 (78.5)	5.50 (57.1)	

† Back transformed least squares mean and 95% confidence interval from mixed effects model performed on natural log transformed values.
‡ Median; minimum, maximum
§ Geometric mean (GM%CV)
rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effects model. rMSE*100% approximates the within subject percent CV on the raw scale.

Source: [P008MK4482: adam adpp]

Table 2-10
Summary Statistics for NHC-TP Pharmacokinetics in PBMC Following Single Oral Dose Administration of MK-4482 in Healthy Japanese Male Participants Part 1 Per-Protocol

PK Parameter	MK 4482 200 mg	MK 4482 400 mg	MK 4482 800 mg (fasted)	MK 4482 800 mg (fed)	MK 4482 1600 mg	rMSE
N	5	6	7	6	6	
AUC0 inf (h•uM)†	458 (186, 1130)	478 (339, 674)	937 (664, 1320)	1670 (1180, 2350)	1890 (1300, 2760)	0.383
AUC0 last (h•uM)†	56.5 (34.5, 92.7)	273 (174, 428)	648 (427, 985)	553 (352, 869)	1250 (795, 1960)	0.537
AUC0 12 (h•uM)†	52.9 (35.5, 78.7)	205 (143, 295)	419 (292, 603)	303 (211, 436)	785 (546, 1130)	0.431
Cmax (uM)†	10.1 (7.01, 14.7)	27.9 (19.6, 39.8)	68.2 (49.2, 94.6)	44.1 (31.3, 62.2)	88.1 (62.6, 124)	0.252
Tmax (h)‡	8.00 (3.03, 12.02)	3.00 (1.50, 5.00)	5.00 (5.00, 5.02)	4.00 (3.00, 5.03)	4.00 (3.00, 8.00)	
t1/2 (h)§	17.9 (.)	15.1 (49.5)	13.1 (25.7)	37.6 (85.6)	13.4 (14.9)	

† Back transformed least squares mean and 95% confidence interval from mixed effects model performed on natural log transformed values.

‡ Median; minimum, maximum

§ Geometric mean (GM%CV)

rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effects model. rMSE*100% approximates the within subject percent CV on the raw scale.

N 1 for AUC0 inf and t1/2 in MK 4482 200 mg. N 6 for AUC0 inf, AUC0 12 and t1/2 in MK 4482 800 mg fasted. N 5 for AUC0 inf and t1/2 in MK 4482 1600 mg.

AUC0 inf had >25% extrapolated in one participant at 200 mg (1 out of 1 participant), five participants at 400 mg (5 out of 6 participants), four participants at 800 mg fasted (4 out of 6 participant), six participants at 800 mg fed (6 out of 6 participants), and five participants at 1600 mg SD (5 out of 5 participants).

Source: [P008MK4482: adam adpp]

Table 2-11
Summary Statistics for NHC Plasma Pharmacokinetics Following Multiple Oral Dose Administration of MK-4482 Q12H for 5.5 Days in Healthy Japanese Male Participants MK-4482 400 mg
Part 2 Per-Protocol

	Day 1			Day 6			Accumulation Ratio (Day 6 /Day 1) ‖		
PK Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	rMSE
AUC0 12 (h•ng/mL)†	15	5240	(4790, 5730)	15	5410	(4950, 5920)	1.03	(0.99, 1.08)	0.067
Cmax (ng/mL)†	15	2340	(2080, 2620)	15	2320	(2070, 2600)	0.99	(0.91, 1.08)	0.140
Tmax (h)‡	15	1.50	(1.00, 2.00)	15	1.50	(1.00, 2.00)			
t1/2 (h)§				15	11.5	(18.6)			
Ctrough (ng/mL)§	15	4.53	(38.6)	15	8.60	(31.1)			

† Back transformed least squares mean and 95% confidence interval from mixed effects model performed on natural log transformed values.
‡ Median; minimum, maximum
§ Geometric mean (GM%CV)
rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effects model. rMSE*100% approximates the within subject or residual percent CV on the raw scale.
‖ Back transformed least squares mean difference and 90% confidence interval from mixed effects model performed on natural log transformed values.

Source: [P008MK4482: adam adpp]

Table 2-12
Summary Statistics for NHC Plasma Pharmacokinetics Following Multiple Oral Dose Administration of MK-4482 Q12H for 5.5 Days in Healthy Japanese Male Participants MK-4482 800 mg
Part 2 Per-Protocol

	Day 1			Day 6			Accumulation Ratio (Day 6 /Day 1) ‖		
PK Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	rMSE
AUC0 12 (h•ng/mL)†	15	12100	(11100, 13300)	13	12700	(11600, 13900)	1.05	(1.00, 1.10)	0.067
Cmax (ng/mL)†	15	5000	(4450, 5610)	13	4660	(4130, 5260)	0.93	(0.85, 1.02)	0.140
Tmax (h)‡	15	1.50	(1.00, 2.00)	13	1.50	(1.00, 2.50)			
t1/2 (h)§				13	10.2	(49.4)			
Ctrough (ng/mL)§	15	11.0	(35.9)	13	21.5	(30.8)			

† Back transformed least squares mean and 95% confidence interval from mixed effects model performed on natural log transformed values.
‡ Median; minimum, maximum
§ Geometric mean (GM%CV)
rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effects model. rMSE*100% approximates the within subject or residual percent CV on the raw scale.
‖ Back transformed least squares mean difference and 90% confidence interval from mixed effects model performed on natural log transformed values.

Source: [P008MK4482: adam adpp]

Table 2-13
Summary Statistics for NHC-TP Pharmacokinetics in PBMC Following Multiple Oral Dose Administration of MK-4482 Q12H for 5.5 Days in Healthy Japanese Male Participants MK-4482 400 mg
Part 2 Per-Protocol

	Day 1			Day 6			Accumulation Ratio (Day 6 /Day 1) ‖		
PK Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	rMSE
AUC0 12 (h•uM)†	15	156	(132, 183)	15	387	(329, 456)	2.49	(2.19, 2.83)	0.206
Cmax (uM)†	15	21.0	(16.9, 26.0)	15	48.9	(39.5, 60.6)	2.33	(1.89, 2.89)	0.342
Tmax (h)‡	15	3.00	(1.50, 5.00)	15	3.00	(0.00, 8.00)			
t1/2 (h)§				13	16.4	(42.2)			
Ctrough (uM)§	15	8.89	(26.8)	15	21.0	(30.0)			

† Back transformed least squares mean and 95% confidence interval from mixed effects model performed on natural log transformed values.
‡ Median; minimum, maximum
§ Geometric mean (GM%CV)
rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effects model. rMSE*100% approximates the within subject or residual percent CV on the raw scale.
‖ Back transformed least squares mean difference and 90% confidence interval from mixed effects model performed on natural log transformed values.

Source: [P008MK4482: adam adpp]

Table 2-14
Summary Statistics for NHC-TP Pharmacokinetics in PBMC Following Multiple Oral Dose Administration of MK-4482 Q12H for 5.5 Days in Healthy Japanese Male Participants MK-4482 800 mg
Part 2 Per-Protocol

	Day 1			Day 6			Accumulation Ratio (Day 6 /Day 1) ‖		
PK Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	rMSE
AUC0 12 (h•uM)†	15	364	(309, 429)	13	964	(812, 1140)	2.65	(2.31, 3.03)	0.206
Cmax (uM)†	15	48.4	(39.1, 59.9)	13	117	(93.1, 147)	2.42	(1.93, 3.02)	0.342
Tmax (h)‡	15	3.00	(1.50, 5.00)	13	5.00	(1.50, 8.00)			
t1/2 (h)§				12	19.2	(28.4)			
Ctrough (uM)§	15	22.1	(34.2)	13	66.2	(38.4)			

† Back transformed least squares mean and 95% confidence interval from mixed effects model performed on natural log transformed values.
‡ Median; minimum, maximum
§ Geometric mean (GM%CV)
rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effects model. rMSE*100% approximates the within subject or residual percent CV on the raw scale.
‖ Back transformed least squares mean difference and 90% confidence interval from mixed effects model performed on natural log transformed values.

Source: [P008MK4482: adam adpp]

CONCLUSIONS:

Safety

Based on the results from this study, the following safety conclusions can be made:

- Single doses of MK-4482 up to 1600 mg were generally well tolerated in healthy Japanese male adult participants.
- Multiple doses of MK-4482 400 mg and 800 mg Q12H for 5.5 days were generally well tolerated in healthy Japanese male adult participants.

Pharmacokinetics

Based on the results from this study, the following PK conclusions for NHC in plasma can be made:

- NHC appeared rapidly in plasma following administration with MK-4482 final market image capsules in the fasted state, with median Tmax between 1.00 and 2.00 hours.
- Administration of MK-4482 final market image capsules at a dose level of 800 mg in the fed state delayed median Tmax for NHC by 1.5 hours and reduced Cmax by 24% when compared to administration in the fasted state. However, AUC0-inf was comparable, which indicates that the rate, but not the extent, of absorption is slightly lower in the fed state.
- AUC0-inf and Cmax of plasma NHC increased approximately in a dose proportional manner following single oral dose administration of MK-4482 200 to 1600 mg in the fasted state to healthy Japanese male participants.
- No meaningful accumulation of NHC was observed following administration of multiple oral doses of MK-4482 400 mg and 800 mg Q12H for 5.5 days.

The following key PK results for NHC-TP in PBMC were also observed:

- Following single oral dose administration of MK-4482 final market image capsules in the fasted state to healthy Japanese male participants, NHC-TP PBMC concentrations reached Cmax with a median Tmax between 3.00 and 8.00 hours, and NHC-TP was eliminated with a GM apparent terminal t1/2 of 13.1 to 17.9 hours.
- AUC and Cmax for NHC-TP in PBMC generally increased with dose following single oral dose administration of MK-4482 200 to 1600 mg in the fasted state.
- The GM and corresponding 90% CI for accumulation ratio (Day 6/Day 1) at 800 mg was 2.65 (2.31, 3.03) and 2.42 (1.93, 3.02) for AUC0-12 and Cmax, respectively, consistent with t1/2 of NHC-TP and Q12H dosing.

PUBLICATION: As of the date of this report, there are no publications based on this study.

REPORT DATE: [redacted]-[redacted]-20[redacted]

2 SYNOPSIS

SPONSOR: Merck, Sharp & Dohme Corp., Whitehouse Station, NJ USA (MSD)

COMPOUND NAME: Molnupiravir (MK-4482)

PROTOCOL TITLE: A Multiple Ascending Dose Clinical Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Molnupiravir in Healthy Participants

STUDY IDENTIFIERS:

IND: N/A	EudraCT: 2021-000860-30

STUDY PHASE: Phase 1

INDICATION: Treatment or prevention of COVID-19

STUDY CENTERS: This study was conducted at 1 center in 1 country.

STUDY STATUS: This study is complete.

First Patient, First Visit	Last Patient, Last Visit	Database Lock Date
[redacted]	[redacted]	[redacted]

NOTE: Patient = Participant

METHODOLOGY:

This was a randomized, placebo-controlled, multiple-ascending dose, double-blind study of molnupiravir (MOV; MK-4482; formerly EIDD-2801) in healthy participants.

A total of 32 participants (4 panels of 8 participants each) were randomized in a 3:1 ratio to receive oral doses of MOV or placebo every 12 hours (Q12H) for 10.5 days. Doses of MOV 400 mg, 600 mg, and 800 mg (Panels A, B, and C, respectively) or placebo were administered. Blood samples for pharmacokinetic (PK) evaluation were collected and safety was evaluated. Panel A initiated; review of available safety data (eg, vital signs, electrocardiograms [ECG], labs, and adverse events [AEs]) was conducted prior to escalation to the next panels. Following the completion of Panel C, Panel D was enrolled, assessing the dose of MOV 800 mg Q12H for 10.5 days, expanding the number of subjects at the 800-mg dose level. A poststudy follow up visit was conducted approximately 14 days after the last dose of study intervention.

Intervention	Unit Dose and Frequency	Route of Administration
MK-4482 (MOV; Panel A)	400 mg Q12H for 10.5 days	Oral
MK-4482 (MOV; Panel B)	600 mg Q12H for 10.5 days	Oral
MK-4482 (MOV; Panels C and D)	800 mg Q12H for 10.5 days	Oral
Placebo	0 mg Q12H for 10.5 days	Oral

MOV=molnupiravir; Q12H=every 12 hours

This study was conducted during the COVID-19 pandemic. The Sponsor continued to follow its Standard Operating Procedures for study conduct, monitoring, and oversight during the pandemic and employed a risk-based approach to assess and mitigate impact on study conduct.

ELIGIBILITY CRITERIA: Healthy male or female participants of 25 to 60 years of age (inclusive) with a body mass index of 18 to 35 kg/m^2, inclusive, who were considered skeletally mature.

OBJECTIVES AND ENDPOINTS:

Primary Objective	Primary Endpoints
To evaluate the safety and tolerability of multiple oral dosing of molnupiravir in healthy participants Q12H for 10.5 days	Adverse events, vital signs (temperature, heart rate, blood pressure, respiratory rate), electrocardiogram, laboratory safety tests (serum chemistry, hematology, and urinalysis)
Secondary Objective	**Secondary Endpoints**
To evaluate the plasma pharmacokinetics of N-hydroxycytidine (the nucleoside metabolite) following multiple oral dose administration of molnupiravir	Cmax, Tmax, t1/2, AUC0-12hr, AUC0-last, AUC0-inf, Ctrough and accumulation ratio on Cmax and AUC0-12hr
Tertiary/Exploratory Objective	**Tertiary Endpoints**
To evaluate the peripheral blood mononuclear cell pharmacokinetics of N-hydroxycytidine-triphosphate (the pharmacologically active triphosphate form) following multiple oral dose administration of molnupiravir	NHC-TP concentration at sampling times

NUMBER OF PARTICIPANTS (planned and analyzed): The planned enrollment total was 32 participants. As of database lock for this report, 32 participants were randomized. All 32 participants (8 in each panel) were included in the safety analyses and all 24 participants who received MOV were included in the PK analyses (6 in each panel).

STATISTICAL METHODS:

Safety: Summary statistics and plots were generated for raw laboratory safety tests, ECGs, and vital signs as well as for change from baseline, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline was computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline).

Model-Based Pharmacokinetic Summary: PK parameter values of N-hydroxycytidine (NHC) maximum concentration (Cmax), area under the concentration-time curve from time 0 to 12 hours (AUC0-12) and AUC to the last quantifiable concentration (AUC0-last) were natural log transformed and evaluated with separate linear mixed effects models containing a fixed effect for treatment, day (Day 1, Day 11), and treatment by day interaction and a random effect for participant. Ninety-five percent confidence intervals (CIs) for the least-squares means (LSMs) by treatment and day were constructed on the natural log scale and referenced the t-distribution. Exponentiating the LSMs and lower and upper limits of these CIs yielded estimates for the population geometric means and CIs about the geometric means on the original scale for each treatment and day. Similarly, the LSM differences (Day 11 Day 1) and 90% CIs from this model were back-transformed to obtain the geometric mean accumulation ratio (Day 11/Day 1) and 90% CI for Cmax and AUC0-12.

PK parameter values of NHC AUC extrapolated to infinity ([AUC0-inf], following last dose only) were natural log transformed and evaluated with a linear mixed effects models containing a fixed effect for treatment and a random effect for participant.
Ninety-five percent CIs for the LSMs by treatment were constructed on the natural log scale and referenced the t-distribution. Exponentiating the LSMs and lower and upper limits of these CIs yielded estimates for the population geometric means and CIs about the geometric means on the original scale for each treatment.

The same analyses were performed for NHC-TP in PBMCs as a post-hoc analysis. In addition, dose proportionality of AUC0-12 and Cmax for both analytes was assessed in a post-hoc analysis.

RESULTS:

Participant Disposition: 32 randomized (24 MOV and 8 placebo), 32 treated, 32 completed treatment, 32 completed study.

Demographics and Baseline Characteristics:

- **Overall Median Age (range):** 45.0 years (27 to 59 years)
- **Sex:** 16 (50.0 %) male, 16 (50.0 %) female
- **Ethnicity:** 32 (100.0 %) not Hispanic or Latino
- **Race:** 32 (100.0 %) white

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Safety:

- Overall, 27 participants (84.4%) reported at least 1 AE; 21 participants (87.5%) receiving MOV, with a comparable frequency across doses, and 6 participants (75.0%) receiving placebo.
- There were no serious AEs, deaths, discontinuations due to AEs, or events of clinical interest.
- No action regarding study intervention was taken and all but 3 AEs resolved at the end of the study.
- The most frequently reported AEs (≥2 participants) following MOV administration were headache (10 participants, 41.7%), malaise (4 participants, 16.7%), nausea, vomiting, fatigue, puncture site hematoma, myalgia, dizziness, presyncope and skin irritation (2 participants each, 8.3%). Of these events, headache (5 events in 1 participant) and dizziness (2 events in 1 participant) were considered by the investigator to be related to study intervention.
- The most frequently reported AEs (≥2 participants) following placebo administration were headache and skin irritation (2 participants each, 25.0%).
- All AEs were categorized as mild or moderate in severity.
- No clinically meaningful dose-related findings in laboratory assessments, vital signs, or ECGs were observed.

Adverse Event Summary

	MK 4482 400 mg		MK 4482 600 mg		MK 4482 800 mg		MK 4482 Total		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	6		6		12		24		8		32	
with one or more adverse events	5	(83.3)	6	(100.0)	10	(83.3)	21	(87.5)	6	(75.0)	27	(84.4)
with no adverse event	1	(16.7)	0	(0.0)	2	(16.7)	3	(12.5)	2	(25.0)	5	(15.6)
with drug related[a] adverse events	0	(0.0)	1	(16.7)	1	(8.3)	2	(8.3)	0	(0.0)	2	(6.3)
with serious adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
with serious drug related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a drug related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Adverse Event Summary

	MK 4482 400 mg		MK 4482 600 mg		MK 4482 800 mg		MK 4482 Total		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
discontinued drug due to a serious drug related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the drug.
The MK 4482 800 mg column was pooled across Panel C and D.
The MK 4482 Total column was pooled across all panels.
The Placebo column was pooled across all panels.
Adverse event terms are from MedDRA Version 24.0

Source: [P012MK4482: adam adsl; adae]

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Pharmacokinetics:

Following multiple-dose administration of MOV, plasma NHC concentrations were detectable at the first measured timepoint, 0.5 hour, with a median time to Cmax (Tmax) ranging from 1.50 to 1.98 hours after the first dose and 1.50 to 1.75 hours after the last dose (on Day 11). NHC concentrations was detectable up to 72 hours (the last measured plasma concentration) following the last dose on Day 11.

Biphasic elimination of NHC was apparent after this last dose, where it exhibited a rapid distributional phase followed by an extended terminal elimination phase. The geometric mean apparent terminal half-life (t1/2) on Day 11 ranged from 16.41 to 20.65 hours over the dose range of 400 to 800 mg. Minimal to no accumulation of NHC exposure, in terms of AUC0-12 and Cmax, was observed.

Dose-proportionality analysis demonstrated that AUC0-12 and Cmax increased in a dose-proportional fashion over the dose range studied.

Summary Statistics of Plasma NHC Pharmacokinetics Following Administration of Multiple Oral Doses (Q12H for 10.5 Days) of 400 mg to 800 mg MOV to Healthy Participants

Pharmacokinetic Parameters	400 mg N 6	600 mg N 6	800 mg N 12
Day 1 (First Dose)			
AUC0 12 (h*nmol/L)[a]	18000 (14200, 22900)	26700 (21000, 33900)	38100 (32200, 45200)
AUC0 last (h*nmol/L)[a]	18000 (14200, 22900)	26700 (21000, 33900)	38100 (32200, 45200)
Cmax (nmol/L)[a]	8320 (6150, 11300)	11000 (8120, 14900)	14000 (11300, 17300)
Tmax (hr)[b]	1.50 (0.50, 1.55)	1.50 (1.50, 2.00)	1.98 (1.50, 4.00)
Day 11 (Last Dose)			
AUC0 inf (h*nmol/L)[a]	20500 (16300, 25700)	27300 (21800, 34300)	45500 (38700, 53500)
AUC0 12 (h*nmol/L)[a]	19700 (15500, 25000)	26100 (20500, 33200)	43900 (37000, 52000)
AUC0 last (h*nmol/L)[a]	20300 (16000, 25800)	27100 (21300, 34500)	45300 (38200, 53600)
Cmax (nmol/L)[a]	8400 (6210, 11400)	8920 (6600, 12100)	16200 (13100, 20100)
Tmax (hr)[b]	1.50 (0.57, 2.00)	1.75 (1.50, 2.00)	1.50 (1.50, 2.02)
Apparent t1/2 (hr)[c]	16.41 (117.05)	20.65 (22.67)	20.64 (10.99)
Accumulation Ratio: Day 11 / Day 1			
AUC0 12 (h*nmol/L)[d]	1.09 (0.97, 1.23)	0.98 (0.87, 1.10)	1.15 (1.06, 1.25)
Cmax (nmol/L)[d]	1.01 (0.81, 1.26)	0.81 (0.65, 1.02)	1.16 (0.99, 1.36)

NHC N hydroxycytidine
Q12H Every 12 hours
MOV Molnupiravir
[a] Back transformed least squares mean and 95% confidence interval from linear mixed effects model performed on natural log transformed values.
[b] Median (min, max) reported for Tmax (hr).
[c] Geometric mean and percent geometric CV reported for Apparent t1/2 (hr).
[d] Back transformed least squares mean difference and 90% confidence interval from linear mixed effects model performed on natural log transformed values.
Square root of conditional mean squared error (residual error) from the linear mixed effect model 0.268 for AUC0 inf (h*nmol/L), 0.116 for AUC0 12 (h*nmol/L), 0.115 for AUC0 last (h*nmol/L), 0.227 for Cmax (nmol/L). When multiplied by 100, provides estimate of the pooled within subject coefficient of variation.
Single AM dose was administered on Day11.

Source: [P012MK4482: adam adpp]

NHC triphosphate (NHC-TP) concentrations measured in peripheral blood mononuclear cells (PBMCs) were detectable at the first measured timepoint, 4 hours, with a median Tmax ranging from 4.00 to 8.06 hours after the first dose (Day 1) and from 4.00 to 8.00 hours after the last dose (Day 11). NHC-TP concentrations were detectable up to 24 hours (the last measured PBMC concentration) following the last dose on Day 11 in all but 2 MOV treated participants from the 800 mg dose group.

The geometric mean apparent t1/2 on Day 11 ranged from 13.60 to 18.04 hours over the dose range of 400 to 800 mg. The LSM accumulation ratio of AUC0-12 and Cmax ranged from 2.10 to 2.65 and 1.92 to 2.49, respectively.

Dose-proportionality analysis demonstrated that AUC0-12 and Cmax increased in a less than dose-proportional fashion over the dose range studied.

Overall exposures, in terms of AUC0-12 of NHC-TP in PBMCs, correlated well with NHC exposure in plasma.

Summary Statistics of PBMC NHC-TP Pharmacokinetics Following Administration of Multiple Oral Doses (Q12H for 10.5 Days) of 400 mg to 800 mg MOV to Healthy Participants

Pharmacokinetic Parameters	400 mg N 6	600 mg N 6	800 mg N 12
Day 1 (First Dose)			
AUC0 12 (h*nmol/L)[a]	88400 (69100, 113000)	139000 (109000, 178000)	144000 (120000, 172000)
AUC0 last (h*nmol/L)[a]	88400 (68100, 115000)	139000 (107000, 181000)	148000 (123000, 178000)
Cmax (nmol/L)[a]	10500 (7920, 13800)	16700 (12700, 22000)	17100 (14000, 20800)
Tmax (hr)[b]	8.06 (4.00, 12.00)	4.00 (4.00, 4.00)	4.00 (3.98, 8.15)
Day 11 (Last Dose)			
AUC0 inf (h*nmol/L)[a]	334000 (158000, 707000)	651000 (466000, 909000)	978000 (751000, 1270000)
AUC0 12 (h*nmol/L)[a]	234000 (183000, 299000)	292000 (229000, 374000)	354000 (298000, 421000)
AUC0 last (h*nmol/L)[a]	356000 (274000, 461000)	459000 (353000, 595000)	532000 (442000, 640000)
Cmax (nmol/L)[a]	26000 (19700, 34300)	32100 (24300, 42300)	38500 (31700, 46900)
Tmax (hr)[b]	8.00 (3.92, 8.03)	4.00 (4.00, 12.03)	4.00 (0.00, 8.08)
Apparent t1/2 (hr)[c]	13.60 (.)	14.06 (28.52)	18.04 (46.49)
Accumulation Ratio: Day 11 / Day 1			
AUC0 12 (h*nmol/L)[d]	2.65 (2.29, 3.07)	2.10 (1.81, 2.44)	2.46 (2.20, 2.76)
Cmax (nmol/L)[d]	2.49 (2.05, 3.02)	1.92 (1.58, 2.33)	2.26 (1.97, 2.59)

NHC N hydroxycytidine
Q12H Every 12 hours
MOV Molnupiravir
[a] Back transformed least squares mean and 95% confidence interval from linear mixed effects model performed on natural log transformed values.
[b] Median (min, max) reported for Tmax (hr).
[c] Geometric mean and percent geometric CV reported for Apparent t1/2 (hr).
[d] Back transformed least squares mean difference and 90% confidence interval from linear mixed effects model performed on natural log transformed values.
Square root of conditional mean squared error (residual error) from the linear mixed effect model 0.322 for AUC0 inf (h*nmol/L), 0.149 for AUC0 12 (h*nmol/L), 0.157 for AUC0 last (h*nmol/L), 0.193 for Cmax (nmol/L). When multiplied by 100, provides estimate of the pooled within subject coefficient of variation.
Single AM dose was administered on Day11.

Source: [P012MK4482: adam adpp]

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CONCLUSIONS:

Safety

- The following key safety results were observed:
- Daily Q12H doses of 400, 600, and 800 mg MOV for 10.5 days were generally well tolerated in healthy adult study participants.
- No clinically meaningful dose-related findings in laboratory assessments, including hematology laboratory parameters, vital signs, or ECGs were observed following administration of MOV Q12H for 10.5 days.

Pharmacokinetics

The following key PK results were observed:

NHC in Plasma

- A biphasic elimination of NHC was apparent after the last dose on Day 11, where it exhibited a rapid distributional phase followed by an extended terminal elimination phase. The geometric mean apparent terminal t1/2 on Day 11 was estimated to be 16.41 to 20.65 hours over the dose range of 400 to 800 mg.
- NHC AUC0-12 and Cmax increased in a dose proportional manner over the dose range of 400 to 800 mg at steady state.

NHC-TP in PBMCs

- The median Tmax of NHC-TP in PBMCs was 4.00 to 8.06 hours. The geometric mean apparent terminal elimination t1/2 of NHC-TP was estimated to be 13.60 to 18.04 hours across the dose range explored, with a t1/2 of 18.04 hours at the 800-mg dose.
- The LSM accumulation ratio of NHC-TP in PBMCs AUC0-12 and Cmax on Day 11 compared to Day 1 ranged from 2.10 to 2.65 and 1.92 to 2.49, respectively.
- NHC-TP AUC0-12 and Cmax on Day 11 increased in a less than dose-proportional manner over the dose range of 400 to 800 mg.
- Overall exposures of NHC-TP in PBMCs correlated well with NHC exposure in plasma.

PUBLICATIONS: As of the date of this report, there are no publications based on this study.

REPORT DATE: [redacted]-[redacted]-20[redacted]

SPONSOR: Merck, Sharp & Dohme Corp., Whitehouse Station, NJ USA (MSD)

COMPOUND NAME: Molnupiravir (MOV; MK-4482)

PROTOCOL TITLE: A Phase 2/3, Randomized, Placebo-Controlled, Double-Blind Clinical Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MK-4482 in Non-Hospitalized Adults with COVID-19

In this section, the analysis results of the Japanese sub-population in the Phase 3 part of this study are described. Other study information is same as 4482-P002V03.

RESULTS in Japanese sub-population:

Participant Disposition (All Randomized Participants):

- A total of 8 non-hospitalized Japanese participants with COVID-19 were randomized into 2 treatment groups. Five participants received MOV 800 mg and 2 participants received placebo. One participant in the placebo group randomized by mistake (error) and was not treated with study medication.

- Three participants in the MOV group and 2 participants in the placebo group completed study medication. Two participants in the MOV group discontinued the study medication. One discontinued due to an adverse event (Hypoxia) and the other discontinued due to withdrawal by the subject.

- Four participants in the MOV group and 2 participants in the placebo group completed follow-up through Day 29.

Disposition of Participants
All Randomized Participants, Japanese Subgroup
MK-4482-002 Part 2 Day 29 DBL

	MK-4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	5		3		8	
Status for Study Medication						
Started	5		2		7	
Completed	3	(60.0)	2	(100.0)	5	(71.4)
Discontinued	2	(40.0)	0	(0.0)	2	(28.6)
Adverse Event	1	(20.0)	0	(0.0)	1	(14.3)
Withdrawal By Subject	1	(20.0)	0	(0.0)	1	(14.3)
Status for Day 29 Milestone[a]						
Started	5		2		7	
Completed	4	(80.0)	2	(100.0)	6	(85.7)
Discontinued	1	(20.0)	0	(0.0)	1	(14.3)
Withdrawal By Subject	1	(20.0)	0	(0.0)	1	(14.3)
Status for Trial Through LFU						
Discontinued	1	(20.0)	1	(33.3)	2	(25.0)
Randomized By Mistake Without Study Treatment	0	(0.0)	1	(33.3)	1	(12.5)
Withdrawal By Subject	1	(20.0)	0	(0.0)	1	(12.5)
Status Not Recorded	4	(80.0)	2	(66.7)	6	(75.0)

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

Source: [P002V03MK4482: adam-adsl]

Demographics and Baseline Characteristics (All Randomized Participants, Japanese Subgroup):

- Median age was 63.0 years (25 to 73 years) and 31.0 years (29 to 61 years) in the MOV group and placebo group, respectively.
- One participant in the MOV group was female and others were males.

Participant Characteristics
All Randomized Participants, Japanese Subgroup
MK-4482-002 Part 2 Day 29 DBL

	MK-4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	5		3		8	
Sex						
Male	4	(80.0)	3	(100.0)	7	(87.5)
Female	1	(20.0)	0	(0.0)	1	(12.5)
Age (years)						
18 to 49	1	(20.0)	2	(66.7)	3	(37.5)
50 to 64	2	(40.0)	1	(33.3)	3	(37.5)
65 to 74	2	(40.0)	0	(0.0)	2	(25.0)
≤60	1	(20.0)	2	(66.7)	3	(37.5)
>60	4	(80.0)	1	(33.3)	5	(62.5)
Participants with data	5		3		8	
Mean	58.4		40.3		51.6	
SD	19.3		17.9		19.8	
Median	63.0		31.0		61.0	
Range	25 to 73		29 to 61		25 to 73	
Race						
Asian	5	(100.0)	3	(100.0)	8	(100.0)
Ethnicity						
Not Hispanic Or Latino	5	(100.0)	3	(100.0)	8	(100.0)
Region						
Asia Pacific	5	(100.0)	3	(100.0)	8	(100.0)
Time from Symptom Onset to Randomization						
≤3 Days	1	(20.0)	1	(33.3)	2	(25.0)
>3 Days	4	(80.0)	1	(33.3)	5	(62.5)

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Participant Characteristics
All Randomized Participants, Japanese Subgroup
MK-4482-002 Part 2 Day 29 DBL

	MK-4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Unknown[a]	0	(0.0)	1	(33.3)	1	(12.5)
Participants with data	5		2		7	
Mean	4.0		3.5		3.9	
SD	0.7		0.7		0.7	
Median	4.0		3.5		4.0	
Range	3 to 5		3 to 4		3 to 5	
Risk Factors for Severe Illness from COVID-19						
At least one risk factor	5	(100.0)	2	(66.7)	7	(87.5)
Age >60 years	4	(80.0)	1	(33.3)	5	(62.5)
Obesity (BMI ≥ 30)	1	(20.0)	1	(33.3)	2	(25.0)
Diabetes Mellitus	2	(40.0)	0	(0.0)	2	(25.0)
Baseline COVID Severity						
Mild	1	(20.0)	0	(0.0)	1	(12.5)
Moderate	4	(80.0)	2	(66.7)	6	(75.0)
Unknown[a]	0	(0.0)	1	(33.3)	1	(12.5)
Stratification Factor at Randomization Collected via IRT: Time from Symptom Onset to Randomization						
≤3 Days	1	(20.0)	1	(33.3)	2	(25.0)
>3 Days	4	(80.0)	2	(66.7)	6	(75.0)
SARS-CoV-2 RNA at Baseline in Nasopharyngeal Sample (Qualitative Assay)						
Detectable	5	(100.0)	2	(66.7)	7	(87.5)
Unknown[a]	0	(0.0)	1	(33.3)	1	(12.5)
SARS-CoV-2 Baseline Antibody						
Negative	5	(100.0)	2	(66.7)	7	(87.5)
Unknown[a]	0	(0.0)	1	(33.3)	1	(12.5)
SARS Qual Assay Viral Load at Baseline						
high VL [>10^6 copies/mL]	4	(80.0)	2	(66.7)	6	(75.0)

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Participant Characteristics
All Randomized Participants, Japanese Subgroup
MK-4482-002 Part 2 Day 29 DBL

	MK-4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Unknown[a]	1	(20.0)	1	(33.3)	2	(25.0)
[a] Missing data, invalid sample, tests not done, or results reported as "Unknown" are categorized as Unknown.						

Source: [P002V03MK4482: adam-adsl]

Efficacy (All Randomized Participants, Japanese Subgroup):

Evaluation of efficacy in Japanese participants was based on all-cause hospitalization or death (primary endpoint). Efficacy analyses were based on the MITT population, which included all randomized participants who received at least 1 dose of study intervention and were not hospitalized prior to administration of the first dose of study intervention. Seven Japanese participants (5 in the MOV group and 2 in the placebo group) were included in the efficacy analysis.

Primary Efficacy Endpoint – Hospitalization or Death Through Day 29

- One participant in the MOV group was hospitalized by Day 29. The participant was 6[redacted] years old and had diabetes mellitus as a specific co-morbidity. The COVID-19 severity at baseline was moderate. The participant was hospitalized on Day 6 because of transient hypoxia. This participant discontinued the study due to hypoxia, as described in Participant Disposition. Although oxygen therapy was not required, the participant was hospitalized because of available capacity for hospital beds, and monitored respiratory status. The participant was medically ready for discharge at the discretion of the investigator on Day 7 and discharged from the site due to the resolution of symptom on Day 8. No participant in the placebo group was hospitalized.

- No death was reported in both intervention groups.

Summary of Hospitalization or Death Through Day 29
Modified Intent-To-Treat Population, Japanese Subgroup
MK-4482-002 Part 2 Day 29 DBL

	MK-4482 800 mg		Placebo	
	n	(%)	n	(%)
Participants in population	5		2	
Hospitalization or Death	1	(20.0)	0	(0.0)
Hospitalization	1	(20.0)	0	(0.0)
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; adeff1]

Safety (All Randomized Participants, Japanese Subgroup):

Overall, in Japanese participants, no specific safety findings associated with MOV 800 mg Q12H treatment were observed.

- Two adverse events (hypoxia and vessel puncture site haemorrhage) in the MOV group and 1 adverse event (blood sodium decreased) in the placebo group were reported and all adverse events were considered not-related to study intervention as determined by the investigator.
- Hypoxia occurred in the MOV group was considered a serious adverse event due to hospitalization. The participant discontinued the study intervention due to the adverse event after the ninth dose. Hypoxia occurred prior to the last dose of study medication on Day 6 and recovered on Day 8.
- No participant had laboratory values that met the predefined event of clinical interest criteria for potential drug-induced liver injury.
- No evidence of hematologic or hepatic toxicity was observed in the MOV group.

Adverse Event Summary
During Treatment and 14-Day Follow-Up Period
All Participants as Treated Population, Japanese Subgroup
MK-4482-002 Part 2 Day 29 DBL

	MK-4482 800 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	5		2		7	
with one or more adverse events	2	(40.0)	1	(50.0)	3	(42.9)
with no adverse event	3	(60.0)	1	(50.0)	4	(57.1)
with drug-related[a] adverse events	0	(0.0)	0	(0.0)	0	(0.0)
with serious adverse events	1	(20.0)	0	(0.0)	1	(14.3)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	1	(20.0)	0	(0.0)	1	(14.3)
discontinued drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	1	(20.0)	0	(0.0)	1	(14.3)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the drug.

Source: [P002V03MK4482: adam-adsl; adae]

CONCLUSIONS:

Based on the results, the following conclusions may be made in non-hospitalized Japanese participants with mild or moderate laboratory-confirmed COVID-19:

- While the small number of Japanese participants limits comparison of safety and efficacy with the overall population, there are no notable differences between the results of the Japanese participants and those of the overall population.