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 Study to Evaluate the Pharmacokinetics of Molnupiravir (MK-4482; MOV) in Participants with Severe Renal Impairment

The following terms may be used interchangeably in this report:

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

STUDY IDENTIFIERS:

IND: 147734	EudraCT: Not applicable	WHO: Not applicable	NCT: NCT05386758
jRCT: Not applicable	UTN: Not applicable	EU CT: Not applicable	

STUDY PHASE: Phase 1

INDICATION: Treatment of COVID-19

STUDY CENTERS: This study was conducted at 4 centers in 1 country.

STUDY STATUS: This study is complete.

First Participant First Visit	29-JUN-2022
Last Participant Last Visit	01-MAR-2023
Last Data Available	30-JUN-2023
Database Lock Date	11-JUL-2023

METHODOLOGY:

This was a non-randomized, open-label, single-dose, multicenter study of MOV in adult male and female participants with severe RI (eGFR < 30 mL/min based on 2021 CKD-EPIcr_R) (Panel A; n = 8) and healthy mean matched controls (eGFR ≥ 90 mL/min based on 2021 CKD-EPIcr_R) (Panel B; n = 8).

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.

Because this was a Phase 1 assessment of MOV in humans, the PK, pharmacodynamic, and safety profiles of the compound were still being elucidated. 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
Severe Renal Impairment Group	MK-4482 (MOV)	200 mg	800 mg	Oral	Single Dose	Test Product
Healthy Control Group	MK-4482 (MOV)	200 mg	800 mg	Oral	Single Dose	Test Product

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 severe RI (BSA adjusted eGFR < 30 mL/min) and healthy mean matched participants (BSA adjusted eGFR ≥ 90 mL/min, though participants with a value of 80 to 89 mL/min were allowed to enroll in the study at the discretion of the investigator) between the ages of 18 to 75 years with BMI ≥ 18.5 and ≤ 35 kg/m^2 were enrolled in the study. Baseline eGFR was obtained twice (at least 72 hours apart as part of participant screening), and the mean of the 2 values was used to determine eligibility.

Healthy control participants were matched for mean age (± 10 years) and BMI (± 3.5 kg/m^2) of participants with severe RI. In addition, the numbers of males and females of the healthy participants were generally matched to the numbers of severe RI participants within ± 1 participant.

OBJECTIVES AND ENDPOINTS:

Primary Objective	Primary Endpoint
To evaluate the plasma pharmacokinetics of the N-hydroxycytidine, the nucleoside metabolite of molnupiravir, after a single oral dose of 800 mg molnupiravir in participants with severe renal impairment compared to healthy mean matched control participants. Hypothesis: In participants with severe renal 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 (severe renal impairment/healthy control) is less than 2.0. Estimation: In participants with severe renal 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 severe renal impairment.	Adverse events
To evaluate urinary excretion of N-hydroxycytidine after a single oral dose of 800 mg molnupiravir in participants with severe renal impairment compared to healthy mean matched control participants.	Ae and Fe of N-hydroxycytidine in urine and CLr of N-hydroxycytidine

NUMBER OF PARTICIPANTS (planned and analyzed):

The planned enrollment total was 16 to 18 participants. As of the database lock, 16 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 severe RI and healthy control participants were natural log-transformed and evaluated with a linear fixed effects model containing a fixed effect for population (participants with severe RI and healthy control participants). To address the primary hypothesis of comparing participants with severe RI to healthy control participants, the 90% CI for the true GMR (severe RI /healthy control) was constructed. If the 90% CI falls below 2.0, then the hypothesis that in participants with severe RI, 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 severe RI and healthy 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, laboratory values, vital signs, ECGs).

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

RESULTS:

Participant Disposition:

All 16 participants completed the study: 8 participants with severe RI and 8 healthy mean matched control participants. All participants received study intervention as scheduled per protocol. The subject disposition is summarized in [Table 1].

Demographics and Baseline Characteristics:

Eight (8) participants with severe RI (eGFR < 30 mL/min) were enrolled. All participants in the severe RI group were male (100.0%); 6 were white (75.0%) and 2 Black or African American (25%). The 8 healthy mean matched control participants were matched to the mean age, BMI, and male:female ratio demographic variables of the severe RI group as per protocol.

To correct the eGFR for individual BSA in the 2021 CKD-EPIcr_R, eGFR values indexed to BSA 1.73 m^2 were deindexed by dividing the value obtained from the equation by 1.73 and then multiplying by participant BSA. The mean eGFR (adjusted for BSA) was 20.19 mL/min for the severe RI group and 106.21 mL/min for the healthy mean matched control participants [Table 2].

Table 1
Disposition of Participants
All Participants as Treated Population

	Participants with Severe Renal Impairment		Healthy Participants with Normal Renal Function		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	8		8		16	
Status for Trial						
Completed	8	(100.0)	8	(100.0)	16	(100.0)
Status for Study Medication in Trial						
Completed	8	(100.0)	8	(100.0)	16	(100.0)

Each participant is counted once for Trial Disposition and Participant Study Medication Disposition based on the latest corresponding disposition record.
Participants with Severe Renal Impairment = Dose of 800 mg Molnupiravir
Healthy Participants with Normal Renal Function = Dose of 800 mg Molnupiravir

Source: [P003V01MK4482: adam-adsl]

Table 2
Participant Characteristics
All Participants as Treated Population

	Participants with Severe Renal Impairment		Healthy Participants with Normal Renal Function		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	8		8		16	
Sex						
Male	8	(100.0)	7	(87.5)	15	(93.8)
Female	0	(0.0)	1	(12.5)	1	(6.3)
Age (Years)						
< 65	5	(62.5)	8	(100.0)	13	(81.3)
>= 65	3	(37.5)	0	(0.0)	3	(18.8)
Mean	63.5		59.6		61.6	
SD	7.9		2.0		5.9	
Median	PPD					
Range						
Race						
Black Or African American	2	(25.0)	3	(37.5)	5	(31.3)
White	6	(75.0)	5	(62.5)	11	(68.8)
Ethnicity						
Hispanic Or Latino	4	(50.0)	4	(50.0)	8	(50.0)
Not Hispanic Or Latino	4	(50.0)	4	(50.0)	8	(50.0)
Weight (kg)						
Participants with data	8		8		16	
Mean	93.10		86.73		89.91	
SD	18.17		7.14		13.73	
Median	PPD					
Range						
BMI (kg/m^2)						
Participants with data	8		8		16	
Mean	32.20		29.68		30.94	
SD	3.89		0.84		3.02	
Median	PPD					
Range						

Participant Characteristics
All Participants as Treated Population

	Participants with Severe Renal Impairment		Healthy Participants with Normal Renal Function		Total	
	n	(%)	n	(%)	n	(%)
eGFR Adjusted for BSA (mL/min)						
Participants with data	8		8		16	
Mean	20.19		106.21		63.20	
SD	7.07		9.39		45.14	
Median	21.50		108.00		58.00	
Range	9.6 to 28.5		87.5 to 120.0		9.6 to 120.0	

BMI = Body mass index, BSA = Body Surface Area, eGFR = Estimated glomerular filtration rate, SD = Standard deviation

Participants with Severe Renal Impairment = Dose of 800 mg Molnupiravir

Healthy Participants with Normal Renal Function = Dose of 800 mg Molnupiravir

eGFR values were calculated using both baseline eGFR measurements (obtained at least 72 hours apart) and the mean of these values was determined as part of participant screening.

Source: [P003V01MK4482: adam-adsl]

Pharmacokinetics:

The plasma and urine PK endpoints of NHC, a nucleoside metabolite of MOV, were analyzed using data from 16 participants who completed this study. Based on the assessment, the plasma PK of NHC is similar in severe RI participants and healthy mean matched control participants. The urinary excretion of NHC was low in both treatment groups, which was consistent with findings from a previous study in healthy adults (P004).

As expected, the renal clearance of NHC was lower in severe RI participants with reduced eGFR compared to the healthy mean matched control participants.

- The observed GMR (90% CI) of NHC AUC0-inf (severe RI participants/ healthy mean matched control participants) in plasma was 1.24 (0.94, 1.64). Since the 90% CI is less than 2.0, the hypothesis that the GM of AUC0-inf of NHC in severe RI participants is similar to that observed in healthy mean matched control participants following the administration of a single 800-mg oral dose of MOV is supported [Table 3].
- Similar GM values were observed for the Cmax in severe RI participants and healthy mean matched control participants [Table 3].
- The estimated t1/2 for plasma NHC was shorter in healthy participants compared to participants with severe RI due to terminal concentrations falling near the LLOQ, 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].
- In severe RI participants, NHC cumulative amount excreted [Ae], percent of administered dose excreted [Fe], and renal clearance [Clr] were lower compared to healthy matched control participants [Table 4]. High inter-subject variability was observed in both populations.

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

Pharmacokinetic Parameter	Healthy Participants			Severe Renal Impairment Participants			Ratio (Severe Renal 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]	8	8960 (7660, 10500)	19.0	8	11100 (7990, 15400)	40.8	1.24	(0.94, 1.64)
AUC0-12 (hr*ng/mL) [a]	8	8880 (7600, 10400)	18.7	8	10900 (7860, 15100)	40.6	1.23	(0.93, 1.62)
AUC0-last (hr*ng/mL) [a]	8	8960 (7660, 10500)	18.9	8	11100 (7970, 15400)	40.9	1.24	(0.94, 1.63)
Cmax (ng/mL) [a]	8	3240 (2630, 4000)	25.5	8	3920 (2810, 5460)	41.3	1.21	(0.90, 1.62)
C12 (ng/mL) [a]	8	8.96 (6.81, 11.8)	33.6	8	15.5 (7.05, 34.2)	119.9	1.73	(0.90, 3.32)
Tlast (hr) [b]	8	24.00 (23.67, 72.02)		8	47.80 (24.00, 72.00)			
Tmax (hr) [b]	8	1.75 (1.42, 2.00)		8	1.52 (1.50, 3.98)			
AUC%Extrapolated (%) [c]	8	0.0625 (85.3)		8	0.114 (103.4)			
t1/2 (hr) [c]	8	3.18 (98.9)		8	7.59 (92.5)			
CL/F (L/hr) [c]	8	70.2 (19.0)		8	56.8 (40.8)			
Vz/F (L) [c]	8	322 (84.7)		8	621 (79.0)			

GM=Geometric mean; CI=Confidence interval; GMR=Geometric mean ratio; CV=Coefficient of variation; MOV=Molnupiravir, MK-4482; NHC=N-hydroxycytidine

[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, Tlast.

[c] Geometric mean and percent geometric CV reported for AUC%Extrapolated, t1/2, CL/F, 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. Severe Renal Impairment Participants = Dose of 800 mg Molnupiravir

Healthy Participants = Dose of 800 mg Molnupiravir

Source: [P003V01MK4482: adam-adpp]

Table 4
Summary Geometric Mean (%GCV) Pharmacokinetic Parameter Values of NHC in Urine Following Administration of a Single Oral Dose of 800 mg MK-4482 in Participants with Severe Renal Impairment and Healthy Control Participants

Geometric Mean (%GCV)					
Analyte (Matrix)	**Panels**	**N**	**Ae (mg)**	**Fe (%)**	**CLr (L/hr)**
NHC (Urine)	Severe Renal Impairment	8	3.72 (50.9)	0.591 (50.9)	0.338 (62.1)
	Healthy Matched Control	8	14.6 (172)	2.33 (172)	1.64 (162)

Ae = Amount of unchanged drug excreted in urine from time 0 to 24 hours; CLr = Renal clearance; Fe = Percentage of dose recovered in urine from time 0 to 24 hours;
GCV = Geometric coefficient of variation; N = Number of participants;
NHC = N hydroxycytidine.

Source: [P003V01MK4482: adam-adpp]

Safety:

Overall, a single 800-mg dose of MOV was generally well tolerated in severe RI and healthy mean matched control participants. No deaths, ECIs, and/or SAEs were reported. No participant discontinued the study due to an AE.

- Of the 16 participants included in the safety analysis, 3 (18.8%) participants experienced 1 or more AEs during the study and 1 (6.3%) participant reported a drug-related AE [Table 5]. All events were reported in the severe RI participants. All AEs were mild or moderate in intensity. All AEs were followed to resolution.
- Two AEs were reported in two participants during the treatment period (up to 14 days following the dose), [Table 6, Table 7]. One (12.5%) participant in the severe RI group reported an AE of constipation (not related, lasted 1.86 weeks) and one (12.5%) participant in the severe RI group reported an AE of hyperkalemia (related to study intervention, lasted 2 days).
- In addition, 4 AEs were reported in two participants at or after the post-study visit. Two participants reported an AE of hyperkalemia, and AEs of anemia and increased blood urea were each reported in one participant each.
- No other clinically meaningful findings in laboratory assessments, VS, or ECGs were observed following the administration of MOV in severe RI and healthy mean matched control participants.

Table 5
Adverse Event Summary
All Participants as Treated Population

	Participants with Severe Renal Impairment		Healthy Participants with Normal Renal Function		Occurring at Poststudy Visit		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	8		8		16		16	
with one or more adverse events	2	(25.0)	0	(0.0)	2	(12.5)	3	(18.8)
with no adverse event	6	(75.0)	8	(100.0)	14	(87.5)	13	(81.3)
with drug-related[a] adverse events	1	(12.5)	0	(0.0)	0	(0.0)	1	(6.3)
with toxicity grade 3-5 adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
with toxicity grade 3-5 drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
with non-serious adverse events	2	(25.0)	0	(0.0)	2	(12.5)	3	(18.8)
with serious adverse events	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)
with dose modification[b] due to an adverse event	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)
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)	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)
discontinued drug due to a serious adverse event	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)

[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.
Poststudy Visit = Participants returned approximately 14 days postdose for a poststudy visit.
Every participant is counted a single time for each applicable row and column.
All 4 of the adverse events occurring at poststudy visit occurred in the participants with severe renal impairment.

Source: [P003V01MK4482: adam-adsl; adae]

Table 6
Participants With Adverse Events
(Incidence > 0% in One or More Treatment Groups)
All Participants as Treated Population

	Participants with Severe Renal Impairment		Healthy Participants with Normal Renal Function		Occurring at Poststudy Visit		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	8		8		16		16	
with one or more adverse events	2	(25.0)	0	(0.0)	2	(12.5)	3	(18.8)
with no adverse events	6	(75.0)	8	(100.0)	14	(87.5)	13	(81.3)
Blood and lymphatic system disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(6.3)**	**1**	**(6.3)**
Anaemia	0	(0.0)	0	(0.0)	1	(6.3)	1	(6.3)
Gastrointestinal disorders	**1**	**(12.5)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(6.3)**
Constipation	1	(12.5)	0	(0.0)	0	(0.0)	1	(6.3)
Investigations	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(6.3)**	**1**	**(6.3)**
Blood urea increased	0	(0.0)	0	(0.0)	1	(6.3)	1	(6.3)
Metabolism and nutrition disorders	**1**	**(12.5)**	**0**	**(0.0)**	**2**	**(12.5)**	**2**	**(12.5)**
Hyperkalaemia	1	(12.5)	0	(0.0)	2	(12.5)	2	(12.5)

Every participant is counted a single time for each applicable row and column.
Poststudy Visit = Participants returned approximately 14 days postdose for a poststudy visit.
All 4 of the adverse events occurring at poststudy visit occurred in the participants with severe renal impairment.
Adverse event terms are from MedDRA Version 26.0.

Source: [P003V01MK4482: adam-adsl; adae]

Table 7
Participants With Drug-related Adverse Events
(Incidence > 0% in One or More Treatment Groups)
All Participants as Treated Population

	Participants with Severe Renal Impairment		Healthy Participants with Normal Renal Function		Occurring at Poststudy Visit		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	8		8		16		16	
with one or more drug-related adverse events	1	(12.5)	0	(0.0)	0	(0.0)	1	(6.3)
with no drug-related adverse events	7	(87.5)	8	(100.0)	16	(100.0)	15	(93.8)
Metabolism and nutrition disorders	**1**	**(12.5)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(6.3)**
Hyperkalaemia	1	(12.5)	0	(0.0)	0	(0.0)	1	(6.3)

Every participant is counted a single time for each applicable row and column.
Poststudy Visit = Participants returned approximately 14 days postdose for a poststudy visit.
Adverse event terms are from MedDRA Version 26.0.

Source: [P003V01MK4482: 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 observed GMR of NHC AUC0-inf (severe RI participants/ healthy mean matched control participants) in plasma was estimated to be 1.24 (90% CI 0.94, 1.64). Since the 90% CI is less than 2.0, the hypothesis that the GM of AUC0-inf of NHC in severe RI participants is similar to that observed in healthy mean matched control participants following the administration of a single 800-mg oral dose of MOV is supported.

The following key PK result was also observed:

- Urinary excretion of NHC was low in both groups, further supporting that renal excretion is not a major route of elimination of MOV. Urinary excretion of NHC was lower in the severe RI participants compared to the healthy mean matched control participants.

Safety

The following key safety results were also observed:

- A single 800-mg oral dose of MOV was generally well tolerated in severe RI and healthy mean matched control participants in this study.

LIST OF ABBREVIATIONS:

Abbreviation/Term	Definition
AE	adverse event
Ae	cumulative amount excreted in urine from time 0 to 24 hours
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
BSA	body surface area
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
CKD-EPIcr_R	Chronic Kidney Disease Epidemiology Collaboration Creatinine Equation
CL/F	apparent plasma clearance
CLr	renal clearance
CP	Child-Pugh
ECI	events of clinical interest
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
Fe	percentage of dose excreted unchanged in urine over the 24-hour collection interval
GCP	Good Clinical Practice
GM	geometric mean
GMR	geometric mean ratio
ICH	international council on harmonization
IEC	independent ethics committee
INR	international normalized ratio

Abbreviation/Term	Definition
LLOQ	lower limit of quantification
LPLV	last participant, last visit
MOV	Molnupiravir
NHC	N-hydroxycytidine
PK	pharmacokinetic(s)
RI	renal impairment
SAE	serious adverse event
SOP	standard operating procedure
t1/2	half-life
Tlast	time of last observed concentration
Tmax	time to maximum plasma concentration
VS	vital signs
Vz/F	apparent volume of distribution

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

REPORT DATE: 30-OCT-2023

REVISED REPORT DATE: Not applicable