Official Protocol Title:	An Open-Label, Single-Dose Clinical Study to Evaluate the Pharmacokinetics of Molnupiravir (MK-4482) in Participants with Moderate Hepatic Impairment
NCT number:	NCT05386589
Document Date:	18-Aug-2022

Title Page

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME LLC, RAHWAY, NJ, USA (MSD).

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

Protocol Number: 016-02

Compound Number: MK-4482

Sponsor Name:

Merck Sharp & Dohme LLC
(hereafter called the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	147734

Approval Date: 18 August 2022

Sponsor Signatory

Typed Name: Date
Title:

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 2	18-AUG-2022	Exclusion criterion #23 was modified to allow enrollment of participants with hepatic impairment (HI) who use medical marijuana and have a valid medical marijuana card from a licensed healthcare provider. This modification was done to facilitate enrollment of participants with HI due to the prevalent use of medical marijuana in this patient population.
Amendment 1	14-JUN-2022	The definition of nonparticipant women of childbearing potential (WOCBP) partners of male participants was added as well as acceptable contraceptive methods to be used by nonparticipant WOCBP partners during the study.
Original Protocol	11-APR-2022	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 02

Overall Rationale for the Amendments:

Exclusion criterion #23 was modified to allow enrollment of participants with hepatic impairment (HI) who use medical marijuana and have a valid medical marijuana card from a licensed healthcare provider. This modification was done to facilitate enrollment of participants with HI due to the prevalent use of medical marijuana in this patient population.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	The following statement was deleted from footnote c: "the second CP score may be obtained at the time of check-in, but data must be available before dosing on Day 1 to ensure eligibility." The timepoints for the procedures "Assessment of Liver Function Using Child-Pugh Classification" and "PT/INR" were modified to be assessed only during the screening period and not inclusive of the check-in period (Day -1).	These changes are corrections of typographical errors. As per Amendment 01, if conducted, the second assessment of liver function using Child-Pugh Classification (including PT/INR assessment) is to be conducted prior to check-in to allow time for eligibility review and allocation number assignment. Therefore, these clarifications are made to align the text throughout the protocol.

Section # and Name	Description of Change	Brief Rationale
5 Study Population	As stated in the Code of Conduct for Clinical Trials (Appendix 1.1) this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.	This change is a correction of typographical error. This modification was mentioned in the previous Summary of Changes Table in Amendment 01, but was inadvertently not applied to the protocol amendment.
5.2 Exclusion Criteria	A subheading of "All Participants" was added under the "Prior/Concurrent Clinical Study Experience, Diagnostic Assessments, and Other Exclusion" headings	This subheading was added as a clarification of the patient population for which the exclusion criteria apply.
5.2 Exclusion Criteria	The following statement was removed from exclusion criterion #19: "…,or is taking concomitant medications that prolong the QT/QTc interval."	Participants with hepatic impairment may be on medications that are known to prolong the QT/QTc interval to manage their disease (eg, diuretics). This modification to exclusion criterion #19 will not exclude participants that are taking these medications. However, use of these medications during the study for enrolled participants are to be discussed with the Sponsor as per the addition to Section 6.5.

Section # and Name	Description of Change	Brief Rationale
6.5 Concomitant Therapy	The following statement was added: "Medications with known effect on QT/QTc prolongation may be allowed following discussion with the Sponsor."	This statement was added to align Sec. 6.5 with the modification to the exclusion criterion #19 and allows HI participants to continue QT/QTc prolonging medications after discussion with the Sponsor.
5.2 Exclusion Criteria	Exclusion criterion #23 was modified to allow enrollment of participants with hepatic impairment (HI) who use medical marijuana and have a valid medical marijuana card from a licensed healthcare provider.	This modification was done to facilitate enrollment of participants with HI due to the prevalent use of medical marijuana in this patient population. However, participants must refrain from medical marijuana use for the protocol-specified time before and after study intervention administration.
6.5 Concomitant Therapy	The following statement was added: "Participants with a valid medical marijuana card will be allowed to participate in the study at the discretion of the investigator, however use of medical marijuana should be restricted at least 24 hours prior to, and 24 hours after, study intervention administration."	This statement was added to provide restrictions for medical marijuana usage for participants with HI with regards to study intervention administration.

Section # and Name	Description of Change	Brief Rationale
8 Study Assessments and Procedures	The total maximum amount of blood to be collected for participants in Panel A was corrected to 116.5 mL from 105.5 mL.	This change was a correction of a typographical error where the original value did not align with the Blood Volume Table in the finalized Study Operations Manual.
8.3.1 Physical Examinations	"Height and weight will also be measured and recorded at the timepoints listed in the SoA (Sec. 1.3)."	This change was a clarification to align the requirements of the physical exams with the SoA (Sec. 1.3).
Throughout	Minor grammatical and typographical errors were corrected.	These changes were non-substantial editorial corrections.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

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

Short Title: Molnupiravir (MK-4482, MOV) Hepatic Impairment Study

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

The study population includes male and female participants with moderate hepatic impairment between the ages of 18 and 75 years (inclusive) and healthy mean-matched controls.

Objectives	Endpoints
Primary	
• 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

Objectives	Endpoints
Secondary	
• To evaluate the safety and tolerability of molnupiravir in participants with moderate hepatic impairment.	• Adverse events

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Treatment of COVID-19
Population	Participants with moderate hepatic impairment, Healthy participants
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study
Type of Control	Healthy-matched control participants
Study Blinding	Unblinded Open-label
Blinding Roles	No Blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 14 to 17 participants will be allocated.

Intervention Groups and Duration:

Intervention Groups	<table><tr><th>Intervention Group Name</th><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Administration</th><th>Use</th></tr><tr><td>Moderate Hepatic Impairment</td><td>MK-4482 (MOV)</td><td>800 mg</td><td>Once</td><td>Oral</td><td>Test Product</td></tr><tr><td>Healthy- Matched Control Group</td><td>MK-4482 (MOV)</td><td>800 mg</td><td>Once</td><td>Oral</td><td>Test Product</td></tr></table> Other current or former name(s) or alias(es) for study intervention(s) are as follows: Molnupiravir, MOV, EIDD-2801
Total Number of Intervention Groups/ Arms	2
Duration of Participation	Each participant will participate in the study for approximately 6 weeks from the time the participant provides documented informed consent through the final contact.

Study Governance Committees:

Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
There are no governance committees in this study. Regulatory, ethical, and study oversight considerations are outlined in Appendix 1.	

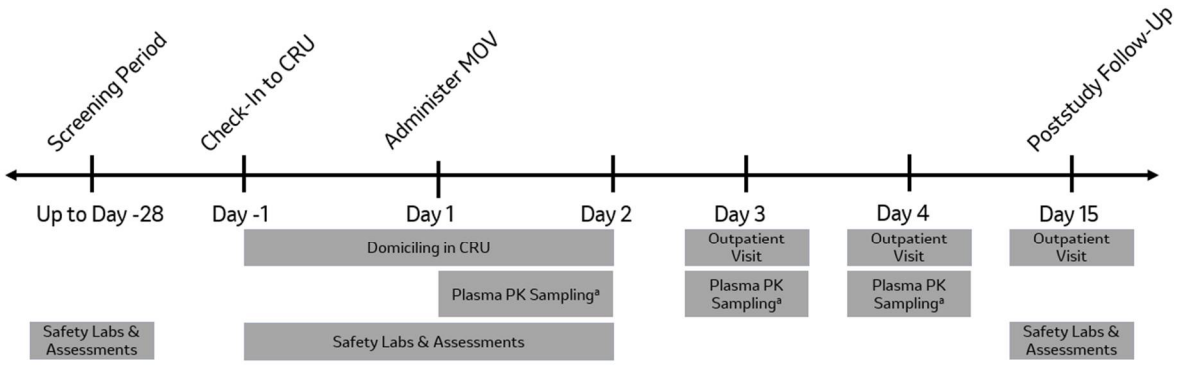
Study Accepts Healthy Volunteers: Yes

A list of abbreviations is in Appendix 10.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Schema



[a]Plasma pharmacokinetic (PK) samples will be collected at the timepoints listed in the Section 1.3.
Study schema includes the same set-up for participants with moderate hepatic impairment and healthy-matched controls.
There is ± 2-day window for the poststudy follow-up visit.

1.3 Schedule of Activities

All Panels																
Study Period	**Screen-ing**	**Check-In**	**Intervention**												**Post-study**	**Notes**
Study Day	**Up to -28**	**-1**	**1**									**2**	**3**	**4**	**~15**	
Scheduled Hour[a]			**Pre-dose**	**0**	**0.5**	**1.5**	**2**	**4**	**6**	**8**	**12**	**24**	**48**	**72**	**Post-study[b]**	
Administrative/Study Procedures																
Informed Consent	X															Sec. 5.1, 8.1.1.1
Informed Consent for FBR	X															Sec. 5.1, 8.1.1.2
Participant ID Card	X															Sec. 8.1.3
Inclusion/Exclusion Criteria	X		X													Review of IC/EC will occur at Screening and specific criteria after predose procedures (if applicable) on Day 1. Sec. 5.1, 5.2, and 8.1.2
Medical History	X															Includes substance abuse (drugs, alcohol, tobacco, and caffeine). Sec. 8.1.4
Assessment of Liver Function Using Child-Pugh Classification	X[c]															To be performed in participants with hepatic impairment only. Sec. 4.1, 5.1

All Panels																
Study Period	**Screen-ing**	**Check-In**	**Intervention**												**Post-study**	**Notes**
Study Day	**Up to -28**	**-1**	**1**									**2**	**3**	**4**	**~15**	
Scheduled Hour[a]			**Pre-dose**	**0**	**0.5**	**1.5**	**2**	**4**	**6**	**8**	**12**	**24**	**48**	**72**	**Post-study[b]**	
Prior/Concomitant Medication Review	X----------X															Sec. 5.2, 6.5, and 8.1.5
Assignment of Screening Number	X															Sec. 8.1.6
Assignment of Treatment/Randomization Number			X													To be provided within 24 hours prior to intervention administration. Sec. 5.5, 8.1.7
Participant Visit to CRU	X	X											X	X	X	
Domiciling		X----------X														Sec. 8.1.11
MOV Administration				X												Sec. 8.1.8.1
Standard Meals								X								Sec. 5.3.1.1
Safety Procedures																
Full PE	X		X												X	Predose PE can be conducted up to 24 hours prior to dosing. Sec. 8.3.1
Height	X															Sec. 8.3.1
Weight	X														X	BMI to be assessed only at Screening.

All Panels																
Study Period	**Screen-ing**	**Check-In**	**Intervention**												**Post-study**	**Notes**
Study Day	**Up to -28**	**-1**	**1**									**2**	**3**	**4**	**~15**	
Scheduled Hour[a]			**Pre-dose**	**0**	**0.5**	**1.5**	**2**	**4**	**6**	**8**	**12**	**24**	**48**	**72**	**Post-study[b]**	
Vital Signs (HR, BP)[d]	X		X			X		X				X			X	Sec. 8.3.2
Vital Signs (RR, Temperature)[e]	X		X									X			X	Sec. 8.3.2
12-lead ECG	X		X[d]									X			X	Sec. 8.3.3
Serum hCG	X		X[f]												X	WOCBP only. Result to be reviewed prior to dosing on Day 1. Sec. 8.3.5, Appendix 2
Serum FSH	X															Postmenopausal females only. Appendix 2
Hepatitis Screen	X															Per site SOP. For healthy participants only. Sec. 8.3.4, Appendix 2
HIV-1 and HIV-2 Screen	X															Per site SOP. Sec. 8.3.4, Appendix 2
UDS/BDS (per site SOP)	X		X[f]													Per Site SOP. Sec. 8.3.4, Appendix 2

All Panels																
Study Period	**Screen-ing**	**Check-In**	**Intervention**												**Post-study**	**Notes**
Study Day	**Up to -28**	**-1**	**1**									**2**	**3**	**4**	**~15**	
Scheduled Hour[a]			**Pre-dose**	**0**	**0.5**	**1.5**	**2**	**4**	**6**	**8**	**12**	**24**	**48**	**72**	**Post-study[b]**	
PT/INR	X[c]															To be performed in participants with hepatic impairment only. Appendix 2
Hematology and Chemistry	X		X[f]									X			X	Participants will fast for at least 8 hours prior to blood sample collection. Sec. 8.3.4, Appendix 2
Urinalysis	X		X[f]									X			X	Sec. 8.3.4, Appendix 2
AE/SAE review	X----------X															Sec. 8.4
Pharmacokinetics																
Blood for Plasma NHC Assay			X		X	X	X	X	X	X	X	X	X	X		Sec. 8.6
Biomarkers																
Blood for Genetic Analysis			X													Sec. 8.8.1

All Panels																
Study Period	**Screen-ing**	**Check-In**	**Intervention**												**Post-study**	**Notes**
Study Day	**Up to -28**	**-1**	**1**									**2**	**3**	**4**	**~15**	
Scheduled Hour[a]			**Pre-dose**	**0**	**0.5**	**1.5**	**2**	**4**	**6**	**8**	**12**	**24**	**48**	**72**	**Post-study[b]**	

AE=adverse event; BDS=blood drug screen; ECG=electrocardiogram; FBR=future biomedical research; FSH=follicle stimulating hormone; hCG=human chorionic gonadotropin; HIV-1/HIV-2=human immunodeficiency virus type 1/type 2; IC/EC=inclusion and exclusion criteria; ID=identification; MOV=molnupiravir, MK-4482; NHC=N-hydroxycytidine; PE= physical exam; PT=prothrombin time; RR=respiratory rate; SAE=serious adverse event; SOP=standard operating procedure; UDS=urine drug screen; VS=vital signs; WOCBP=women of childbearing potential.

[a] The scheduled hour is relative to the time of administration of MOV.

[b] The poststudy follow-up visit will have a ± 2-day window to be completed. If the visit occurs prior to 14 days postdose (Day 15), verbal contact should be made to assess for AEs 14 days postdose (Day 15).

[c] Assessment of liver function using CP classification is to be conducted for all participants with HI at screening. If a historical CP value is not available, a second CP assessment (including PT/INR, albumin, and bilirubin laboratory assessment) will additionally be conducted during the screening period (>72 hours apart) and the mean of the 2 values will be used for group assignment.

[d] Predose measurements will be in triplicate and screening and postdose measurements will be single measurements.

[e] Assessments of RR and temperature will be collected in single measurements.

[f] Predose labs may be completed up to 24 hours prior to dosing.

2 INTRODUCTION

Molnupiravir (also known as MK-4482 and EIDD-2801; hereafter referred to as MOV) is a novel ribonucleoside analog prodrug with broad-spectrum antiviral activity against a range of RNA viruses, including coronaviruses. MOV has been developed for the treatment of mild-to-moderate COVID-19 (laboratory-confirmed SARS-CoV-2 infection with symptoms) in those who are at risk to progress to severe disease. MOV is additionally being evaluated for prophylaxis for COVID-19 in initially asymptomatic individuals ≥18 years of age residing with a person with COVID. This study will evaluate the tolerability and PK of a single 800-mg dose of MOV in participants with moderate HI compared to participants with normal hepatic function.

2.1 Study Rationale

The liver is involved in drug clearance through multiple oxidative and conjugative metabolic pathways and through biliary excretion. For some small molecule therapeutics, HI from acute or chronic liver disease may affect excretion and metabolism, leading to accumulation of drug and metabolites. Hepatic disease can therefore alter the levels of drugs, potentially leading to an effect on efficacy and/or safety.

In preclinical studies, MOV undergoes rapid hydrolysis to NHC via 2 widely distributed high-capacity carboxylesterases during absorption/hepatic first pass metabolism leading to high NHC bioavailability (>50%). NHC is taken up into cells via nucleoside transporters where host kinases phosphorylate NHC to the pharmacologically active metabolite, NHC-TP. The predominate elimination pathway for NHC appears to be through metabolism to uridine and cytidine, which then mix with the endogenous nucleotide pool. Both cytidine deaminase and the mitochondrial amidoxime reducing components have capability to convert NHC to endogenous pyrimidines in vitro. NHC is not bound to plasma proteins and MOV absorption is not expected to be altered in hepatic impairment due to high solubility in buffers with and without bile acids. Given the totality of the preclinical data, hepatic elimination is not expected to be a major route of elimination for NHC.

A PopPK analysis inclusive of Phase 3 data (P002 Part 2) found minimal impact of mild HI on NHC exposures (5% increase in NHC AUC in participants with mild impairment) using a modified CP score. This modified CP 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. Based on PopPK results, the GMR (90% CI) of exposures for participants with mild HI (n=60) compared to participants with no HI (n=1143) was 1.05 (0.962, 1.14). Only 3 participants were classified as having moderate HI based on this method of classification, so a GMR was not calculated for this group.

While the existing preclinical and clinical data (based on a modified CP score) suggest that any degree of HI will not significantly impact metabolism and elimination of MOV, this study is being conducted to further evaluate the effect of HI in individuals with moderate HI (based on CP classification) on plasma NHC PK.

This Phase 1 study will additionally evaluate the general safety, tolerability, and PK (plasma NHC) of a single 800-mg dose of MOV in participants with moderate HI, compared to participants in good health.

2.2 Background

Refer to the IB/approved labeling for detailed background information on MOV.

2.2.1 Pharmaceutical and Therapeutic 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 [Gorbalenya, A. E., et al 2020]. 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 [Wu, Z. 2020] [Grasselli, G., et al 2020] [Guan, W., et al 2020]. 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 [Grasselli, G., et al 2020] [Richardson, S., et al 2020] [Docherty, A. B., et al 2020] [Guan, W., et al 2020] [Dorjee, K., et al 2020] [Galloway, J. B., et al 2020]. There remains a need for direct-acting antiviral agents active against SARS-CoV-2, particularly agents that are administered orally in medically complex populations with multiple medications or comorbidities.

MOV is the 5´-isobutyrate prodrug of the broadly active, direct-acting antiviral ribonucleoside analog NHC. MOV is hydrolyzed by esterases either during or after absorption to deliver NHC into systemic circulation. NHC inhibits replication of multiple viral pathogens from multiple RNA virus families including pathogenic Coronaviruses (eg, MERS, SARS-CoV and SARS-CoV-2), influenza viruses (seasonal, pandemic and avian subtypes), and respiratory syncytial virus (RSV). Inside cells, the active nucleoside triphosphate anabolite of MOV (NHC-TP) acts as a competitive, alternative substrate for the virally encoded RNA-dependent RNA polymerase that upon incorporation into nascent chain RNA, induces increased mutational frequency in the viral genome resulting in induction of viral error catastrophe [Flavell, R. A., et al 1974] [Kabinger F, Stiller C, Schmitzová J, Dienemann C, Kokic G, Hillen HS, et al. 2021]. Incorporation quickly results in the production of nonviable virus. It is anticipated that the high barrier to resistance observed during in vitro passaging studies will translate to slow, if any, emergence of viral resistance in the clinic. Results from clinical studies support the therapeutic benefit of MOV in nonhospitalized individuals with mild-to-moderate COVID-19.

2.2.2 Preclinical Studies

Primary pharmacology studies demonstrating the antiviral activity of MOV against SARS-CoV-2 and other RNA viruses were conducted in vitro and in mouse, guinea pig, hamster, and ferret models of viral infection. In vitro, NHC shows broad-spectrum activity against multiple viruses including coronaviruses SARS-CoV-2, SARS-CoV, and MERS-CoV. NHC was equally effective against SARS-CoV-2 variants of concern, including alpha, beta, gamma, delta, omicron (B.1.1.529 BA.1, BA.1.1, and BA.2), as well as the variant of interest

(lambda) and variant being monitored (mu) compared with the WA1 isolate. NHC was active against coronaviruses that have mutations which reduce susceptibility to remdesivir in cell culture assays.

MOV was evaluated in nonclinical safety studies, including a standard battery of in vitro and in vivo safety pharmacology studies, genotoxicity assays (including Ames assays, in vitro and in vivo micronucleus assays, an in vivo Pig-a assay in rats, and an in vivo mutation assay in Big Blue® [BioReliance] transgenic rats), tolerability/dose-range-finding studies in mice, rats, and dogs, repeat-dose toxicity studies of up to 3 months in rats and 1 month in mice and dogs, fertility studies in male and female rats, embryo-fetal developmental toxicity studies in rats and rabbits, a pre- and post-natal developmental toxicity study in rats, and toxicity studies in juvenile rats. Additional nonpivotal short-term tolerability and/or toxicokinetic studies were conducted in mice, rats, rabbits, and monkeys.

MOV was devoid of effects on CNS, respiratory, or cardiovascular functions in well-characterized safety pharmacology models. Based on the totality of genotoxicity data, MOV is not mutagenic or genotoxic in in vivo mammalian systems.

Target organs of toxicity identified in the repeat-dose toxicity studies were limited to bone marrow in dogs only, and growth plate in rats only. Bone marrow toxicity/hematopoietic finding (with resultant pancytopenia) were observed in the 28-day oral toxicity study in dogs at ≥17 mg/kg/day (0.4-fold the clinical NHC exposure of 75.6 µM.hr at 800 mg Q12H). The adverse hematopoietic findings were dose-related, affected all hematopoietic cell lines, caused subsequent mild hematological abnormalities on Day 7 and progressively more severe hematological changes after 14 to 21 days of continuous dosing, and were shown to be reversible. Changes in the growth plate of the long bones (femur, tibia) were observed in the 3-month oral toxicity study in rats only, in males at ≥500 mg/kg/day (5.4-fold the clinical NHC AUC0-24 at the 800-mg Q12H dose) and in females at 1000 mg/kg/day (9.3-fold the clinical NHC AUC0-24 exposure). These growth plate findings are not considered relevant to adult humans, because growth plates are no longer present in the mature skeleton of adult humans.

In fertility studies in rats there were no MOV-related effects on female or male fertility, or on early embryonic development up to the highest dose tested, 500 mg/kg/day, (2.1/6.1-fold [female/male] the clinical NHC exposure at 800 mg Q12H). In pregnant rats administered MOV during the organogenesis period, developmental toxicity including embryolethality (post-implantation losses) and malformations/teratogenicity was observed at 1000 mg/kg/day (7.5-fold the clinical NHC exposure at 800 mg Q12H), and reduced fetal growth was noted at ≥500 mg/kg/day (≥2.9-fold the clinical NHC exposure at 800 mg Q12H). There was no developmental toxicity at doses up to 250 mg/kg/day (0.8-fold the clinical NHC exposure at 800 mg Q12H). Maternal toxicity included decreased food consumption and body weight losses, resulting in the early sacrifice at 1000 mg/kg/day, and decreased body weight gain at ≥500 mg/kg/day. In pregnant rabbits, developmental toxicity was limited to reduced mean fetal body weights at 750 mg/kg/day (18-fold the clinical NHC exposure at 800 mg Q12H). There was no developmental toxicity in rabbits up to 400 mg/kg/day (6.5-fold the clinical NHC exposure at 800 mg Q12H). Maternal toxicity included decreased food consumption and body weight gain, and abnormal fecal output at ≥400 mg/kg/day. In the pre- and

postnatal developmental study in rats, there was no F0 maternal or F1 generation toxicity up to the highest dose evaluated of 500 mg/kg/day (1.6-fold the clinical NHC exposure at 800 mg Q12H).

Further details of preclinical studies are provided in the IB. Collectively, the safety pharmacology and toxicology results support continued clinical development of MOV.

2.2.3 Completed and Ongoing Clinical Studies

2.2.3.1 Completed Clinical Studies

MOV has been evaluated in 3 completed Phase 1 studies (P004, P008, P012) and 1 completed Phase 2a study (P006). (Refer to the IB Section 5 for the detailed study designs on each study).

Phase 1 Studies:

MK-4482-004 was a randomized, double-blind, placebo-controlled, first in human study designed to evaluate the safety, tolerability, and PK of MOV following oral administration to healthy participants. Oral doses (50 to 1600 mg as a single dose, including 200 mg with a high-fat meal, and 50 to 800 mg as multiple doses [Q12H for 5.5 days]) of MOV or placebo administered to 130 healthy participants were generally well tolerated. Out of these 130 participants, 100 received at least one dose of MOV. No deaths or SAEs were reported.

MK-4482-008 was a single and multiple dose, randomized, placebo-controlled, double-blind study of MOV in healthy Japanese adult male participants. Single doses of MOV up to 1600 mg, including 800 mg with a high-fat meal, and multiple doses of MOV 400 mg and 800 mg Q12H for 5.5 days were generally well tolerated in healthy Japanese male adult participants. Out of 79 randomized participants, 51 received at least 1 dose of MOV. No SAEs, deaths or ECIs were reported.

MK-4482-012 was a randomized, double-blind, placebo-controlled, multiple ascending dose study to evaluate the safety, tolerability, and PK of MOV. Doses of 400, 600, and 800 mg MOV Q12H for 10.5 days were generally well tolerated in healthy adult study participants. Out of 32 randomized participants, 24 received at least 1 dose of MOV. No SAEs, deaths or ECIs were reported and no study intervention-related clinically meaningful changes in vital sign values, ECGs, or safety laboratory values (including hematology) were observed as a function of dose or treatment.

Phase 2a Study:

MK-4482-006 was a Phase 2a, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and efficacy of MOV (Q12H for 5 days) in nonhospitalized adults with COVID-19. The time to undetectable SARS-CoV-2 of viral RNA in nasopharyngeal swabs was shorter in participants receiving 800-mg MOV (median: 14 days) compared with those administered placebo (median: 15 days). MOV 200 mg (n=23), 400 mg (n=62) or 800 mg (n=55) or placebo (n=62) was generally well tolerated with a comparable incidence of AEs across the intervention groups. Four SAEs were reported (3 participants in

the MOV groups combined, 1 in the placebo group); none were considered related to study intervention by the investigator. No participants died while enrolled in the study.

2.2.3.2 Ongoing Clinical Studies

MOV is being evaluated in 1 ongoing Phase 1 study (P010), 1 ongoing Phase 1/2 study (P005), 1 ongoing Phase 2a study (P007), 2 ongoing Phase 2/3 studies (P001, P002), and 1 ongoing Phase 3 study (P013) (Refer to the IB Section 5 for the detailed study designs on each study).

Phase 1 or 1/2 Studies:

MK-4482-010 is a randomized, 4-treatment, 4-period crossover, single site, open-label, relative bioavailability study of MOV oral granules and MOV reference capsule formulations in healthy adult participants. A total of 16 participants were randomized into 4 treatment sequences consisting of a single 800-mg dose of MOV administered as oral granules in water, apple sauce or pudding or as the reference capsule formulation with water. Relative bioavailability was assessed through repeat evaluations of plasma NHC PK. The study is clinically complete, and the clinical study report is being authored.

MK-4482-005 is a Phase 1/2 randomized, multicenter, seamless, adaptive study to determine the optimal dose, safety, and efficacy of MOV for the treatment of COVID-19. The primary efficacy objective is to determine the ability of MOV to reduce serious complications of COVID-19 including hospitalization, reduction in SaO_2 <92%, or death. As of 14-MAR-2022, 18 participants enrolled in Phase 1 (12 received MOV; 300 mg n=4; 600 mg n=4; 800 mg n=4), and 178 participants enrolled in Phase 2. Enrollment is complete and patient activity is ongoing. Based on preliminary review of blinded safety data, 5 SAEs were reported, 1 of which (vomiting) was considered related to study intervention by the investigator. No deaths were reported.

Phase 2a Study:

MK-4482-007 is a Phase 2a randomized, placebo-controlled, double-blind clinical study of MOV in adults who have tested positive for SARS-CoV-2 infection via PCR and are hospitalized with a diagnosis of COVID-19 with symptoms of ≤8 days. The primary efficacy objective is to measure the proportion of nasopharyngeal swabs and saliva from recipients becoming undetectable for SARS-CoV-2 RNA at Day 5 of MOV administration compared with placebo. As of 14-MAR-2022, 71 participants were enrolled in the study and enrollment is closed as of 15-FEB-2022. Based on preliminary review of blinded safety data, SAEs were reported for 4 participants, none were considered related to study intervention by the investigator. Of the 4 participants who had SAE, one had SAE of hypovolemic shock on Day 12 and died of respiratory failure on Day 28, and one had SAE of worsening bradycardia and hypotension that required discontinuation of study intervention. No other deaths or other AEs requiring discontinuation of study intervention have been reported.

Phase 2/3 or 3 Studies:

MK-4482-001 is a Phase 2/3 randomized, placebo-controlled, double-blind clinical study to evaluate the efficacy, safety, and PK of MOV in hospitalized adults with COVID-19. In the Phase 2 portion of the study (Part 1) a total of 218 hospitalized participants with COVID-19 received at least 1 dose of MOV (72 participants received MOV 800 mg) and 75 participants received placebo. MOV was generally well tolerated with a comparable incidence of AEs across the intervention groups. SAEs were reported for 15.4% participants (15.1% MOV groups, 16.0% placebo), with 1 SAE deemed related to study intervention by the investigator (Grade 3 urticaria) for 1 participant in the MOV 200-mg treatment group. A total of 16 participants had AEs leading to death (6.4% MOV groups combined, 2.7% placebo), none of which were considered study intervention-related by investigator assessment. The study was stopped due to lack of clinical benefit in this population (participants already hospitalized prior to randomization) and did not proceed to the Phase 3 portion of the study (Part 2). Enrollment is complete and participants have completed the 7-month poststudy visit.

MK-4482-002 is a Phase 2/3, randomized, placebo-controlled, double-blind, multisite study to evaluate the efficacy, safety, and PK of MOV administered to non-hospitalized adults with laboratory-confirmed COVID-19 and symptom onset within 7 days (Part 1, Phase 2) or within 5 days (Part 2, Phase 3) prior to randomization, and all participants must have at least one risk factor for progressing to severe illness from COVID-19. Enrollment into the study is complete and the study conduct is clinically complete up to Day 29 in Part 2 (Phase 3). Participants are in the 7-month follow up period. MOV 200 mg (n=74), 400 mg (n=77), 800 mg (n=74) or placebo (n=74) Q12H for 5 days in Part 1 and MOV 800 mg (n=710) or placebo (n=701) Q12H for 5 days in Part 2 were generally well tolerated. In Part 2 (Phase 3), the proportion of participants with AEs, drug-related AEs (per investigator assessment), AEs leading to death, SAEs, and AEs leading to study intervention discontinuation, were comparable for the intervention groups. AEs leading to death occurred in a higher proportion of participants who received placebo. Enrollment is complete and participants are being followed until the 7-month poststudy visit.

MK-4482-013 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of MOV for the prevention of COVID-19 (laboratory-confirmed SARS-CoV-2 infection with symptoms) in adults residing with a person with COVID-19. As of 14-MAR-2022, 798 household participants were randomized out of a planned total of 1500 participants.

2.3 Benefit/Risk Assessment

Participants in clinical studies will not receive direct benefit from treatment during participation as clinical studies are designed to provide information about the safety and properties of an investigational medicine.

The totality of the safety data from Phase 1 through Phase 3 clinical studies and post authorization surveillance demonstrate an acceptable safety and tolerability profile of MOV.

There were no effects on cardiovascular, neurological, and respiratory function in several well-characterized safety pharmacology experimental models. The integrated assessment of the mutagenic and genotoxic potential of MOV indicates that MOV is not mutagenic or genotoxic in in vivo mammalian systems.

As described in Section 2.2.2, in a 28-day repeat dose toxicity study with MOV in dogs, reversible hematologic toxicities were noted after Day 7 at exposures 0.4-fold those of the anticipated clinical exposures at the 800-mg Q12H dose. However, to date no clinically meaningful hematological changes have been observed in healthy participants up to 800-mg MOV Q12H for up to 10.5 days or in participants with COVID-19 at multiple doses up to 800 mg Q12H for 5 days.

Histopathology results from the 3-month rat toxicity study demonstrated an increase in the thickness of the growth plate/physis, a finding not observed in 1-month studies in rats, dogs, or mice. These findings are not considered to represent a significant new risk to human adults.

In fertility studies in rats there were no MOV-related effects on female or male fertility, or on early embryonic development up to the highest dose tested, 500 mg/kg/day, (2.1/6.1-fold [female/male] the clinical NHC exposure at 800 mg Q12H). While embryolethality (post-implantation losses) and teratogenicity were limited to rats exposed to 7.5-fold the clinical NHC exposure at 800 mg Q12H during the organogenesis period, and these developmental findings were not observed in rats up to 2.9-fold the clinical NHC exposure at 800 mg Q12H and rabbits up to 18-fold the clinical NHC exposure at 800 mg Q12H, WOCBP will be required to use effective contraception for the duration of treatment and for at least 4 days postdose.

It is important to note that the animal/human AUC0-24 exposure multiples are expected to be approximately 2-fold higher when human participants are dosed only once at 800 mg.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

The study population includes male and female participants with moderate hepatic impairment between the ages of 18 and 75 years (inclusive) and healthy mean-matched controls.

Objectives	Endpoints
Primary	
• 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	
• To evaluate the safety and tolerability of molnupiravir in participants with moderate hepatic impairment.	• Adverse events
Tertiary/Exploratory	
• Objective: To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in the study	• Germline genetic variation and association to clinical data collected in this study

4 STUDY DESIGN

4.1 Overall Design

This is a nonrandomized, multi-site, open-label, single-dose study of MOV in adult male and female participants with moderate HI (Panel A; n=7) and matched healthy adult male and female participants (Panel B; n=7 to 10). Individual age and BMI of healthy-matched control participants will be within the range ± 10 years and ± 3.5 kg/m^2 of the mean age and BMI of participants with HI, respectively. In addition, the numbers of males and females of the healthy participants will be generally matched to the numbers of hepatic impaired participants within ± 1 (for the first 7 participants enrolled). Up to an additional 3 healthy participants may be enrolled as needed, to maintain the mean-matching of the healthy participant panel to the moderate HI panel. If additional healthy-matched control participants are enrolled (beyond the minimum 7 participants), the overall proportion of males and females in the healthy panel should be maintained as close as possible to the overall proportion of males and females in the HI panel. Assignment to a group will be as per [Table 1].

Table 1 Group Assignment

Panel	Impairment Stage	n	Child-Pugh Score[a]
A	Moderate[b]	7	7-9
B	Healthy Matched	7-10[c]	0

CP=Child-Pugh; HI=hepatic impaired; INR=international normalized ratio; n=number of participants

[a] CP score based on standard scoring (see below in [Table 2]). Refer to Sec. 5.1 for guidance on calculating the Child-Pugh score.

[b] At least 2 participants with a score of at least 2 on one of the laboratory parameters (reduced serum albumin, increased serum bilirubin, or increased INR) will be enrolled.

[c] A minimum of 7 healthy participants will be enrolled with the ability to enroll up to 10 participants as needed to maintain the mean-matching of the healthy participant panel to the moderate HI panel.

On Day 1, participants will receive a single-oral dose of 800-mg (4 x 200-mg capsules) MOV, followed by PK sampling until 24-hours postdose in the clinic. There will be additional outpatient visits on Day 3 and Day 4 for the collection of 48- and 72-hour postdose PK samples and a follow-up visit approximately 14 days postdose. Safety will be monitored throughout the study by repeated clinical and laboratory evaluations.

As noted, the CP classification will be used to categorize HI. The CP scale is utilized by clinicians to categorize chronic liver disease and cirrhosis and is also used to categorize participants with HI for PK studies. In the current study, patients with chronic, stable HI with features of cirrhosis due to any etiology will be enrolled, and the CP scale will be used to classify the severity of liver disease [Table 2]. The points from each row are summed, leading to the final CP score. Scores of 5 to 6, 7 to 9, and 10 to 15 are classified as having mild, moderate, or severe HI, respectively. Participants with a CP score of 7 to 9, corresponding to moderate HI, will be selected for enrollment into the current study. To ensure an adequate number of study participants with laboratory abnormalities consistent

with hepatic dysfunction, at least 2 participants will be required to have a score of at least 2 or more on one of the following laboratory parameters: reduced serum albumin, increased serum bilirubin, or increased INR.

Table 2 Severity of Liver Disease Classification (Child-Pugh Classification)

	Points for Increasing Abnormality		
Assessment	**1**	**2**	**3**
Encephalopathy [a]	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
INR	<1.7	1.7 to 2.3	>2.3
Bilirubin (mg/dL)—not PBC[b] Bilirubin (mg/dL)—only for PBC[b]	<2 <4	2 to 3 4 to 10	>3 >10
INR= International normalized ratio; PBC=Primary Biliary Cirrhosis [a]Portal-systemic encephalopathy is Staged 0 to 4. [b] Select only one depending on type of cirrhosis.			

Because this is a Phase 1 assessment of MOV in humans, the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is therefore written with flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Refer to Section 8.10.5 for examples of modifications permitted within the protocol parameters.

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 of the SoA. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

An open-label, single-dose study design has been deemed optimal to evaluate the effect of HI on the PK of NHC based on the PK properties of NHC. PK data from the completed Phase 1 study (P004) following single oral doses of 50 to 1600 mg MOV and multiple doses of 50- to 800-mg MOV (Q12H for 5.5 days) demonstrated Tmax for NHC occurred at ~ 1-hour postdose for the powder in bottle formulation and between 1.50- and 1.75-hours postdose for the capsule formulation. Following peak plasma concentrations, NHC concentrations declined in a biphasic manner and PK was linear across dose ranges. As NHC exhibits linear PK with minimal to no accumulation and single dose PK is predictive of multiple dose PK, administration of a single dose of MOV in this study is considered adequate to evaluate the effect of HI on plasma NHC PK.

Individuals without HI will serve as a control group. To adequately assess the impact of HI, enrolled participants with reasonably matched demographics to mean demographic parameters will be enrolled.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

There are no efficacy endpoints.

4.2.1.2 Safety Endpoints

Based on available clinical safety data to date, evaluation of safety will be adequately assessed from the following standard safety assessments: VS, 12-lead ECG, laboratory safety tests (blood chemistry, hematology, urinalysis) and AEs. Safety evaluations will be conducted throughout the study at intervals dictated by NHC PK properties.

4.2.1.3 Pharmacokinetic Endpoints

Following oral administration of MOV (the prodrug), MOV is only detected at very low levels in systemic circulation due to rapid conversion to NHC (the circulating nucleoside analogue). NHC exposures in plasma have been shown to be well correlated with NHC-TP exposures in PBMCs, with plasma NHC AUC being a consistent strong correlate of NHC-TP exposures. Furthermore, 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 plasma NHC exposures are considered an appropriate surrogate for the pharmacologically active NHC-TP, and therefore plasma NHC will be measured in this study for the evaluation of the primary PK objective.

The primary NHC PK parameters (AUC0-inf, Cmax) in addition to other standard NHC PK parameters (eg, AUC0-last, Tmax, t1/2, CL/F, Vd/F) following single-dose administration of MOV will sufficiently characterize the pharmacokinetic comparison between the HI group relative to control. Collection of blood samples up to 72-hours postdose is adequate based on the terminal t1/2 of NHC.

The GMR value of 2.0 included in the hypothesis for the primary endpoint was chosen based on the upper clinical comparability bound for the program. This estimate was derived based on exposure-response modeling and corresponds to plasma NHC AUC0-12 of approximately 2 times the geometric mean of model predicted AUC0-12 for patients with COVID-19 at the 800-mg dose level. This upper bound ensures that subpopulations are maintained within the range of clinical experience at 800 mg, as an adequate number of participants have achieved plasma NHC AUC0-12 values greater than this threshold in clinical studies without notable alteration in the safety and tolerability profile seen in subgroup analyses of higher exposures.

4.2.1.4 Pharmacodynamic Endpoints

No pharmacodynamic endpoints will be evaluated in this study.

4.2.1.5 Planned Exploratory Biomarker Research

4.2.1.5.1 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, severity, and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug ADME; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples may be used for research related to the study intervention(s), the disease under study, or related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes, the analysis of genetic markers throughout the genome, or analysis of the entire genome. Analysis may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to understand study disease or related conditions.

4.2.1.6 Future Biomedical Research

The Sponsor will conduct FBR on DNA specimens for which consent was provided during this clinical study.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR are presented in Appendix 6.

4.2.2 Rationale for the Use of Comparator/Placebo

Not applicable

4.3 Justification for Dose

A single 800-mg dose of MOV will be administered in this study, which is aligned with the proposed therapeutic dose of 800-mg Q12H for 5 days for adults and was the dose assessed in the pivotal Phase 3 portion of the Phase 2/3 study for the treatment of adults with COVID-19 (P002 Part 2). This dose is similarly being evaluated in an ongoing clinical study for postexposure prophylaxis in adults (P013). Assessing the effect of moderate HI with the 800-mg dose of MOV will ensure the data generated in this study is representative of the selected clinical dose level.

Of note, multiple doses up to 800-mg MOV Q12H for up to 10.5 days and single doses up to 1600-mg, were generally well tolerated in healthy participants.

As this is a Phase 1 assessment of MOV in humans, and the PK, pharmacodynamic and safety profiles of the compound are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants. Details of allowed modifications are provided in Section 8.10.5.

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EAA is defined as First Site Ready (FSR) in any Member State.

A study may be paused during review of newly available preclinical/clinical safety, PK, pharmacodynamic, efficacy, or biologic data or other items of interest, prior to a final decision on continuation or termination of the study. It may be necessary to keep the study open for gathering/reviewing of additional supportive data to optimally complete the objective(s) of the study. If necessary, the appropriate amendment(s) to the protocol and/or appropriate communication(s) will be generated. If the decision has been made to end the study following this review period, the study end will be defined as the date of the Sponsor decision, and this end of study date supersedes the definitions outlined above. The Competent Authority(ies) and IRB(s)/IEC(s) will be apprised of the maximum duration of the study beyond the last participant out and the justification for keeping the study open.

4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant meets all of the following criteria:

Type of Participant and Disease Characteristics

Moderate Hepatic Impairment Participants

1. The participant has a diagnosis of chronic (>6 months), stable HI with features of cirrhosis due to any etiology (stability of hepatic disease should correspond to no acute episodes of illness within the previous 2 months due to deterioration in hepatic function). For the purposes of this study, diagnosis of cirrhosis based on assessment on imaging features (ultrasound, transient elastography, or magnetic resonance elastography) indicative of cirrhosis in combination with clinical features of cirrhosis or biopsy-confirmed cirrhosis will be acceptable.

   Note: Individuals who have undergone a transjugular intrahepatic portosystemic shunt procedure may be considered for inclusion upon consultation with the Sponsor.

2. The participant has a score on the CP scale ranging from 7 to 9 (moderate HI) at screening. At least 2 of the participants must have a score of 2 or higher on at least 1 of the laboratory parameters (ie, albumin, INR, and/or bilirubin) at screening on the CP scale.

   Note: Baseline CP will be obtained by taking the mean of the CP score obtained from screening and from the most recent historical values within a 6-month period prior to screening. If no historical measurement is available, a second baseline CP will be assessed during the screening period (>72 hours apart) and the mean of the 2 values will be used for group assignment.

3. With the exception of HI, the participant is in generally good health based on medical history, physical examination, VS measurements and ECGs performed prior to randomization. Participants with stable, chronic medical or psychiatric conditions may be included at the discretion of the investigator and the Sponsor. Appendix 8 provides a table of the 12-Lead Electrocardiogram Abnormality Criteria.

4. With the exception of HI, the participant is in good health based on laboratory safety tests obtained at the screening visit and prior to study drug administration. Appendix 2 provides a table of laboratory safety tests to be performed. Appendix 9 provides an algorithm for the assessment of out-of-range laboratory values.

   Note: The laboratory safety test parameter values for ALT and AST must be <2X ULN before the participant can be considered eligible for inclusion. Participants with ALT and AST values ≥2X ULN and <3X ULN may be enrolled at the discretion of the investigator following consultation with the Sponsor.

Healthy Participants

5. The participant is in good health based on medical history, physical examination, VS measurements, and ECGs performed before allocation.

   Appendix 8 provides a table of the 12-Lead Electrocardiogram Abnormality Criteria.

6. The participant is in good health based on laboratory safety tests obtained at the screening visit and before administration of the initial dose of study intervention. Appendix 2 provides a table of laboratory safety tests to be performed. Appendix 9 provides an algorithm for the assessment of out-of-range laboratory values.

All Participants

Demographics

7. The participant has a BMI ≥18.5 and ≤35 kg/m^2. See Section 8.3.1 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height $(m)^2$.

8. The participant is male or female, from 18 years to 75 years of age inclusive, at the time of providing informed consent.

Male Participants

9. Male participants must agree to the following during the intervention period and for at least 90 days after the last dose of study intervention:

- Abstains from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agrees to remain abstinent

  OR

- Uses contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause, documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview) as detailed below:

  - Uses a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

  - Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Female Participants

10. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Not a WOCBP

  OR

- A WOCBP and:

  - Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 4 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

  - Has a negative highly sensitive pregnancy test (serum) as required by local regulations) within 24 hours before the first dose of study intervention. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.5.

  - Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

11. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study. The participant may also provide consent/assent for FBR. However, the participant may participate in the study without participating in FBR.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant meets any of the following criteria:

Medical Conditions

<u>Moderate Hepatic Impairment</u>

1. The participant has a history of any illness that, in the opinion of the investigator, might confound the results of the study or poses an additional risk to the participant by their participation in the study.

2. The participant is not in sufficient health, with regard to stability of hepatic impairment, to undergo participation in the study with anticipated survival of <3 months, in keeping with a MELD score of ≥25.

3. The participant is institutionalized or mentally or legally incapacitated at the time of prestudy (screening) visit or expected during the conduct of the study.

4. The participant is positive for HIV-1 or HIV-2 at the prestudy (screening) visit.

5. The participant has received antiviral and/or immune modulating therapy for HBV or HCV within 90 days prior to study start.

6. The participant has an estimated eGFR <45 mL/min/1.73 m^2 based on the CKD-EPI equation.

   CKD-EPI Equation:

   $eGFR = 142 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.200} \times 0.994^{Age} \times 1.012$ [if female]

   eGFR=estimated glomerular filtration rate (mL/min/1.73 m^2); SCr=serum creatinine (mg/dL), κ=0.7 for females and 0.9 for males, α= -0.302 for males and -0.241 for females, min indicates the minimum of Scr/k or 1, max indicates the maximum of Scr/k or 1.

   At the discretion of the investigator a measured CrCl, as determined by a 24-hour urine collection, may be used in place of, or in conjunction with, the estimate of the eGFR.

   Participants who have an eGFR or measured CrCl of up to10% below of either 45 mL/min (for CrCl) or 45 mL/min/1.73 m^2 (for eGFR) may be enrolled in the study at the discretion of the investigator.

Healthy Participants

7. The participant has a history of clinically significant endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or diseases. Participants with a remote history of uncomplicated medical events (eg, uncomplicated kidney stones, as defined as spontaneous passage and no recurrence in the last 5 years, or childhood asthma) may be enrolled in the study at the discretion of the investigator.

8. The participant is positive for HBsAg, hepatitis C antibodies or HIV-1 or HIV-2 at the prestudy (screening) visit.

9. The participant is mentally or legally incapacitated, has significant emotional problems at the time of prestudy (screening) visit or expected during the conduct of the study or has a history of clinically significant psychiatric disorder of the last 5 years. Participants who have had situational depression may be enrolled in the study at the discretion of the investigator.

All Participants

10. The participant has a history of cancer (malignancy).

    Exceptions: (1) Adequately treated nonmelanomatous skin carcinoma or carcinoma in situ of the cervix or; (2) Other malignancies that have been successfully treated with appropriate follow up and therefore unlikely to recur for the duration of the study, in the opinion of the investigator and with agreement of the Sponsor (eg, malignancies that have been successfully treated ≥10 years prior to the prestudy [screening] visit).

11. The participant has a history of significant multiple and/or severe allergies (eg, food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability (ie, systemic allergic reaction) to prescription or non-prescription drugs or food.

12. The participant has known hypersensitivity to the active substance or any of the excipients of the study drug.

13. The participant had a major surgery and/or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the prestudy (screening) visit.

Prior/Concomitant Therapy

Moderate Hepatic Impairment

14. The participant is taking medications to treat chronic medical conditions and has not been on a stable regimen for at least 1 month and/or is unable to withhold the use of the medication(s) within 4 hours prior to and 8 hours after administration of the study drug. Exceptions may be granted for participants in whom a medication regimen has been adjusted within the one-month window, at the discretion of the Investigator and following consultation with the Sponsor. See Section 5.1 for allowed medical conditions, and Section 6.5 for allowed medications.

15. The participant does not agree to follow the smoking restrictions as defined by the CRU.

Healthy Participants

16. The participant is unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs or herbal remedies beginning approximately 2 weeks (or 5 half-lives) prior to administration of the initial dose of study intervention, throughout the study (including washout intervals between treatment periods), until the poststudy visit. There may be certain medications that are permitted (see Section 6.5).

17. The participant is a smoker and/or has used nicotine or nicotine-containing products (eg, nicotine patch and electronic cigarette) within 3 months of screening.

Prior/Concurrent Clinical Study Experience

All Participants

18. The participant has participated in another investigational study within 4 weeks (or 5 half-lives, whichever is greater) prior to the prestudy (screening) visit. The window will be derived from the date of the last visit in the previous study.

Diagnostic Assessments

All Participants

19. The participant meets any of the following cardiac parameters prior to study intervention administration: QTc interval ≥470 msec for males and ≥480 msec for females, a history of risk factors for Torsades de Pointes (eg, heart failure/cardiomyopathy or family history of long QT syndrome), uncorrected hypokalemia or hypomagnesemia.

Other Exclusions

All Participants

20. The participant is under the age of legal consent.

21. The participant consumes greater than 3 servings of alcoholic beverages (1 serving is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day. Participants who consume 4 servings of alcoholic beverages per day may be enrolled at the discretion of the investigator.

22. The participant consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.

23. The participant is a regular user of cannabis (refer to exception below for use of cannabis with a medical marijuana card for HI participants) or any illicit drugs or has a history of drug (including alcohol) abuse within approximately 3 months. Participants must have a negative UDS/BDS prior to allocation. Participants with HI may be included with a positive UDS for opiates, benzodiazepines, or cannabanoids if they have an active prescription and/or medical marijuana card from a licensed health care provider.

24. The participant is unwilling to comply with the study restrictions (see Section 5.3 for a complete summary of study restrictions).

25. The investigator has any concern regarding safe participation in the study or for any other reason the investigator considers the participant inappropriate for participation in the study.

26. The participant is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

5.3.1.1 Diet Restrictions

On Day 1, participants will fast from all food and drinks, except water, for at least 8 hours before study intervention administration. Participants will fast from all food and drinks, except water, between study intervention administration and the first scheduled meal (approximately 4-hours postdose). After the 4-hour postdose standard meal has been completed, subsequent meals and snacks will be unrestricted in caloric content, composition, and timing.

To the extent possible, laboratory safety tests (hematology and chemistry) will be performed after approximately an 8-hour fast

The study intervention will be administered with approximately 240 mL of water. Additional water in approximately 50 mL increments may be provided, if needed. Water will be restricted 1 hour before and 1 hour after study intervention administration.

Instructions on whether to take MOV with or without food and/or drink may be modified during the study based on newly available data.

5.3.1.2 Fruit Juice Restrictions

Participants will refrain from the consumption of grapefruit juice, grapefruits, and grapefruit products beginning approximately 2 weeks before administration of the initial dose of study intervention, until the poststudy visit.

Participants also will refrain from the consumption of all fruit juices 24 hours before and after study intervention administration. On all other days during the study, consumption of fruits and fruit juices (except for grapefruit, grapefruit juices, and grapefruit products) is allowed.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

5.3.2.1 Caffeine Restrictions

Participants will refrain from consumption of caffeinated beverages or xanthine-containing products from 12 hours before the prestudy and poststudy visits until the completion of the study procedures and from 12 hours before and after study intervention administration. At all other times, caffeinated beverages or xanthine-containing products will be limited to no more than 6 units per day (1 unit = 120 mg of caffeine).

5.3.2.2 Alcohol Restrictions

Participants will refrain from consumption of alcohol 24 hours before the prestudy and poststudy visits until the completion of the study procedures and from 24 hours before and after study intervention administration. At all other times, alcohol consumption is limited to no more than approximately 3 alcoholic beverages or equivalent servings (1 serving is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day.

5.3.2.3 Tobacco Restrictions

Smoking (and/or the use of nicotine/nicotine-containing products) is not permitted during the study for healthy participants.

Participants in the moderate HI group will follow the smoking restrictions (and if applicable, the use of electronic cigarettes or nicotine/nicotine-containing products) defined by the CRU.

5.3.3 Activity Restrictions

Participants will avoid unaccustomed strenuous physical activity (ie, weightlifting, running, bicycling, etc) from the prestudy (screening) visit until administration of the initial dose of study intervention, throughout the study until the poststudy visit.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen-failure information may be included, as outlined in the eCRF entry guidelines. Minimal information may include demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements.

5.5 Participant Replacement Strategy

If a participant withdraws from the study a replacement participant may be enrolled if deemed appropriate by the investigator and Sponsor. The replacement participant will generally receive the same intervention or intervention sequence (as appropriate) as the participant being replaced. The replacement participant will be assigned a unique treatment/randomization number.

The study site should contact the Sponsor for the replacement participant’s treatment/allocation number.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies (MOV 200-mg capsules) will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted before dosing the replacement participant. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention to be used in this study is outlined in [Table 3]. Country-specific differences are noted in Section 10.7.

Table 3 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Moderate HI	Experimental	MK-4482 (MOV)	Drug	Capsule	200 mg	800 mg	Oral	Panel A single dose	Test Product	IMP	Provided by the Sponsor
Healthy Matched	Experimental	MK-4482 (MOV)	Drug	Capsule	200 mg	800 mg	Oral	Panel B single dose	Test Product	IMP	Provided by the Sponsor

EEA=European Economic Area;IMP=investigational medicinal product; MOV=molnupiravir, MK-4482; NIMP/AxMP=noninvestigational/auxiliary medicinal product.

The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

All supplies indicated in [Table 3] will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

Refer to Section 8.1.8 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is in Section 4.3.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Participants in this study will be allocated by nonrandom assignment.

A sample allocation schedule is shown in [Table 4].

Table 4 Sample Allocation Schedule of Participants to Treatment

Panel	Hepatic Impairment Stage	n	Treatment
A	Moderate	7	MOV 800 mg
B	Healthy Matched	7 to 10	MOV 800 mg

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the intervention administered.

6.4 Study Intervention Compliance

Participants will be dosed at the site; they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study-site staff other than the person administering the study intervention. Study-site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5 Concomitant Therapy

If a participant does not discontinue all prior medications within 14 days or 5 half-lives of the dose of study intervention, they may be included in the study if the investigator can rationalize that the specific use of a prior medication is not clinically relevant within the context of the study.

Concurrent use of any prescription or nonprescription medication, or concurrent vaccination, during the ongoing study (ie, after randomization or intervention allocation) OR during time periods specified by this protocol for that medication or vaccination must first be discussed between the investigator and Sponsor before administration, unless appropriate medical care necessitates that therapy or vaccination should begin before the investigator and Sponsor can consult. The participant will be allowed to continue in the study if both the Sponsor and the investigator agree.

Paracetamol/acetaminophen (up to 2 g total per day for participants with hepatic impairment or up to 4 g total per day for healthy participants) may be used for minor ailments without prior consultation with the Sponsor.

In addition, the following concomitant medications/vaccinations are permitted:

COVID-19 vaccine may be administered. Study intervention must be given at least 72 hours following or at least 48 hours prior to any COVID-19 vaccination.

For Participants with Moderate Hepatic Impairment:

Participants who are taking medications to treat general medical conditions and/or conditions associated with hepatic disease (eg, hypertension, non-insulin dependent diabetes mellitus, hypercholesterolemia, hypo- or hyperthyroidism, gout, depression) will be allowed to participate in the study at the discretion of the Investigator and following consultation with the Sponsor Clinical Monitor. Participants must be on a stable regimen for at least 1 month prior to study intervention administration and able to withhold the use within 4 hours prior to and 8 hours after study drug administration. Any exceptions to this must first be discussed between the Investigator and Sponsor.

Certain prescription medications used to treat manifestations of hepatic disease (eg, lactulose, neomycin, etc.) will be allowed during the study, but the participant must be on a steady dose, drug, and regimen for at least 1 month prior to dosing on Day 1. Lactulose should be restricted at least 6 hours prior to and 6 hours after dosing on Day 1 since it may potentially affect absorption.

Examples of types of medications that would be used for chronic medical conditions that would be allowed include (but are not limited to) the following:

- Angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, diuretics
- Beta blockers
- Metformin, thiazolidinediones, sulfonylureas, DPP-4 inhibitors, alpha-glucosidase inhibitors, incretin mimetics
- Statins
- Levothyroxine
- Colchicine, allopurinol
- Selective serotonin uptake inhibitors (SSRIs), tricyclic antidepressants
- Proton pump inhibitors

Participants with a valid medical marijuana card will be allowed to participate in the study at the discretion of the investigator, however use of medical marijuana should be restricted at least 24 hours prior to, and 24 hours after, study intervention administration.

Any medication (including over-the-counter) that, by the determination of the Investigator, might interfere with the study must be discontinued at least 2 weeks (or 5 half-lives of the compound, whichever is longer) prior to study intervention administration.

Medications with known effect on QT/QTc prolongation may be allowed following discussion with the Sponsor.

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified for use in this study.

6.6 Dose Modification

Dose modifications are not applicable to this study.

6.6.1 Stopping Rules

The following stopping rules will be used during the conduct of this study.

If any of the below stopping rules are met, the study will be paused, and no further dosing will occur until the Sponsor has reviewed the totality of data available. To continue the study (upon joint agreement with the Sponsor and investigator), an amendment will be submitted for approval.

1. An individual participant reports an SAE considered related to the study intervention by the investigator.

2. Two (2) or more participants report Severe Nonserious AEs considered related to the study intervention by the investigator.

6.7 Intervention After the End of the Study

There is no study-specified intervention after the end of the study.

6.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study-site personnel, the Sponsor, and/or designee are not blinded. Study intervention (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

6.9 Standard Policies

Not applicable for this study.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

In clinical studies with a single intervention, discontinuation of study intervention can only occur before the intervention. Therefore, participants who receive a single-dose intervention cannot discontinue study intervention.

7.2 Participant Withdrawal From the Study

Participants may withdraw from the study at any time for any reason. If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

A participant must be withdrawn from the study if:

- The participant or participant's legally acceptable representative withdraws consent from the study.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

- All study-related medical decisions must be made by an investigator who is a qualified physician.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be used for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study will not exceed 116.5 mL for Panel A and 93.5 mL for Panel B (refer to Study Operations Manual for Blood Volume Table). If additional pharmacokinetic and/or safety analysis is necessary, additional blood (no more than 50 mL in total) may be obtained.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study or FBR. If there are

changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

Specifics about the study and the study population are to be included in the study informed consent form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after

the participant provides documented informed consent. At the time of intervention allocation, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 14 days prior to administration of study intervention.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before intervention allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.11.1.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be allocated, by nonrandom assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation. Once a treatment/randomization number is assigned to a participant, it can never be reassigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

8.1.8 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or study staff. A hand and mouth check will be performed immediately after drug administration to ensure that the study drug has been swallowed.

8.1.8.1 Timing of Dose Administration

Participants will be dosed according to the SoA (Section 1.3). On Day 1, participants will receive a single oral dose of 800-mg MOV (4 x 200-mg capsules) at Hour 0 following an overnight fast of at least 8 hours. Dosing of MOV will take place in the morning.

The exact clock time of study intervention administration will be recorded.

8.1.9 Discontinuation and Withdrawal

The investigator or study coordinator must notify the Sponsor when a participant has been discontinued/withdrawn from the study. If a participant discontinues for any reason at any time during the course of the study, the participant may be asked to return to the clinic (or be contacted) for a poststudy visit as per the number of days described in Section 1.3 to have the applicable procedures conducted. However, the investigator may decide to perform the poststudy procedures at the time of discontinuation or as soon as possible after discontinuation. If the poststudy visit occurs prior to the safety follow-up time frame as specified in Section 8.4.1, the investigator should perform a follow-up telephone call at the end of the follow-up period (Section 8.4.1) to confirm if any AEs have occurred since the poststudy clinic visit. Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for FBR will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.10 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study. The emergency unblinding call center will be available so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.11 Domiciling

Participants will report to the CRU on Day -1 before the scheduled day of study intervention administration on Day 1 and remain in the unit until after completion of the 24-hours postdose procedures (Day 2). At the discretion of the investigator, participants may be requested to remain in the CRU longer.

Participants may be permitted to leave the unit, for emergency situations only, during the domiciling period at the discretion of the investigator after discussion with the Sponsor. The decision how to monitor the participant will be at the discretion of the investigator after discussion with the Sponsor.

8.1.12 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy/Immunogenicity Assessments

There are no direct efficacy or immunogenicity assessments in this study.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood to be drawn over the course of the study (from prestudy [screening] to poststudy visits), including approximate blood volumes drawn by visit and by sample type per participant, can be found in the Study Operations Manual.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard. Height and weight will also be measured and recorded at the timepoints listed in the SoA (Sec. 1.3).

Symptom driven physical examinations may be performed at other times at the Investigator’s discretion.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

BMI

BMI equals a person's weight in kilograms divided by height in meters squared (BMI=kg/m^2). BMI will be rounded to the nearest whole number according to the standard convention of 0.1 to 0.4 round down and 0.5 to 0.9 round up.

Body weight and height will be obtained with the participant's shoes off and jacket or coat removed.

8.3.2 Vital Signs

- Body temperature, HR, RR, and BP will be assessed.
- Body temperature will be assessed with an appropriate thermometer.
- BP and pulse measurements will be assessed in a semirecumbent position with a completely automated device. Manual techniques will be used only if an automated device is not available.

8.3.2.1 Resting Vital Signs

Vital Sign Measurements (Heart Rate and Blood Pressure)

Participants should be resting in a quiet setting without distractions in a semirecumbent position for at least 10 minutes before having VS measurements obtained. Semirecumbent VS will include HR, systolic and diastolic BP, RR, and body temperature at timepoints indicated in the SoA. The correct size of the BP cuff and the correct positioning on the participants' arm is essential to increase the accuracy of BP measurements.

The screening HR and BP will be single measurements. This may be repeated on a second screening day at the discretion of the study investigator.

The predose (baseline) HR and BP will be triplicate measurements, obtained at least 1 to 2 minutes apart within 3 hours of dosing MOV. The median of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). Postdose VS measurements will be single measurements.

Body Temperature

Body temperature will be measured. The same method must be used for all measurements for each individual participant and should be the same for all participants.

8.3.3 Electrocardiograms

- 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. Refer to Appendix 8 for evaluation and potentially significant findings.

- At each time point when triplicate ECG are required, 3 individual ECG tracings should be obtained at least 1 to 2 minutes apart, but no more than 2 minutes apart. The full set of triplicates should be completed in no more than 6 minutes.

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry before lead placement. Participants may need to be shaved to ensure proper lead placement. Female participants may need to remove interfering garments.

Participants should be resting in a semirecumbent position for at least 10 minutes before each ECG measurement.

The correction formula to be used for QTc is Fridericia.

If repeat ECGs are required, the clinical site will decide whether to leave the electrodes in place or mark the position of the electrodes for subsequent ECGs. To mark the position of the electrodes, 12-lead electrode sites will be marked on the skin of each participant with an ECG skin-marker pen to ensure reproducible electrode placement.

Predose ECGs will be obtained in triplicate at least 1 to 2 minutes apart within 3 hours before dosing MOV. The median of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). All other ECG measurements including screening, all postdose assessments and poststudy will be single measurements.

During the treatment period, if a participant demonstrates an increase in QTc interval ≥60 msec compared with median predose baseline measurement, the ECG will be repeated twice within 5 minutes. The median value of the QTc interval from the 3 ECGs will represent the value at that time point. If the median QTc interval increase from baseline for any postdose time point is ≥60 msec, the participant will continue to be monitored by repeat 12-lead ECGs every 15 minutes for at least 1 hour or until the QTc is within 60 msec of baseline. If prolongation of the QTc interval ≥60 msec persists, a consultation with a study cardiologist may be appropriate and the Sponsor should be notified.

During the treatment period, if a participant demonstrates a QTc interval ≥500 msec on a postdose ECG, the ECG will be repeated twice within 5 minutes. The median value of the QTc interval from the 3 ECGs will represent the value at that time point. If the median QTc interval is ≥500 msec, the Sponsor should be notified and the ECGs should be reviewed by a cardiologist. The participant should be telemetry monitored (until the QTc is <500 msec) or should be considered for transfer to a location where closer monitoring and definitive care (eg, a CCU or ICU) is available.

If at any time the QRS duration is prolonged ≥200 msec (and change is not considered rate related or pacing induced), then the Sponsor should be notified. The ECGs should be reviewed by a cardiologist and the participant should be considered for transfer to a location where closer monitoring and definitive care (eg, a CCU or ICU) is available.

If the participant has unstable hemodynamics, or has any clinically significant dysrhythmias noted on telemetry, the participant should be immediately transferred to an acute care setting for definitive therapy.

If prolongation of the QTc is noted, concomitant medications that prolong QTc should be held until the QTc is within 60 msec of baseline and the QTc is <500 msec.

A cardiologist will be consulted by the investigator as needed to review ECG tracings with significant abnormalities.

8.3.4 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.5 Pregnancy Testing

- Pregnancy testing:

  - Pregnancy testing requirements for study inclusion are described in Section 5.1.

  - Pregnancy testing (serum) should be conducted at the poststudy visit.

- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3.6 Photograph of Rash

Photographs of the rash are highly recommended to be taken immediately, along with any additional information that may assist the investigator to evaluate the skin reaction, skin eruption or rash occurrence in determining etiology and drug relationship.

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an AE and/or SAE was associated with a medication error, misuse, or abuse.

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention allocation, must be reported by the investigator under any of the following circumstances:

- if the participant is receiving placebo run-in or other run-in treatment,
- if the event causes the participant to be excluded from the study,
- if it is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, placebo, or a procedure.

From the time of intervention allocation through 14 days after cessation of intervention, all AEs, SAEs and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator any time outside the period specified in the previous paragraph also must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in .

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

Table 5 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period	Reporting Time Period: After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period	Reporting Time Period: After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential DILI - require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 24 hours of learning of event

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event.

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events,

including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in allocated participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Not applicable to this study.

8.4.7 Events of Clinical Interest

Selected serious and nonserious AEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.5.

2. An elevated AST or ALT laboratory value that is greater than or equal to 3X the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2X the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2X the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).

It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Clinical Director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this study.

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose of any drug administered as part of the study exceeding the dose prescribed by the protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.

There is no specific guidance available regarding overdose due to the lack of clinical experience with overdosing. In case of acute overdosage, specific medical therapy should be performed as clinically appropriate and supportive care provided through local acute care facilities as needed. Additional measures such as emptying the stomach may be considered. The Sponsor clinical director should be contacted immediately.

8.6 Pharmacokinetics

The decision as to which plasma samples collected will be measured for evaluation of PK will be collaboratively determined by the Sponsor. If indicated, these samples may also be measured and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

8.6.1 Blood Collection for Plasma NHC Assay

Sample collection, storage, and shipment instructions for plasma samples will be provided in the Study Operations Manual.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants as specified in the SoA:

- Blood for genetic analysis

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant provides documented informed consent for FBR. If the planned genetic analysis is not approved, but future biomedical research is approved, this sample will be collected for the purpose of FBR.

Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the Operations/Laboratory Manual.

8.9 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for FBR, the following specimens will be obtained as part of FBR:

- Leftover DNA for future research

8.10 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.10.1 Screening

Approximately 28 days before intervention allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

Participants may be rescreened after consultation with the Sponsor. Rescreening should include all screening procedures listed in the SoA, including consent review. Rescreen procedures cannot be conducted the day prior to intervention allocation if there are Day -1 procedures planned per protocol.

8.10.2 Treatment Period

Refer to the SoA (Section 1.3) and Administrative and General Procedures (Section 8.1).

8.10.3 Poststudy

Participants will be required to return to clinic approximately 14 days (± 2 days) after the last dose of study intervention for the poststudy visit. If the poststudy visit occurs less than 14 days after the last dose of study intervention, a subsequent follow-up verbal contact should be made at 14 days post the last dose of study intervention to determine if any AEs have occurred since the poststudy clinic visit.

8.10.4 Critical Procedures Based on Study Objectives: Timing of Procedure

For this study, the blood sample for plasma NHC assay is the critical procedure.

At any postdose time point, the blood sample for plasma NHC assay needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible. Study procedures can be performed before or after the prescribed/scheduled time.

The order of priority can be changed during the study with joint agreement of the investigator and the Sponsor Clinical Director.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

The following variance in procedure collection times will be permitted.

- PK Collection as outlined in [Table 6].

Table 6 Pharmacokinetic (Blood for Plasma NHC Assay) Collection Windows

Plasma NHC PK Collection	PK Collection Window[a]
Predose	Within 3 h prior to dosing
0 to <1 h	5 min
1 to <12 h	10 min
12 to <24 h	15 min
24 to <48 h	1 h
48 to 72 h	2 h

NHC=N-hydroxycytidine; PK=pharmacokinetic(s)
[a] PK collection windows are +/- relative to the time of dosing on Day 1

- Predose (Day 1) laboratory safety tests, serum pregnancy test (WOCBP only), UDS/BDS, and physical exam within 24 hours prior to study intervention administration

- Predose standard safety evaluations: VS (HR, BP, RR, BT) and ECG within 3 hours prior to study intervention administration

- Postdose standard safety evaluations: VS (HR, BP, RR, BT), ECG, laboratory safety tests, and physical exam

  - Prior to 24-hours postdose may be obtained within 15 minutes of the theoretical time

  - 24-hours postdose may be obtained within 1 hour of the theoretical time

8.10.5 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

This is a Phase 1 assessment of MOV in humans, and the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently outlined may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants.

As such, some alterations from the currently outlined dose and/or dosing regimen may be permitted based on newly available data, but the maximum daily dose may not exceed those currently outlined in the protocol.

- Decrease in the dose of the study intervention administered in any given panel

- Instructions to take study intervention with or without food or drink may also be modified based on newly available data

- Modification of the plasma NHC PK sample processing and shipping details based on newly available data

The PK sampling scheme currently outlined in the protocol may be modified during the study based on newly available PK data (eg, to obtain data closer to the time of peak plasma concentrations). If indicated, these collected samples may also be assayed in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

Up to additional 50 mL of blood may be drawn for safety, and/or PK analyses. The total blood volume withdrawn from any single participant will not exceed the maximum allowable volume during his/her participation in the entire study (refer to the Study Operations Manual).

The timing of procedures for assessment of safety procedures (eg, vital signs, ECG, safety laboratory tests, etc) may be modified during the study based on newly available data. Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information. These changes will not increase the number of study procedures for a given participant during his/her participation in the entire study.

It is understood that the current study may use some or none of the alterations described above. Any alteration made to this protocol to meet the study objectives must be detailed by the Sponsor in a letter to the Study File and forwarded to the investigator for retention. The letter may be forwarded to the IRB/IEC at the discretion of the investigator.

9 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

This section contains a summary of the statistical analyses for this study. Full detail is in the Statistical Methods (Section 9.6).

Pharmacokinetics:

Individual values of plasma NHC AUC0-inf after a single-dose administration of 800-mg MOV to participants with moderate HI and healthy-matched control participants will be 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-matched control) will be 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-matched control participants following a single dose of 800 mg will be supported.

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

Safety:

AEs will be tabulated by population. Summary statistics and plots will be generated for raw laboratory safety tests, ECGs, and/or VS as well as for change from baseline, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline).

Sample Size and Power Calculations:

The between-subject SD (on the natural log scale) for plasma NHC AUC0-inf and Cmax after administration of 800-mg MOV are 0.314 ln(hr*nmol/L) and 0.206 ln(nmol/L), respectively, based on the MK-4482 P004 study (1600-mg single-dose group).

With 7 participants in each panel, assuming the true GMR (HI/healthy-matched control) is 1.00, there is 98.7% power to support the hypothesis that in participants with moderate HI, the AUC0-inf of NHC is similar to that observed in the healthy-matched control participants. The true GMR can be as high as 1.28 to still maintain 80% power.

With 7 participants in each panel, the half width of 90% CI for GMR for plasma NHC Cmax on the log scale will be 0.196. The lower and upper 90% confidence limits for the true GMRs will be given by OBS/1.22 and OBS*1.22 for plasma NHC Cmax, where OBS is the observed GMR.

9.2 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be conducted by, or under the direct auspices of, the Early Clinical Development Statistics Department in collaboration with the Quantitative Pharmacology and Pharmacometrics Department and Translational Medicine Department of the Sponsor. If, after the study has begun, changes are made to the statistical analysis plan stated below, then these deviations to the plan will be listed, along with an explanation as to why they occurred, in the CSR.

9.3 Hypotheses/Estimation

Hypothesis:

In participants with moderate hepatic impairment, the GM AUC0-inf of NHC is similar to that observed in the healthy-matched control participants following a single dose of 800-mg MOV; that is, the true NHC AUC0-inf GMR (moderate hepatic impairment/healthy mean-matched control) is less than 2.0.

Estimation:

In participants with moderate HI, plasma PK (Cmax) of NHC following a single 800-mg MOV dose will be estimated and compared to those observed in healthy mean-matched control participants.

9.4 Analysis Endpoints

- Primary Endpoint: The primary PK endpoints include AUC0-inf and Cmax of plasma NHC

- Secondary Endpoint: The secondary safety endpoint is AEs.

9.5 Analysis Populations

The following populations are defined for the analysis and reporting of data. All participants will be reported, and their data analyzed, according to the treatment(s) they actually received.

All Participants as Treated: The All Participants as Treated Population consists of all participants who received at least one dose of treatment. This population will be used for assessments of safety and tolerability.

Per-Protocol: The Per-Protocol Population consists of the subset of participants who comply with the protocol sufficiently to ensure that generated data will likely exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations. Important protocol deviations will be identified to the extent possible by individuals responsible for data collection/compliance, and its analysis and interpretation. Any participants or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR. At the end of the study, all participants who are compliant with the study procedure as aforementioned and have available data considered sufficient to exhibit the effect of treatment will be included in the Per-Protocol dataset. This population will be used for the PK analyses.

9.6 Statistical 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-matched control participants will be natural log-transformed and evaluated with a linear fixed effects model containing a fixed effect for population (participants with moderate hepatic impairment and healthy control participants). An unstructured covariance matrix will be used to allow for unequal population variances via the REPEATED and GROUP statement in SAS PROC MIXED. Kenward and Roger's method will be used to calculate the denominator degrees of freedom for the fixed effect (DDFM=KR). Covariates including age, BMI, and gender may be considered. Ninety-five percent (95%) CIs for the least squares means for each population will be constructed on the natural log scale and will reference the t-distribution. Exponentiation of the least-squares

means and their corresponding 95% CIs will yield estimates for the population GMs and CIs about the GMs on the original scale. Sample SAS code is given below:

```
proc mixed data=data;
class population;
model lnpk=population /ddfm=kr;
repeated/group=population type=UN;
lsmeans population /cl alpha=0.05;
estimate 'moderate/normal' population 1 -1/cl alpha=0.1;
run;
```

To address the primary hypothesis of comparing participants with moderate HI to healthy-matched control participants, a two-sided 90% CI for the true difference in mean (moderate HI – healthy-matched control) will be calculated using the mean square error from the model and referencing a t-distribution. These confidence limits will be exponentiated to obtain the 90% CI for the true GMR (moderate hepatic impairment/healthy control). 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-matched control participants following a single dose of 800 mg will be supported.

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

The relationship between plasma PK of NHC and hepatic insufficiency will be examined in an exploratory manner via a scatter plot of PK values (NHC plasma AUC0-inf, Cmax) versus the CP score. Plots of PK values (NHC plasma AUC0-inf, Cmax) and the baseline laboratory components of the CP score (ie, bilirubin, albumin levels, and prothrombin time) will be provided. Plots of PK parameter values (NHC plasma AUC0-inf, Cmax) vs age and body weight will also be provided.

Individual values will be listed for each PK parameter including AUC0-inf, AUC0-last, Cmax, Tmax, t1/2, CL/F, and Vd/F of plasma NHC by population, and the following (non-model-based) descriptive statistics will be provided: N (number of participants with non-missing data), arithmetic mean, SD, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, GM, and geometric percent CV (calculated as 100 x sqrt(exp(s2) - 1), where s2 is the observed variance on the natural log-scale).

Safety:

AEs will be tabulated. Summary statistics and plots will be generated for raw laboratory safety tests, ECGs, and/or vital signs as well as for change from baseline, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline).

9.7 Interim Analyses

Not applicable.

9.8 Multiplicity

Since there is only 1 hypothesis in the primary objective, no multiplicity adjustment is needed.

9.9 Sample Size and Power Calculations

The between-subject SD (on the natural log scale) for plasma NHC AUC0-inf and Cmax after administration of 800-mg MOV are 0.314 ln(hr*nmol/L) and 0.206 ln(nmol/L), respectively, based on the MK-4482 P004 study (1600-mg single-dose group).

With 7 participants in each panel, assuming the true GMR (moderate HI/healthy-matched control) is 1.00, there is 98.7% power to support the hypothesis that in participants with moderate HI, the AUC0-inf of NHC is similar to that observed in the healthy-matched control participants. The true GMR can be as high as 1.28 to still maintain 80% power.

With 7 participants in each panel, the half width of 90% CI for GMR for plasma NHC Cmax on the log scale will be 0.196. The lower and upper 90% confidence limits for the true GMRs will be given by OBS/1.22 and OBS*1.22 for plasma NHC Cmax, where OBS is the observed GMR.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp and Dohme LLC, Rahway, NJ, USA (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage

underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on

behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.6 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

10.1.7 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study

completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.9 Study and Site Closure

The Sponsor or its designee may stop the study or study-site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in [Table 7] will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 7 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	BUN	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is above the ULN)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose (fasting)	Calcium	Alkaline phosphatase	Magnesium
Coagulation	• PT/INR (International normalized ratio, for hepatic impaired participants only)			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (if blood or protein is abnormal)			
Pregnancy Testing	• Highly sensitive serum hCG pregnancy test for WOCBP only			

Laboratory Assessments	Parameters
Other Screening Tests	• FSH for postmenopausal WONCBP only • Serum or urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) per site SOP • Serology (HIV-1 and HIV-2 antibodies in all participants, HBsAg, and hepatitis C virus antibody in healthy participants only)
ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; HBsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WBC=white blood cell; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential Notes: To the extent possible, laboratory safety tests (hematology and chemistry) will be performed after approximately an 8-hour fast. Predose Day 1 laboratory procedures can be conducted up to 24 hours prior to study intervention administration.	

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product for a perceived psychological or physiological reward or desired non-therapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

- Note: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.

- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. **Results in death**

b. **Is life-threatening**

   - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. **Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

- In offspring of participant taking the product regardless of time to diagnosis.

f. **Other important medical events**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer

- Is associated with an overdose

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:

  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).

  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).

  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

  - **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

    ◦ If yes, did the AE resolve or improve?

    ◦ If yes, this is a positive dechallenge.

    ◦ If no, this is a negative dechallenge.

    (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

  - **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?

    ◦ If yes, did the AE recur or worsen?

◦ If yes, this is a positive rechallenge.

◦ If no, this is a negative rechallenge.

(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

  - Yes, there is a reasonable possibility of Sponsor's product relationship:

    ◦ There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

  - No, there is not a reasonable possibility of Sponsor's product relationship:

    ◦ Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important

that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
    - Reference Section 8.4.1 for reporting time requirements.

- The site will enter the SAE data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).

- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device and Drug-device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Women of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Women of Childbearing Potential (WOCBP) Nonparticipant Only

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

- Women in the following categories are not considered WOCBP:
  - Premenarchal
  - Premenopausal female with 1 of the following:
  - Hysterectomy
  - Bilateral salpingectomy
  - Bilateral oophorectomy

- Permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity.

- Postmenopausal female

  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

10.5.2 Contraception Requirements

The following contraceptive methods should be used by WOCBP participants in the study (Section 5.1)

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[b,c] • IUS[c] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [c] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

The following contraceptive methods should be used by nonparticipant WOCBP partners of male participants in the study (Section 5.1)

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[c] • IUS[d] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly***.**
• Combined (estrogen- and progestogen- containing) hormonal contraception[c] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [c] If locally required, in accordance with CTFG guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation. [d] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research[3, 4]

The specimens consented and/or collected in this study as outlined in Section 8.9 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways with which drugs/vaccines may interact
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research[3, 4]

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research[3, 4]

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history and intervention outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage[3, 4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses using the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research[3, 4]

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens[3, 4]

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according

to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3, 4]

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants[3, 4]

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population[3, 4]

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research[3, 4]

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@MSD.com.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618

2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: 12-Lead Electrocardiogram Abnormality Criteria

	Screen Failure Criteria	Potentially Significant Postrandomization Findings
RHYTHM		
Sinus Tachycardia	>110 bpm	HR >110 bpm and HR increase of ≥25 bpm from baseline
Sinus Bradycardia	<40 bpm	HR <40 bpm and HR decrease of ≥5 bpm from baseline
Sinus Pause/Arrest	>2.0 seconds	>2.0 seconds
Atrial Premature Complex	> 1 beat	≥ 3 beats
Ventricular Premature Complex	All	≥ 3 beats
Ectopic Atrial Rhythm	None	None
Junctional Rhythm	Junctional Rhythm with HR <40 bpm	Junctional Rhythm with HR <40 bpm
Idioventricular Rhythm	All	All
Atrial Fibrillation	All	All
Atrial Flutter	All	All
Supraventricular Tachycardia	All	All
Ventricular Tachycardia	All	All
AXIS		
Left Axis Deviation	RBBB With LAHB	New Onset LAHB
Right Axis Deviation	RBBB With LPHB	New Onset LPHB
CONDUCTION		
1st Degree AV Block	PR ≥230 ms	PR ≥ 230 ms + Increase of >15 ms; or PR Increase of >25%
2nd Degree AV Block	Mobitz Type II	Mobitz Type II
3rd Degree AV Block	All	All
LBBB	All	All
RBBB	RBBB With LAHB/LPHB as Defined Above	New Onset RBBB (Not Including Rate-related)
ICRBBB (QRS <120 ms)	No Exclusion	Nothing

	Screen Failure Criteria	Potentially Significant Postrandomization Findings
Short PR/Preexcitation Syndrome	Delta Wave + PR <120 ms	Delta Wave + PR <120 ms
Other Intra-Ventricular Conduction Delay	QRS ≥130 ms	QRS ≥130 ms + Increase of ≥10 ms
QTc (B or F)		
Male	QTc ≥470 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
Female	QTc ≥480 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
HYPERTROPHY		
Atrial Abnormalities	Definite Evidence of P Mitrale or P Pulmonale	Definite Evidence of P Mitrale or P Pulmonale
Ventricular Abnormalities	Voltage Criteria for LVH Plus Strain Pattern	Voltage Criteria for LVH Plus Strain Pattern
MYOCARDIAL INFARCTION		
Acute or Recent	All	All
Old	All	All
ST/T MORPHOLOGY		
ST Elevation Suggestive of Myocardial Injury	In 2 or more contiguous leads	In 2 or more contiguous leads
ST Depression Suggestive of Myocardial Ischemia	In 2 or more contiguous leads	In 2 or more contiguous leads
T-wave Inversions Suggestive of Myocardial Ischemia	In 2 or more contiguous leads	In 2 or more contiguous leads
Non-specific ST-T Changes (In 2 or More Leads)	No exclusion	In 2 or more contiguous leads
PACEMAKER	All	All

AV=atrioventricular; bpm=beats per minute; HR=heart rate: ICRBBB=incomplete right bundle branch block; LAHB=left anterior hemiblock; LPHB=left posterior hemiblock; LVH=left ventricular hypertrophy; mm=millimeter; ms=milliseconds, PR=pulse rate; QTcB=QT correction using Bazett's formula; QTcF=QT correction using Fridericia formula; RBBB=right bundle branch block; ST/T=ST-segment/T wave.

Baseline is defined as Predose Day 1

10.9 Appendix 9: Algorithm for Assessing Out of Range Laboratory Values

For all laboratory values obtained at prestudy (screening) visit and/or predose evaluation:

A. If all protocol-specified laboratory values are normal, the participant may enter the study.

B. If a protocol specified laboratory value is outside of the parameter(s) outlined in the inclusion/exclusion criteria (including a repeat if performed), the participant will be excluded from the study.

C. If ≥1 protocol-specified laboratory value not specified in the inclusion/exclusion criteria is outside the normal range, the following choices are available:

    1. The participant may be excluded from the study;
        a. The participant may be included in the study if the abnormal value(s) is NCS (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document).
        b. The participant may be included in the study if the abnormality is consistent with a pre-existing medical condition which is not excluded per protocol (eg, elevated eosinophil count in a participant with asthma or seasonal allergies), the medical condition should be annotated on the laboratory report.

    OR

    2. The abnormal test may be repeated (refer items a. and b. below for continuation of algorithm for repeated values).
        a. If the repeat test value is within the normal range, the participant may enter the study.
        b. If the repeat test value is still abnormal, the study investigator will evaluate the potential participant with a complete history and physical examination, looking especially for diseases that could result in the abnormal laboratory value in question. If such diseases can be ruled out, and if the abnormal laboratory value is not clinically relevant, then the participant may enter the study.

D. If there is any clinical uncertainty regarding the significance of an abnormal value, the participant will be excluded from the study.

10.10 Appendix 10: Abbreviations

Abbreviation	Expanded Term
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BDS	blood drug screen
BMI	body mass index
BP	blood pressure
CCU	cardiac care unit
CG	Cockcroft-Gault
CI	confidence interval
Cmax	maximum plasma concentration
CNS	central nervous system
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
CL/F	oral clearance
COVID-19	Coronavirus disease 2019
CP	Child-Pugh
CrCl	creatinine clearance
CRF	Case Report Form
CRU	clinical research unit
CSR	Clinical Study Report
CTFG	Clinical Trial Facilitation Group
CV	coefficient of variation
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GM	geometric mean
GMR	geometric mean ratio
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HI	hepatic impairment

Abbreviation	Expanded Term
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ICU	intensive care unit
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
LAM	lactational amenorrhea method
MERS	Middle East respiratory syndrome
MERS-CoV	Middle East respiratory syndrome coronavirus
MOV	molnupiravir, MK-4482, EIDD-2801
NCS	not clinically significant
NHC	N-hydroxycytidine
NHC-TP	N-hydroxycytidine triphosphate
NOAEL	no observed adverse effect level
OBS	observed GMR
P	protocol (number)
PBC	primary biliary cirrhosis
PCL	protocol clarification letter
PCR	polymerase chain reaction
PK	pharmacokinetic
PopPK	population pharmacokinetics
Q12H	every 12 hours
RNA	ribonucleic acid
RR	respiratory rate
RSV	respiratory syncytial virus
SAE	serious adverse event
SARS-CoV	severe acute respiratory syndrome coronavirus
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SaO_2	arterial oxygen saturation
SD	standard deviation
SLAB	supplemental laboratory test(s)
SoA	schedule of activities
SOP	standard operating procedures
SUSAR	suspected unexpected serious adverse reaction

Abbreviation	Expanded Term
Tmax	time to maximum plasma concentration
t1/2	half life
UDS	urine drug screen
ULN	upper limit of normal
Vd	volume of distribution
Vd/F	apparent volume of distribution
VEEV	Venezuelan equine encephalitis virus
VS	vital signs
WBC	white blood cell
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential

11 REFERENCES

[Docherty, A. B., et al 2020]	Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ. 2020;369:m1985.	[05JQSM]
[Dorjee, K., et al 2020]	Dorjee K, Kim H, Bonomo E, Dolma R. Prevalence and predictors of death and severe disease in patients hospitalized due to COVID-19: a comprehensive systematic review and meta-analysis of 77 studies and 38,000 patients. PLoS One. 2020 Dec 7;15(12):e0243191.	[05Q59Q]
[Flavell, R. A., et al 1974]	Flavell RA, Sabo DL, Bandle EF, Weissmann C. Site-directed mutagenesis: generation of an extracistronic mutation in bacteriophage Qbeta RNA. J Mol Biol. 1974;89:255-72.	[05JF06]
[Galloway, J. B., et al 2020]	Galloway JB, Norton S, Barker RD, Brookes A, Carey I, Clarke BD, et al. A clinical risk score to identify patients with COVID-19 at high risk of critical care admission or death: an observational cohort study. J Infect. 2020;81:282-88.	[05Q59S]
[Gorbalenya, A. E., et al 2020]	Gorbalenya AE, Baker SC, Baric RS, de Groot RJ, Drosten C, Gulyaeva AA, et al. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol. 2020 Mar;5:536-44.	[05JRQN]
[Grasselli, G., et al 2020]	Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. JAMA Intern Med. 2020 Oct;180(10):1345-55.	[05Q339]

[Grasselli, G., et al 2020]	Grasselli G, Pesenti A, Cecconi M. Critical care utilization for the COVID-19 outbreak in Lombardy, Italy: early experience and forecast during an emergency response. JAMA. 2020 Apr 28;323(16):1545-6.	[05Q368]
[Guan, W., et al 2020]	Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020 Apr 30;382(18):1708-20.	[05H4S0]
[Kabinger F, Stiller C, Schmitzová J, Dienemann C, Kokic G, Hillen HS, et al. 2021]	Kabinger F, Stiller C, Schmitzová J, Dienemann C, Kokic G, Hillen HS, et al. Mechanism of molnupiravir-induced SARS-CoV-2 mutagenesis. Nat Struct Mol Biol. 2021 Aug 11.	[06G338]
[Richardson, S., et al 2020]	Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. 2020 May 26;323(20):2052-9. Erratum in: JAMA. 2020 May 26;323(20):2098.	[05Q3GB]
[Wu, Z. 2020]	Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020 Apr 7;323(13):1239-42.	[05J92M]