2 SYNOPSIS

Abbreviations are defined in the list of abbreviations located at the end of the Synopsis.

SPONSOR: Merck Sharp & Dohme LLC, Rahway, NJ, USA (hereafter called the Sponsor or MSD)

COMPOUND NAME: molnupiravir (MK-4482)

PROTOCOL TITLE: An Open-Label, Single-Dose Clinical Study to Evaluate the Pharmacokinetics of Molnupiravir (MK-4482) in Participants with Moderate Hepatic Impairment

The following terms may be used interchangeably in this report:

- Participant and subject
- Intervention and treatment and medication and drug.
- Study and trial

STUDY IDENTIFIERS:

IND: 147734	EudraCT: Not applicable	WHO: Not applicable	NCT: NCT05386589
jRCT: Not applicable	UTN: Not applicable	EU CT: Not applicable	

STUDY PHASE: Phase 1

INDICATION: COVID-19 treatment

STUDY CENTERS: This study was conducted at 3 centers in 1 country.

STUDY STATUS: This study is complete.

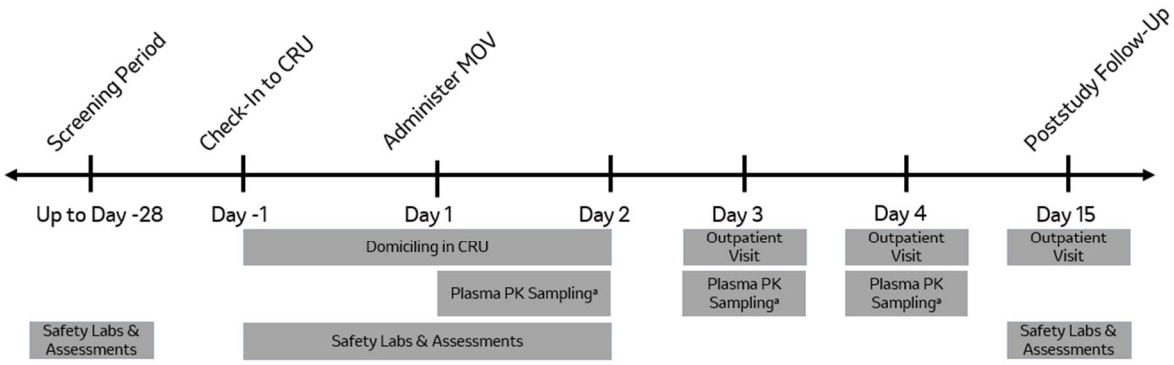
First Participant, First Visit	Last Participant, Last Visit	Database Lock Date
14-JUN-2022	05-JAN-2023	20-APR-2023

METHODOLOGY:

This study was a nonrandomized, multiple-site, open-label, single-dose study to compare the PK of MOV (molnupiravir) in moderate HI (based on the CP classification) (Panel A; n=7) and heathy adult participants (Panel B; n=7). The healthy participant's demographics (ie, age, BMI and male: female sex ratio) were matched to the demographics of moderate HI participants.

On Day 1, participants received a single oral dose of 800 mg (4 x 200 mg capsules) MOV, followed by PK sampling until 72-hours postdose. Participants returned approximately 14 days postdose for a poststudy visit. Safety was monitored throughout the study by repeated clinical and laboratory evaluations including monitoring for AEs, vital signs, 12-lead electrocardiogram, blood chemistry, hematology, and urinalysis [Figure 1].

Figure 1
Study schema



[a]Plasma pharmacokinetic (PK) samples were collected at the timepoints listed in the Schedule of Activities in the protocol. Study schema includes the same set-up for participants with moderate hepatic impairment and healthy-matched controls. There was ± 2-day window for the poststudy follow-up visit.

CRU = clinical research unit; MOV = Molnupiravir.

Participants with chronic, stable HI with features of cirrhosis due to any etiology were enrolled; the CP scale was used to classify the severity of liver disease (CP scores of 5 to 6, 7 to 9, and 10 to 15 are considered mild, moderate, and severe HI respectively). Participants with a CP score of 7 to 9, corresponding to moderate HI, were selected for enrollment.

Because this was a Phase 1 assessment of MOV in humans, the PK, pharmacodynamic, and safety profiles of the compound were still being elucidated at the time of conduct. This protocol was therefore written with flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies.

Arm Name	Intervention Name	Unit Dose Strength	Dosage Level	Route of Administration	Regimen	Use
Moderate HI	MK-4482 (MOV)	200 mg	800 mg	Oral	Panel A single dose	Test Product
Healthy Matched	MK-4482 (MOV)	200 mg	800 mg	Oral	Panel B single dose	Test Product

HI = Hepatic impairment; MOV = Molnupiravir.

This study was conducted during the COVID-19 pandemic. There were no changes in the planned conduct of the study implemented by protocol amendment as a result of the COVID-19 pandemic.

No contingency measures were implemented to manage study conduct because of the pandemic.

ELIGIBILITY CRITERIA:

Male and female participants with moderate HI (CP score of 7 to 9) and healthy mean matched participants between the ages of 18 and 75 years with BMI ≥18.5 and ≤35 kg/m^2 were enrolled in the study. At least 2 of the moderate HI participants were to have a score of 2 or higher on at least 1 of the following laboratory parameters (ie, albumin, bilirubin, or INR) on the CP scale at screening.

The individual age and BMI of the healthy participants were within the range ±10 years and ±3.5 kg/m^2 of the mean values for the participants with moderate HI, respectively. In addition, the numbers of males and females of the healthy participants were matched to the numbers of HI participants within ± 1 participant.

OBJECTIVES AND ENDPOINTS:

Primary Objective	Primary Endpoint
To evaluate the plasma pharmacokinetics of N-hydroxycytidine, the nucleoside metabolite of molnupiravir, after a single-oral dose of 800-mg of molnupiravir in participants with moderate hepatic impairment compared to healthy mean matched control participants. - Hypothesis: In participants with moderate hepatic impairment, the geometric mean AUC0-inf of N-hydroxycytidine is similar to that observed in the healthy mean matched control participants following a single dose of 800-mg molnupiravir; that is, the true AUC0-inf geometric mean ratio (moderate hepatic impairment/healthy control) is less than 2.0. - Estimation: In participants with moderate hepatic impairment, plasma pharmacokinetics (Cmax) of N-hydroxycytidine following a single 800-mg molnupiravir dose will be estimated and compared to those observed in healthy mean matched control participants.	AUC0-inf and Cmax of plasma N-hydroxycytidine
Secondary Objectives	**Secondary Endpoints**
To evaluate the safety and tolerability of molnupiravir in participants with moderate hepatic impairment.	Adverse events

NUMBER OF PARTICIPANTS (planned and analyzed): The planned enrollment total was 14 to 17 participants. As of the database lock, 14 participants were allocated, and all were included in the analysis.

STATISTICAL AND ANALYSIS METHODS:

Pharmacokinetics:

Individual values of plasma NHC AUC0-inf after a single-dose administration of 800-mg MOV to participants with moderate HI and healthy mean matched control participants were natural log-transformed and evaluated with a linear fixed effects model containing a fixed effect for population (participants with moderate HI and healthy matched control

participants). To address the primary hypothesis of comparing participants with moderate HI to healthy control participants, the 90% CI for the true GMR (moderate HI/healthy control) for NHC AUC0-inf was constructed. If the 90% CI falls below 2.0, then the hypothesis that in participants with moderate HI, the AUC0-inf of plasma NHC is similar to that observed in the healthy mean matched control participants following a single dose of 800 mg would be supported.

Plasma Cmax of NHC after a single dose of 800-mg MOV to participants with moderate HI and healthy mean matched control participants was estimated via a similar model.

Safety:

For all participants, the safety and tolerability of MOV was monitored by clinical assessment of adverse experiences and other safety measurements (eg, labs, vital signs, ECGs).

No changes were made to the planned analysis of the study.

RESULTS:

Participant Disposition:

All 14 participants completed the study: 7 participants with moderate HI and 7 healthy control participants. All participants received study intervention as scheduled per protocol. The subject disposition is summarized in [Table 1].

Demographics and Baseline Characteristics:

Seven (7) participants with moderate HI (CP score of 7 to 9) were enrolled. The majority were male (57.1%) and white (78.6%). The 7 healthy control participants were matched to the mean age, BMI, and male:female ratio demographic variables of the moderate HI group as per protocol.

The mean eGFR was 106.4 mL/min/1.73 m^2 for the moderate HI group and 104.2 mL/min/1.73 m^2 for the healthy participants [Table 2].

Table 1
Disposition of Participants

	Moderate Hepatic Impairment Participants		Healthy Participants		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	7		7		14	
Subject Study Medication Disposition						
Started	7		7		14	
Completed	7	(100.0)	7	(100.0)	14	(100.0)
Study Disposition						
Completed	7	(100.0)	7	(100.0)	14	(100.0)
Each subject is counted once for Trial Disposition, Subject Study Medication Disposition based on the latest corresponding disposition record.						

Source: [P016V01MK4482: adam-adsl]

Table 2
Participant Characteristics

	Moderate Hepatic Impairment Participants		Healthy Participants		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	7		7		14	
Sex						
Male	4	(57.1)	4	(57.1)	8	(57.1)
Female	3	(42.9)	3	(42.9)	6	(42.9)
Age (Years)						
18 to 75 years	7	(100.0)	7	(100.0)	14	(100.0)
Mean	54.0		54.6		54.3	
SD	10.2		2.9		7.2	
Median	PPD					
Range						
Race						
Asian	1	(14.3)	0	(0.0)	1	(7.1)
Black Or African American	0	(0.0)	2	(28.6)	2	(14.3)
White	6	(85.7)	5	(71.4)	11	(78.6)
Ethnicity						
Hispanic Or Latino	6	(85.7)	4	(57.1)	10	(71.4)
Not Hispanic Or Latino	1	(14.3)	3	(42.9)	4	(28.6)
Weight (kg)						
Participants with data	7		7		14	
Mean	77.3		81.6		79.4	
SD	9.0		10.3		9.6	
Median	PPD					
Range						
Height (cm)						
Participants with data	7		7		14	
Mean	161.2		166.7		164.0	
SD	7.4		9.0		8.4	
Median	PPD					
Range						
BMI (kg/m^2)						
Participants with data	7		7		14	
Mean	29.7		29.3		29.5	
SD	2.4		2.0		2.1	
Median	PPD					

Participant Characteristics

	Moderate Hepatic Impairment Participants		Healthy Participants		Total	
	n	(%)	n	(%)	n	(%)
Range	PPD					
eGFR (mL/min/1.73 m^2)						
Participants with data	7		7		14	
Mean	106.4		104.2		105.3	
SD	15.1		4.6		10.8	
Median	111.1		104.6		106.0	
Range	87.2 to 124.0		98.6 to 109.6		87.2 to 124.0	
Child-Pugh Score						
Participants with data	7		.		7	
Mean	7.8				7.8	
SD	0.9				0.9	
Median	7.5				7.5	
Range	7.0 to 9.0				7.0 to 9.0	

BMI = Body mass index; eGFR = Estimated glomerular filtration rate; MOV = Molnupiravir; SD = Standard deviation.
Moderate Hepatic Impairment Participants = 800 mg MOV
Healthy Participants = 800 mg MOV

Source: [P016V01MK4482: adam-adsl]

Pharmacokinetics

The plasma PK endpoints of NHC, a nucleoside metabolite of MOV, were analyzed using data from 14 participants who completed this study. Based on the assessment, the plasma PK of NHC is similar in moderate HI participants and healthy participants.

- The 90% CI for the true GMR of NHC AUC0-inf (moderate HI/healthy participants) in plasma was (0.92, 1.64), ie, less than 2.0, hence satisfying the hypothesis that the GM of AUC0-inf of NHC in moderate HI is similar to that observed in healthy matched participants following the administration of a single 800-mg oral dose of MOV [Table 3].
- Similar GM values of the other plasma PK parameters, such as AUC0-last, AUC0-12 and Cmax, were observed in moderate HI participants and healthy participants.
- The median Tmax for NHC was 1.5 hours for both the moderate HI participants and healthy participants, suggesting no difference in the observed absorption rate for NHC.
- In moderate HI participants, the CL/F was modestly reduced (GM 70.5 L/h versus 57.6 L/h) and C12 was lower (median 8.13 ng/mL versus 17.4 ng/mL) compared to healthy participants.
- The estimated t1/2 for plasma NHC was shorter and more variable in healthy participants compared to participants with moderate HI due to terminal concentrations falling near the lower limit of quantitation, resulting in uncertainty in estimating terminal half-life (ie, beta phase). The impact on AUC was negligible due to the small contribution of AUC% extrapolated.

Table 3
Summary Comparison of NHC Plasma Pharmacokinetics Following Administration of Single Oral Doses of 800 mg MOV in Participants With Moderate Hepatic Impairment and Healthy Participants

Pharmacokinetic Parameter	Healthy Participants			Moderate Hepatic Impairment Participants			Ratio (Moderate Hepatic Impairment Participants / Healthy Participants)	
	N	GM (95% CI)	% CV[d]	N	GM (95% CI)	% CV[d]	GMR	90% CI
AUC0-inf (hr*ng/mL) [a]	7	8930 (6560, 12100)	34.2	7	10900 (8510, 14000)	27.5	1.22	(0.92, 1.64)
AUC0-12 (hr*ng/mL) [a]	7	8840 (6500, 12000)	34.2	7	10700 (8370, 13700)	27.2	1.21	(0.91, 1.62)
AUClast (hr*ng/mL) [a]	7	8920 (6550, 12100)	34.3	7	10900 (8490, 14000)	27.5	1.22	(0.92, 1.63)
Cmax (ng/mL) [a]	7	3660 (2730, 4900)	32.3	7	3790 (3260, 4420)	16.6	1.04	(0.81, 1.33)
C12 (ng/mL) [a]	7	8.13 (5.67, 11.6)	40.4	7	17.4 (10.5, 28.8)	59.1	2.13	(1.35, 3.37)
Tmax (hr) [b]	7	1.50 (1.42, 2.00)		7	1.50 (1.50, 2.00)			
Tlast (h) [b]	7	24.03 (24.00, 48.00)		7	48.00 (47.48, 48.00)			
AUC% Extrapolated (%) [c]	7	0.141 (22.1)		7	0.191 (41.8)			
CL/F (L/h) [c]	7	70.5 (34.2)		7	57.6 (27.5)			
t1/2 (hr) [c]	7	5.49 (47.5)		7	10.7 (16.1)			
Vz/F (L) [c]	7	559 (44.6)		7	893 (37.8)			

NHC = N-hydroxycytidine; MOV = Molnupiravir; GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval.
[a] Back transformed least squares mean (mean difference) and confidence interval from linear fixed-effects model performed on natural log-transformed values.
[b] Median (min, max) reported for Tmax and Tlast.
[c] Geometric mean and percent geometric CV reported for AUC% Extrapolated (%), CL/F, t1/2, and Vz/F.
[d] % CV= 100*sqrt(exp(σ)-1),where σ is the estimated variance on the log scale obtained for each population in fixed effect model.
Moderate Hepatic Impairment Participants = 800 mg MOV
Healthy Participants = 800 mg MOV

Source: [P016V01MK4482: adam-adpp]

Safety:

Overall, a single 800 mg dose of MOV was generally well tolerated in moderate HI and healthy participants. No deaths, events of clinical interest, and/or serious AEs were reported. No participant discontinued the study due to an AE.

- Of the 14 participants included in the safety analysis, 1 (7.1%) healthy participant experienced 2 AEs of respiratory disorder and headache (both were mild and not related to study intervention). Both the events resolved at the end of the study [Table 4] and [Table 5].
- No AEs were reported by moderate HI participants.
- No clinically meaningful findings in laboratory assessments, vital signs, or ECGs were observed following the administration of MOV in moderate HI and healthy participants.

Table 4
Adverse Event Summary
All Participants as Treated Population

	Moderate Hepatic Impairment Participants		Healthy Participants		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	7		7		14	
with one or more adverse events	0	(0.0)	1	(14.3)	1	(7.1)
with no adverse event	7	(100.0)	6	(85.7)	13	(92.9)
with drug-related[a] adverse events	0	(0.0)	0	(0.0)	0	(0.0)
with serious adverse events	0	(0.0)	0	(0.0)	0	(0.0)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)
with dose modification[b] due to an adverse event	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	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)
discontinued drug due to a serious adverse event	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)

[a] Determined by the investigator to be related to the drug.
[b] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Every participant is counted a single time for each applicable row and column.
No follow-up adverse events reported.

Source: [P016V01MK4482: adam-adsl; adae]

Table 5
Participants With Adverse Events
(Incidence > 0% in One or More Treatment Groups)
All Participants as Treated Population

	Moderate Hepatic Impairment Participants		Healthy Participants		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	7		7		14	
with one or more adverse events	0	(0.0)	1	(14.3)	1	(7.1)
with no adverse events	7	(100.0)	6	(85.7)	13	(92.9)
Nervous system disorders	**0**	**(0.0)**	**1**	**(14.3)**	**1**	**(7.1)**
Headache	0	(0.0)	1	(14.3)	1	(7.1)
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**1**	**(14.3)**	**1**	**(7.1)**
Respiratory disorder	0	(0.0)	1	(14.3)	1	(7.1)

Every participant is counted a single time for each applicable row and column.
Adverse event terms are from MedDRA Version 25.1.

Source: [P016V01MK4482: adam-adsl; adae]

CONCLUSIONS:

Pharmacokinetics

Based on the results from this study of a single 800-mg oral dose of MOV, the following key PK conclusion can be made:

The 90% CI for the true GMR of NHC AUC0-inf (moderate HI /healthy participants) is less than 2.0, hence satisfying the hypothesis that the GM AUC0-inf of NHC in moderate HI is similar to that observed in healthy participants.

The following PK key result was observed:

- There was no clinically meaningful difference observed in NHC absorption, as Tmax and Cmax were comparable between moderate HI participants and healthy participants.

Safety

The following key safety results were also observed:

- A single 800-mg oral dose of MOV was generally well tolerated in moderate HI and healthy participants.

LIST OF ABBREVIATIONS:

Abbreviation/Term	Definition
AE	adverse event
AUC	area under the 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 to infinity
AUC0-last	area under the concentration-time curve from time 0 to the last measurable time point
BMI	body mass index
COVID-19	coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
Cmax	maximum plasma concentration
C12	plasma concentration at 12 hours
CI	confidence interval
CL/F	apparent plasma clearance
CP	Child-Pugh
eGFR	estimated glomerular filtration rate
GCP	Good Clinical Practice
GM	geometric mean
GMR	geometric mean ratio
HI	hepatic impairment
ICH	international council on harmonization
IEC	independent ethics committee
INR	international normalized ratio
LPLV	last participant, last visit
MOV	molnupiravir
NHC	N-hydroxycytidine
PK	pharmacokinetic(s)
SAE	serious adverse event
SOP	standard operating procedure
t1/2	half-life
Tlast	time of last observed concentration
Tmax	time to maximum plasma concentration
Vz/F	apparent volume of distribution

PUBLICATIONS: As of the date of this report, there are no publications based on this study.

REPORT DATE: 01-SEP-2023

REVISED REPORT DATE: Not applicable