Official Protocol Title:	An Open-Label, Single-Dose Study to Investigate the Influence of Hepatic Impairment on the Pharmacokinetics of MK-6482
NCT number:	NCT04995484
Document Date:	24-Nov-2022

Title Page

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Protocol Title: An Open-Label, Single-Dose Study to Investigate the Influence of Hepatic Impairment on the Pharmacokinetics of MK-6482

Protocol Number: 020-02

Compound Number: MK-6482

Sponsor Name:

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

Legal Registered Address:

126 East Lincoln Avenue

PO Box 2000

Rahway, New Jersey, 07065, USA

Regulatory Agency Identifying Number(s):

IND	132,120

Approval Date: 24 Nov 2022

Sponsor Signatory

Typed Name: Title:	Date

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: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 02	24-Nov-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address. Updates were also made to the statistical analysis language.
Amendment 01	23-Nov-2021	Protocol amended per regulatory agency request to reduce the dose of MK-6482 to be administered from 120 mg to 80 mg for all participants and to add the exclusion of UGT2B17 and CYP2C19 dual poor metabolizers.
Original Protocol-Final	26-MAY-2021	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 02

Overall Rationale for the Amendment:

Sponsor underwent an entity name change and update to the address. Minor edits in the statistical analysis language were also made.

Related sections within the protocol were updated to reflect these changes, as noted in chronological order below.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Title Page 10.1.1 Code of Conduct for Clinical Trials	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
9.6.2 PK Statistical Analysis	Minor corrections were made in the statistical analysis of PK. **from**: Separately for each PK parameter, individual values of MK-6482 AUC0-inf, AUC0-24, and Cmax will be natural log-transformed and evaluated with a linear fixed effects model containing a fixed effect for population (hepatic impairment group and normal hepatic function group).	Changes were made to correct details in the statistical analysis language.

Section # and Name	Description of Change	Brief Rationale

	to: Separately for each PK parameter, individual values of MK-6482 AUC0-inf, AUC0-24, and Cmax will be natural log-transformed and evaluated with a linear mixed effects model containing a fixed effect for population (hepatic impairment group and normal hepatic function group).
	
	from: Sample SAS code is given below:
	proc mixed data=data;
	class population;
	model lnpk = population /ddfm=kr;
	repeated/ group= population;
	lsmeans population /cl alpha=0.1;
	run;
	to: 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=0.1;
	run;	

Section # and Name	Description of Change	Brief Rationale
	from: To compare participants with hepatic impairment to participants with normal hepatic function, a two sided 90% CI for the difference in means (hepatic impairment – normal hepatic function) will be calculated for each PK parameter using the mean square error from the model and referencing a t-distribution. **to**: To compare participants with hepatic impairment to participants with normal hepatic function, a two sided 90% CI for the difference in least-squares means (hepatic impairment – normal hepatic function) will be calculated for each PK parameter using the aforementioned model.	

Amendment: 01

Overall Rationale for the Amendment:

To minimize the possibility of exposing participants to unanticipated higher exposures, the dose of MK-6482 in the study is being reduced to 80 mg and UGT2B17 and CYP2C19 dual poor metabolizers will be excluded from participation.

Related sections within the protocol were updated to reflect these changes, as noted in chronological order below.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Throughout the protocol	Dose to be administered changed from MK-6482 120 mg to 80 mg.	Dose reduced to minimize the possibility of exposing participants with moderate hepatic impairment to unanticipated higher exposures.
1.1 Synopsis 3 Hypotheses, Objectives, and Endpoints	The endpoints for the Secondary Objective revised **from**: AEs, clinical safety laboratory tests, ECGs, pulse oximetry, vital signs, and physical examinations **to**: AEs and discontinuation from study due to AEs	Change made to align with the Sponsor's anticipated disclosure of results on ClinicalTrials.gov. The full list of safety assessments for the study remain unchanged (see Sec. 4.2.1.2).
1.3 Schedule of Activities	Addition of blood collection for CYP2C19 genotyping at Screening.	CYP2C19 genotyping added for eligibility assessment.

Section # and Name	Description of Change	Brief Rationale
2 Introduction	Description of MK-6482 updated **from**: MK-6482 is a potent oral small molecule inhibitor of HIF-2α, and is currently being evaluated as a treatment option for patients with advanced renal cell carcinoma and von Hippel-Lindau disease-associated renal cell carcinoma. **to**: MK-6482 (belzutifan) is a potent oral small molecule inhibitor of HIF-2α, that is indicated for the treatment of adult patients with VHL-RCC, CNS hemangioblastomas, or pancreatic neuroendocrine tumors not requiring immediate surgery. MK-6482 is also being evaluated as a treatment option for patients with solid tumor and patients with advanced RCC.	Information updated to be more current.
2.2.1 Pharmaceutical and Therapeutic Background	Updated description of the results of preclinical study in mouse VHL-deficient tumor xenograft models.	Information updated for consistency with the most recent Investigator's Brochure (Edition 9).
2.2.2.3 Clinical Studies 2.2.3 Ongoing Clinical Studies	Updated information on MK-6482 exposures and completed/ongoing studies. Added information on a case of multiple organ dysfunction syndrome reported in MK-6482-005.	Information updated to be more current and to align with the most recent Investigator's Brochure (Edition 9).

Section # and Name	Description of Change	Brief Rationale
4.1 Overall Design 5 Study Population 5.1.1 Inclusion Criteria for Participants With Healthy Hepatic Function 5.1.2 Inclusion Criteria for Participants With Moderate Hepatic Impairment	• Added the potential for male participants to have been **surgically sterilized**. • For male participants, the requirement for abstinence or contraception extended to at least 7 days after study drug administration.	• Flexibility added to allow for inclusion of male participants who have been surgically sterilized, but not vasectomized. • Timeframe for required abstinence or contraception revised to align with time needed for MK-6482 to be eliminated.
5.2.1 Exclusion Criteria for Participants With Healthy Hepatic Function 5.2.2 Exclusion Criteria for Participants With Moderate Hepatic Impairment	Added the exclusion of participants with a UGT2B17 and CYP2C19 genotype consistent with a dual poor metabolizer phenotype.	Exclusion criterion added to avoid unintended high MK-6482 exposure in study participants.
4.1 Overall Design 5 Study Population	Added additional guidance in the case that a UGT2B17 PM moderate hepatic impairment participant is enrolled in the study but a UGT2B17 PM healthy matched control participant is not enrolled.	Additional guidance added to provide clarity for the investigator.

Section # and Name	Description of Change	Brief Rationale
4.3 Justification for Dose	Added rationale for MK-6482 80 mg dose.	Provided rationale for reduction of dose in the study to MK-6482 80 mg.
8 Study Assessments and Procedures	Revised maximum amount of blood collected from each participant over the duration of the study.	Change due to addition of CYP2C19 genotyping assessment.
8.1.3 Genotyping of UGT2B17 and CYP2C19	Section added for the genotyping to be done at Screening.	Addition of previously missed section.
10.2 Appendix 2: Clinical Laboratory Tests	• Added the CYP2C19 genotyping to be done at screening. • Added erythropoietin test which was inadvertently missed in Table 7.	• CYP2C19 genotyping added for eligibility assessment. • Addition of previously missed test in Table 7.
10.8 Appendix 8: Blood Volume Table	Added blood collection for CYP2C19 genotyping and updated total blood volume per participant.	Change due to addition of CYP2C19 genotyping assessment.
10.10 Appendix 10: Abbreviations	Added the abbreviations “CNS”, “RCC” and “VHL-RCC.”	Abbreviations added for completeness.
11 References	Removal of the reference “Kranidiotis GP, Voidonikola PT, Dimopoulos MK, Anastasiou-Nana MI. Stauffer's syndrome as a prominent manifestation of renal cancer: a case report. Cases. J. 2009;2(1):49. Published 2009 Jan 13. doi:10.1186/1757-1626-2-49.”	Reference removed as it is not cited in the protocol.

Section # and Name	Description of Change	Brief Rationale
Throughout the protocol	Removal of gender-specific pronouns (eg, he/she, his/her).	Adoption of gender neutral language.
Throughout the protocol	Minor editorial revisions.	Correction of typos and other minor changes for clarity and/or to align with Sponsor protocol template changes.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: An Open-Label, Single-Dose Study to Investigate the Influence of Hepatic Impairment on the Pharmacokinetics of MK-6482

Short Title: MK-6482 Hepatic Impairment Study

Acronym: Not Applicable

Hypotheses, Objectives, and Endpoints:

The following objectives will be evaluated in male and female participants with moderate hepatic impairment and matched control participants with normal hepatic function.

Objectives	Endpoints
Primary	
• To compare the plasma PK of MK-6482 following a single oral 80 mg dose of MK-6482 in participants with moderate hepatic impairment to that of healthy matched control participants. • Estimation: The plasma PK (AUC0-inf and Cmax) of MK-6482 following a single oral 80 mg dose of MK 6482 to participants with moderate hepatic impairment will be estimated and compared to those in healthy matched control participants.	• AUC0-inf, AUC0-24, Cmax, Tmax, and apparent terminal t½ of plasma MK-6482.
Secondary	
• To evaluate the safety and tolerability of a single oral 80 mg dose of MK-6482 in participants with moderate hepatic impairment.	• AEs and discontinuation from study due to AEs.

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Renal Cell Carcinoma
Population	Adult male and female participants with moderate hepatic impairment and healthy adult male and female 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 8 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 16 participants will be allocated as described in Section 9.10.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Intervention Group Name</th><th>Drug</th><th>Dose Level</th><th>Dose Frequency</th><th>Route of Administration</th><th>Treatment Period</th><th>Use</th></tr>
<tr><td>Moderate Hepatic Impairment Group</td><td>MK-6482</td><td>80 mg</td><td>Single dose</td><td>Oral</td><td>1 day</td><td>Experimental</td></tr>
<tr><td>Healthy Control Group</td><td>MK-6482</td><td>80 mg</td><td>Single dose</td><td>Oral</td><td>1 day</td><td>Experimental</td></tr>
</table>
Other current or former name or alias for study intervention is as follows: PT2977.
</td></tr>
<tr><td>Total Number of Intervention Groups/ Arms</td><td>2</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate in the study for approximately 6 weeks from the time the participant provides documented informed consent through the final contact.</td></tr>
</table>

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 for the study are outlined in Appendix 1.	

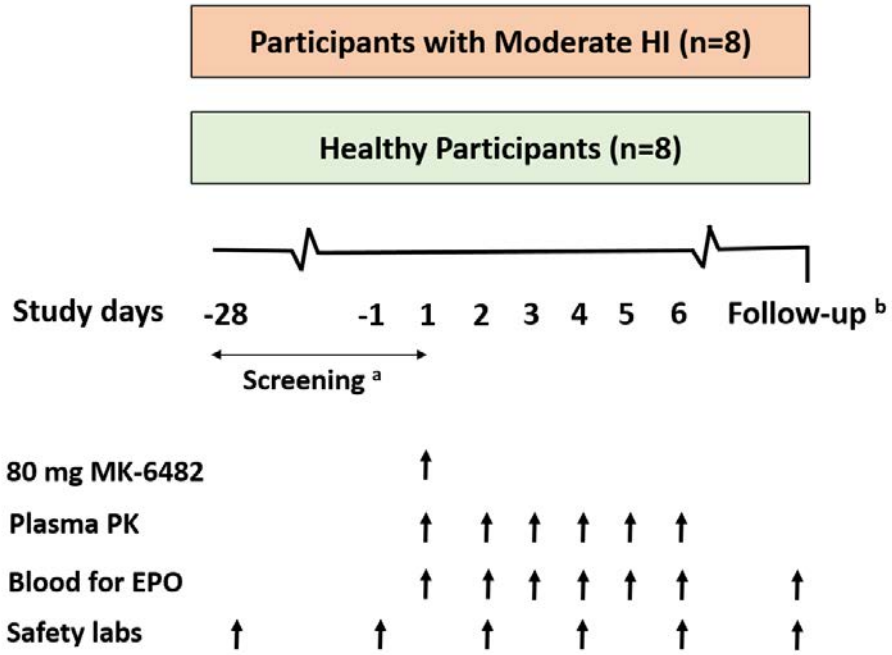
Study Accepts Healthy Volunteers: Yes

A list of abbreviations is in Appendix 10.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Schema



[a] Screening will occur within 28 days prior to Day 1
[b] Follow up will occur approximately 14 days after the study intervention administration

1.3 Schedule of Activities

All Groups										
		Intervention								Notes
Scheduled Day	**Scr**	**-1 (C-I)**	**1**	**2**	**3**	**4**	**5**	**6**	**Poststudy or ET**	Poststudy (follow-up) will occur approximately 14 days after study intervention administration [Sec. 8.11.4].
Administrative Procedures										
Informed Consent	X									Screening will occur within 28 days prior to study intervention administration [Sec. 8.1.1.1].
Informed Consent for Future Biomedical Research	X									Sec. 8.1.1.2.
Assignment of Screening Number	X									Sec. 8.1.7.
Inclusion/Exclusion Criteria	X	X								Only specific criteria will be reviewed at check-in. [Sec. 5.1 and 5.2].
Medical History	X									Includes review of substance usage (illicit drugs, alcohol, tobacco, and caffeine).
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	Sec. 6.5.
Assignment of Treatment/Allocation Number			X							Sec. 8.1.8.
Domiciling		X	X	X	X	X	X	X		Sec. 8.1.12.
Safety Procedures										
Complete Physical Examination	X								X	To be conducted also for participants who discontinue/withdraw from the study.
Symptom-driven Physical Examination		X	X	X	X	X	X	X		Only to be conducted if the participant's symptoms warrant an examination or at the investigator's or designee discretion.
Height	X									
Weight	X	X							X	BMI to be calculated only at Screening.
HR, BP, and RR	X	X	X	X	X	X	X	X	X	To be performed at Day -1, predose, and at 24, 48, 72, 96 and 120 hours postdose, and poststudy or prior to early termination from the study.
T	X	X	X	X	X	X	X	X	X	To be performed at Day -1, predose, and at 24, 48, 72, 96 and 120 hours postdose, and poststudy or prior to early termination from the study.

All Groups										
		Intervention								Notes
Scheduled Day	**Scr**	**-1 (C-I)**	**1**	**2**	**3**	**4**	**5**	**6**	**Poststudy or ET**	Poststudy (follow-up) will occur approximately 14 days after study intervention administration [Sec. 8.11.4].
12-lead ECG	X	X		X		X		X	X	To be performed at Day -1, and at 24, 72, and 120 hours postdose, and poststudy or prior to early termination from the study.
Pulse Oximetry	X	X	X	X	X	X	X	X	X	To be performed at Day -1, predose, and at 24, 48, 72, 96 and 120 hours postdose, and poststudy or prior to early termination from the study.
Child-Pugh Classification	X									To be for participants with hepatic impairment only. At least five (5) participants will be required to have total bilirubin within the range of >1.5X ULN and ≤3X ULN.
NCI-ODWG Classification	X									To be for participants with hepatic impairment only. At least five (5) participants will be required to have total bilirubin within the range of >1.5X ULN and ≤3X ULN.
Blood for UGT2B17 Genotyping	X									At least 2 UGT2B17 IM and at least 2 UGT2B17 EM will be enrolled per group.
Blood for CYP2C19 Genotyping	X									
Serum FSH (postmenopausal females only)	X									
HIV, Hepatitis B and C screen	X									
Urine/Saliva Drug Screen	X	X								
Urine/Blood/Breathalyzer Alcohol Screen	X	X								
Hem, Serum Chem, and UA	X	X		X		X		X	X	To be performed at Day -1, and at 24, 72, and 120 hours postdose, and poststudy or prior to early termination from the study.
Coagulation	X								X	To be performed also for participants who discontinue/withdraw from the study.
AE/SAE review	X	X	X	X	X	X	X	X	X	Sec. 8.4 or poststudy contact details.
Study Intervention Administration										
MK-6482 Administration			X							
Pharmacokinetics										
Blood for Plasma MK-6482 and PT3317 Assay			X	X	X	X	X	X		To be collected at predose, and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 24, 36, 48, 72, 96, and 120 hours postdose.

All Groups										
		Intervention								Notes
Scheduled Day	**Scr**	**-1 (C-I)**	**1**	**2**	**3**	**4**	**5**	**6**	**Poststudy or ET**	Poststudy (follow-up) will occur approximately 14 days after study intervention administration [Sec. 8.11.4].
Blood for Protein Binding			X							To be collected at predose.
Pharmacodynamics										
Blood for Erythropoietin			X	X	X	X	X	X	X	To be collected at predose, and at 24, 48, 72, 96, and 120 hours postdose and poststudy.
Biomarkers										
Blood for Genetic Analysis			X							To be collected predose from enrolled participants only [Sec. 8.8].

Abbreviations: AE=adverse event, BMI=body mass index, BP=blood pressure, C-I=check-in, Chem=chemistry, CRU=clinical research unit, CYP=cytochrome P450, ECG=electrocardiogram, EM=extensive metabolizer, EPO=erythropoietin, ET=early termination, FSH=follicle-stimulating hormone, Hem=hematology, HIV=human immunodeficiency virus, HR=heart rate, IM=intermediate metabolizer, NCI-ODWG=National Cancer Institute - Organ Dysfunction Working Group, RR=respiratory rate, SAE=serious adverse event(s), Scr=screening, T=body temperature, UA=urinalysis, UGT=uridine 5'-diphospho-glucuronosyltransferase.

2 INTRODUCTION

MK-6482 (belzutifan) is a potent oral small molecule inhibitor of HIF-2α, that is indicated for the treatment of adult patients with VHL-RCC, CNS hemangioblastomas, or pancreatic neuroendocrine tumors not requiring immediate surgery. MK-6482 is also being evaluated as a treatment option for patients with solid tumor and patients with advanced RCC. HIF-2α is a transcription factor that is overexpressed in many cancers and promotes tumorigenesis. HIF-2α forms a heterodimeric complex with HIF-1β (also called ARNT), and subsequently binds to hypoxic response elements of target genes which regulate hypoxic signaling, tumor cell growth and survival. MK-6482 binds to HIF-2α, preventing its heterodimerization with HIF-1β, and resulting in decreased transcription and expression of HIF-2α target genes. The proposed therapeutic dose of MK-6482 is 120 mg once daily.

2.1 Study Rationale

The liver is involved in the clearance of many drugs through a variety of oxidative and conjugative metabolic pathways and/or through biliary excretion of the unchanged drug or metabolites. Alterations of excretion and metabolism by hepatic insufficiency can lead to lower drug clearance. Hepatic disease can alter the absorption and disposition of drugs as well as their efficacy and safety. In accordance with the FDA hepatic impairment guidance (FDA 2003), a Sponsor should evaluate the PK of its investigational drug in hepatic impaired participants when hepatic metabolism and/or excretion accounts for a substantial portion (>20% of the absorbed drug) of the elimination of the parent or active metabolite.

In vitro, MK-6482 is a substrate of UGT2B17, CYP2C19 and CYP3A4. UGT2B17 and CYP2C19 are polymorphic enzymes and the relative contribution of these 2 enzymes to the elimination of MK-6482 has been elucidated by multiple means including an exploratory pharmacogenetic analysis, a population PK analysis, and a clinical evaluation of the impact of specific UGT2B17 and CYP2C19 variants on the single-dose PK of MK-6482. The collective results of these analyses indicate that UGT2B17 is the major route of elimination in individuals who express this enzyme. MK-6482 glucuronide (PT3317), represents the major circulating human metabolite formed by UGT2B17. Accordingly, PT3317 exposures are greatly reduced in participants who have decreased or absent UGT2B17 activity. In individuals with absent UGT2B17 activity, CYP2C19 is a major route of elimination. The overall contribution of CYP3A4 to MK-6482 metabolism is anticipated to be minor in individuals with intact UGT2B17 and CYP2C19 enzyme activity. A human ADME study (MK-6482-008) is currently ongoing, and anticipated to confirm that hepatic metabolism represents a major elimination pathway (>20% of the absorbed drug) for MK-6482.

Since MK-6482 is anticipated to be predominantly eliminated by hepatic metabolism, evaluation of the impact of hepatic impairment on MK-6482 PK is useful. The primary objective of this study is to investigate the impact of moderate hepatic impairment on MK-6482 PK.

2.2 Background

Refer to the IB for detailed background information on MK-6482.

2.2.1 Pharmaceutical and Therapeutic Background

MK-6482 is a potent and selective inhibitor of HIF-2α both *in vitro* and *in vivo*. HIF-2α is known to form a heterodimeric complex with HIF-1β, which is also referred to as ARNT; the heterodimer can then bind to hypoxic response elements in target genes and induce their transcription. The PAS domains of HIF are essential for heterodimerization of the HIF-2α:HIF-1β subunits, a prerequisite for target gene induction. A unique ligand-binding pocket has been identified in the PAS-B domain of HIF-2α (Scheuermann et al., 2013). MK-6482 binds in this pocket, thereby disrupting HIF-2α:ARNT heterodimerization and directly inhibiting the function of HIF-2α.

In tumor cells in which HIF-2α is activated, MK-6482 block the transcription of several genes involved in oncogenesis, including cyclin D1, VEGF-A, and the glucose transporter SLC2A1. MK-6482 has showed antitumor activity in mouse VHL-deficient tumor xenograft models with nearly complete regression of established tumors after oral administration of MK-6482 at 0.3 mg/kg bid. No activity was observed with MK-6482 treatment in VHL-proficient ccRCC tumors. MK-6482 showed no off-target activity against a panel of 76 receptors and 8 ion channels (at concentrations up to 12.5 μM), and no off-target activity at 10 μM against a panel of 40 protein kinases and 2 protein phosphatases.

2.2.2 Preclinical and Clinical Studies

2.2.2.1 Preclinical Pharmacokinetics and Metabolism

MK-6482 PK was evaluated in mice, rats, dogs, and monkeys. MK-6482 has low aqueous solubility and high permeability (BCS Class 2) and is well absorbed following oral administration in animals at clinically relevant doses. The oral bioavailability of MK-6482 was shown to be high in mice (approximately 100%), moderate in dogs and monkeys (33% and 53%, respectively), and low in rats (18%). The *in vitro* plasma protein binding of MK-6482 ranged from 45 to 61% across species (45% in human plasma).

Following an oral dose of [^{14}C]MK-6482 in rats, radioactivity distributed rapidly to most tissues and was reversible. The mean overall recovery of dose ranged from 93.9% to 97.1%. Biliary excretion accounted for 85% and 80.2% of the radioactive dose in bile-duct cannulated male and female rats, respectively.

In vitro and *in vivo* metabolism studies for MK-6482 revealed primarily oxidation and O glucuronidation biotransformation pathways. The oxidation biotransformation pathways were greatest in rats, and similar between humans and dogs. PT3317, the primary metabolite of MK-6482 found in dog and monkey plasma samples, was confirmed by chemical synthesis to be a glucuronide. UGT reaction phenotyping with recombinant UGTs was used

to determine that PT3317 formation is mediated by UGT2B17, which is mainly expressed in the small intestine. Importantly, PT3317 has no activity against HIF-2α.

Urinary excretion was found to be a minor pathway for elimination of MK-6482 (≤4% of dose) and PT3317 (≤13% of dose) for rats, dogs and monkeys.

A summary of MK-6482 nonclinical PK and metabolism is contained in the IB supplied by the Sponsor. The IB should be reviewed in conjunction with this study protocol.

2.2.2.2 Preclinical Toxicology

MK-6482 was not genotoxic in the in vitro bacterial mutagenicity assay (Ames), nor in the in vitro micronucleus assay, indicating a low genotoxic risk from MK-6482 exposure.

The in vivo safety pharmacology assessments of the cardiovascular, central nervous, and respiratory systems included in general toxicology studies did not yield any adverse findings. The cardiovascular system was assessed by hemodynamic and electrocardiographic parameters in the GLP 28-day and 13-week repeat-dose toxicity studies in dogs, and no change from baseline was observed with MK-6482 treatment.

The toxicity of orally administered MK-6482 was evaluated in 28-day and 13-week repeat dose GLP studies in rats and dogs. Effects on the RBC compartment were observed consistently in both species, where RBC count, hemoglobin and hematocrit levels were decreased by approximately 30 to 50 % at all doses. The effects on the RBC compartment were reversed once MK-6482 administration stopped and are considered an “on-target” pharmacologic activity of HIF-2α antagonism on EPO production.

In the rat toxicity studies with MK-6482, off-target organ toxicity was identified in the male reproductive system. The MK-6482 related effects involved testes (smaller/soft testes and decreased weight associated with hypo-spermatogenesis, germ cell degeneration and multinucleated giant cells), and epididymis (oligospermia), and were not reversible within 26-week recovery periods. These findings were associated with decreased sperm motility and sperm counts, and increased number of abnormal sperms in the sperm analysis. No effects on sperm evaluation and histopathology of testes/epididymides were observed in male dogs. No effects on the female reproductive organs were observed in either rats or dogs.

In a preliminary embryofetal toxicity study where pregnant rats were administered MK-6482, a significant level of post implantation loss indicative of embryofetal lethality and/or reduced fetal body weight, reduced ossification, and malformations in surviving fetuses was observed at an exposure close to the clinically relevant exposure at 120 mg/day.

A summary of MK-6482 nonclinical toxicology is contained in the IB supplied by the Sponsor. The IB should be reviewed in conjunction with this study protocol.

2.2.2.3 Clinical Studies

As of a cutoff date of 15-JUN-2021, MK-6482 has been administered as single or multiple doses to a total of 135 healthy participants. In addition, MK-6482 is being evaluated as monotherapy or in combination with other anticancer treatments in participants with solid tumors.

Based on the overall integrated safety summary of MK-6482 monotherapy (N=181) across MK-6482-001 and MK-6482-004 studies, the adverse drug reactions identified for MK-6482 include anemia due to decreased EPO, fatigue, nausea, dyspnea, hypoxia, and dizziness. Most anemia events were ≤Grade 2. Anemia is an on-target effect of MK-6482 because of the impact of HIF on EPO expression and reduction in EPO and HGB levels with MK-6482 administration. Anemia has been medically managed with erythropoiesis stimulating agent administration and/or blood transfusion as indicated and dose interruption/reduction. Hypoxia is managed by oxygen supplementation as indicated and dose interruption/reduction. Anemia due to decreased EPO and hypoxia should be closely monitored and medically managed as indicated.

Single MK-6482 doses up to 200 mg have been evaluated in 4 completed single-dose Phase 1 studies in healthy participants, and multiple daily doses up to 7 days of 120 mg have been administered to healthy participants in the completed midazolam DDI study (MK-6482-009). MK-6482 was generally well tolerated in these studies. All reported AEs were categorized as either mild or moderate in intensity. In healthy participant studies, there have been no SAEs and no discontinuations due to AEs attributed to MK-6482 treatment. There have been no reports of anemia, hypoxia, or fatigue in the completed healthy participant studies. In addition, no clinically significant reductions in HGB or HCT have occurred in healthy participants in the 4 completed single-dose Phase 1 studies. Mean reductions in HGB and HCT of about 12% from baseline were observed in the completed midazolam DDI study (MK-6482-009) after multiple daily doses of 120 mg, consistent with the anticipated on-target effect of EPO suppression for MK-6482.

A summary of the MK-6482 clinical development program is contained in the IB supplied by the Sponsor. The IB should be reviewed in conjunction with this study protocol.

CCI [redacted] In the ongoing trials, MK-6482 appears to have a tolerable and manageable safety profile with low numbers of discontinuations due to an AE and most AEs being mild to moderate in severity.

PPD [redacted] The Sponsor considers that there is no conclusive evidence to support a causal relationship between MK-6482 and the aforementioned events since there were several confounding factors in the causality assessment reported for these AEs, including but not limited to prior/concomitant medications, daily alcohol consumption and possible concurrent illnesses. However, the Sponsor cannot definitively exclude the possibility of a causal relationship between MK-6482 treatment and the reported events. Of note, more than 600 participants with solid tumors/advanced RCC have received MK-6482 as monotherapy or in combination with other anticancer treatments and no other case of multiple organ failure has been reported. The Sponsor will continue to monitor the safety profile of MK-6482 in the clinical program.

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. An indirect health benefit to the participants enrolled in this study is the free medical tests received at screening and during the study.

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.

The safety monitoring practices employed by this protocol (ie, 12-lead ECG, pulse oximetry, vital signs, clinical laboratory tests, AE questioning, and physical examination) are adequate to protect the participants' safety and should detect all expected treatment-emergent AEs.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

The following objectives will be evaluated in male and female participants with moderate hepatic impairment and matched control participants with normal hepatic function.

Objectives	Endpoints
Primary	
• To compare the plasma PK of MK-6482 following a single oral 80 mg dose of MK-6482 in participants with moderate hepatic impairment to that of healthy matched control participants. • Estimation: The plasma PK (AUC0-inf and Cmax) of MK-6482 following a single oral 80 mg dose of MK 6482 to participants with moderate hepatic impairment will be estimated and compared to those in healthy matched control participants.	• AUC0-inf, AUC0-24, Cmax, Tmax, and apparent terminal t½ of plasma MK-6482
Secondary	
• To evaluate the safety and tolerability of a single oral 80 mg dose of MK-6482 in participants with moderate hepatic impairment.	• AEs and discontinuation from study due to AEs.
Tertiary/Exploratory	
• To compare the plasma PK profile of PT3317 following a single oral 80 mg dose of MK-6482 in participants with moderate hepatic impairment to that of healthy matched control participants	• AUC0-inf, AUC0-24, Cmax, Tmax and apparent terminal t½

• To evaluate and compare erythropoietin levels following a single oral 80 mg dose of MK-6482 in participants with moderate hepatic impairment to that of healthy matched control participants.	• Erythropoietin levels
• To explore the PK of MK-6482 following a single oral 80 mg dose of MK-6482 in participants with moderate hepatic impairment by the NCI classification.	• AUC0-inf, AUC0-24, Cmax, Tmax, and apparent terminal t½ plasma MK-6482
• 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 this study.	• Germline genetic variation and association to clinical data collected in this study.
• To investigate the relationship between the genetic polymorphisms of UGT2B17 and CYP2C19 and the PK of MK-6482. Variation in UGTB17 and CYP2C19 alleles may be analyzed for association with any laboratory or clinical data collected in this study.	• Germline genetic variation in UGT2B17 and CYP2C19 and association to clinical data collected in this study.

4 STUDY DESIGN

4.1 Overall Design

This is a nonrandomized, parallel-group, multi-site, open-label study of MK-6482 in participants with moderate hepatic impairment and healthy matched control participants.

Screening of participants will occur within 28 days prior to study intervention administration.

A total of approximately 16 adult male (vasectomized or surgically sterilized) and female (non-childbearing potential only) participants will be enrolled: 8 participants with moderate hepatic impairment and 8 matched control participants with normal hepatic function.

Assignment to hepatic function group will be as follows:

Impairment Stage	N	Child-Pugh Score [a]
Moderate	8 [b]	7-9 [c]
Healthy	8 [b]	Not applicable

a. A Child-Pugh classification will be performed only for participants with impaired hepatic function at Screening.

b. At least 2 UGT2B17 IMs and at least 2 EMs will be enrolled per group.

c. At least five (5) participants with moderate hepatic impairment will be required to have total bilirubin within the range of >1.5X ULN and ≤3X ULN.

Following enrollment of all participants with moderate hepatic impairment, the healthy matched control participants will be enrolled. Each healthy control participant will be matched to the mean age (± 15 years) and mean BMI (±20%), sex (similar males/female ratio in each group), and UGT2B17 genotype (at least 2 IMs and 2 EMs) of participants with moderate hepatic impairment. If a UGT2B17 PM moderate hepatic impairment participant is enrolled in the study, a UGT2B17 PM healthy matched control participant will be included. If after reasonable efforts, a UGT2B17 PM healthy matched control participant is not enrolled, an additional participant with moderate hepatic impairment (ie, a 9th moderate hepatic impairment participant), who is not UGT2B17 PM, will be enrolled. This additional moderate hepatic impairment participant should be matched to the mean age (± 15 years) and BMI (± 20%) of the other 8 hepatically impaired participants. The final healthy matched control participant (ie, the 8th healthy control participant), who is also not UGT2B17 PM, should also be matched to the mean age (± 15 years), BMI (± 20%), and sex (with a similar male/female ratio in each group) of the 8 moderate hepatic impairment participants (ie, not including the 9th hepatically impaired participant).

On Day 1, participants will receive a single oral dose of 80 mg MK-6482, followed by serial blood sampling collection up to 120 hours postdose to characterize the PK of MK-6482 and PT3317. Serial blood sampling will be collected up to poststudy for erythropoietin measurements. Safety will be monitored throughout the study.

Because this is a Phase 1 assessment of MK-6482 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 8.11.6 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

Available preclinical data indicate that MK-6482 is anticipated to be predominantly eliminated by hepatic metabolism, therefore hepatic impairment may affect the PK of MK-6482. The purpose of this study is to compare PK of MK-6482 in participants with moderate hepatic impairment to the PK in participants with normal hepatic function.

This study employs healthy control participants with normal hepatic function that will be reasonably matched to the mean demographic parameters of the moderate hepatic impairment group to control for the influence of covariates.

The sample size of approximately 8 participants enrolled in each group (moderate hepatic impairment and healthy control) has been selected following the FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function (FDA 2003). Additional participant(s) may be enrolled if a participant discontinues from the study before the completion of the PK assessment to ensure there are at least 8 evaluable participants in each group.

The Child-Pugh classification (Table 1) will be used to categorize hepatic impairment due to its widespread use and acceptance by regulatory agencies (including the US FDA [FDA 2003]). The general study design is aligned with the relevant FDA guidelines for drugs that undergo substantial hepatic metabolism. A survey by the FDA of several PK studies conducted in participants with varying degrees of hepatic impairment, where Child-Pugh scale was used to assess hepatic impairment, has demonstrated a correlation between oral drug clearance and degree of hepatic impairment. In the current study, participants with chronic, stable moderate hepatic insufficiency will be enrolled using the Child-Pugh scale. The scale employs five clinical measures of liver disease as listed in Table 1 and Table 2. Assessment of each clinical measure is scored on a scale of 1 to 3, with 3 indicating most severe derangement. A composite of all five scores for each clinical measure is determined for each participant. Participants with composite scores of 7 to 9 on this Child-Pugh scale are classified as having moderate hepatic impairment.

Table 1 Derivation of Child-Pugh Classification Score [1]

Parameter	1 point	2 points	3 points
Serum albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
Total serum bilirubin (mg/dL)	<2	2 to 3	>3
International normalized ratio or prothrombin time (sec prolonged)	<1.7 <4	1.7 to 2.2 4 to 6	>2.2 >6
Ascites	Absent	Slight or participant on one medication to control ascites	Moderate or participant on medications to control ascites
Hepatic encephalopathy grade (see Table 2)	None	Grade 1 or 2(or suppressed with medication)	Grade 3 or 4

Table 2 Determination of Hepatic Encephalopathy Grade [1]

Hepatic Encephalopathy Grade	Definition
0	Normal consciousness, personality, neurological examination, electroencephalogram
1	Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles/sec waves
2	Lethargic, time-disoriented, inappropriate behavior, asterixis, ataxia, slow triphasic waves
3	Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
4	Unrousable coma, no personality/behavior, decerebrate, slow 2 to 3 cycles/sec delta activity

[1] Adapted from U.S. Department of Health and Human Services. Guidance for Industry. Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (2003).

An alternative classification system for hepatic impairment has been developed by the NCI ODWG to guide chemotherapy dosing for NCI sponsored clinical trials (Patel et al., 2004). The NCI classification system is a simpler method to employ in a clinical practice setting since it uses 2 laboratory parameters to grade hepatic dysfunction: total bilirubin and aspartate aminotransferase. Of note, discordance between the Child-Pugh and NCI classifications for categorizing hepatic impairment was recently reported, which may have implications for dosing recommendations for oncology therapeutics (Elmeliegy et al., 2021). To ensure that the majority of participants in this study would be categorized as having moderate hepatic impairment using both classification methods, at least five (5) participants with moderate hepatic impairment will be required to have total bilirubin values at screening within the range of >1.5X ULN and ≤3X ULN.

Mild hepatic impairment, as defined using the NCI classification, was not identified as a significant covariate based on a population PK analysis using concentration data across multiple MK-6482 clinical studies. Specifically, the geometric mean for steady-state AUC was ~1.37-fold for participants categorized as having mild hepatic impairment (N=8) compared to participants with normal hepatic function (N=109) (23.34 µg*h/mL versus 17.06 µg*h/mL). As noted above, discordance between the Child-Pugh and NCI classifications for hepatic dysfunction was reported (Elmeliegy et al., 2021). Specifically, 64.9%, 73.7%, and 61.5% of participants with mild, moderate, and severe hepatic impairment, respectively, via Child-Pugh were classified as at least 1 category less impaired via NCI. Since the Child-Pugh scale is more commonly used in PK studies in participants with hepatic impairment and recommended by both FDA and EMA for these types of studies, it will be used to determine participant eligibility and to assess hepatic impairment in this study.

4.2.1 Rationale for Endpoints

4.2.1.1 Pharmacokinetic Endpoints

The primary endpoints for this study will include the PK parameters of AUC0-inf and Cmax of MK-6482. Plasma PK parameters included in this primary endpoint will be evaluated and compared between participants with moderate hepatic impairment with Child-Pugh classification compared to participants with healthy hepatic function, using GMR and CI to assess differences between two groups. Additional PK parameters include AUC0-last, AUC0-24, Tmax, apparent terminal t½, C24, CL/F, and Vz/F.

The exploratory endpoints will include comparison of MK-6482 PK parameters between participants with hepatic impairment by NCI classification compared to participants with healthy hepatic function.

In addition to assessing the parent MK-6482 levels, the PT3317 metabolite PK parameters will be evaluated as exploratory endpoints in healthy and hepatically impaired participants. This assessment will help in understanding the role of hepatic impairment in formation of PT3317 metabolite.

4.2.1.2 Safety Endpoints

Safety and tolerability of MK-6482 monotherapy has been studied in Phase 1 and Phase 2 clinical studies. Overall, MK-6482 has a tolerable and manageable safety profile with low numbers of discontinuations due to an AE and most AEs being mild to moderate in severity. The most common adverse drug reactions identified based on the integrated aggregate safety assessment of all available information includes hypoxia, anemia, fatigue, dyspnea, dizziness. Therefore, the standard safety monitoring of AEs, physical examinations, 12-lead ECGs, pulse oximetry, vital signs, laboratory tests (hematology, serum chemistry, and urinalysis), obtained throughout the study should be adequate to assess safety and tolerability of MK-6482 in this study.

4.2.1.3 Pharmacodynamic Endpoints

Circulating serum levels of erythropoietin will be used as a pharmacodynamic marker of MK-6482 activity. Erythropoietin expression is regulated by HIFs, therefore MK-6482 inhibition of HIF is expected to cause erythropoietin reduction which could cause decrease in hemoglobin levels.

4.2.1.4 Planned Exploratory Biomarker Research

4.2.1.4.1 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.

In addition to studying variation across the human genome, UGT2B17 and CYP2C19 polymorphisms will be investigated specifically for their impact on MK-6482 PK and drug response.

4.2.1.5 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.

4.3 Justification for Dose

The proposed MK-6482 dose for this trial is 80 mg daily. Since MK-6482 clearance is predicted to occur predominantly by hepatic metabolism, MK-6482 exposures in patients with moderate hepatic impairment are anticipated to be increased compared to healthy control participants. Based on a population PK analysis using concentration data across multiple MK-6482 clinical studies, the geometric mean for steady-state AUC for 120 mg daily is ~1.37-fold for participants categorized as having mild hepatic impairment (N=8) using the NCI classification compared to participants with normal hepatic function (N=109) (23.34 µg*h/mL versus 17.06 µg*h/mL). By leveraging the previously reported relationship between Child Pugh and NCI classifications (Elmeliegy M et al. 2021), the geometric mean for steady-state AUC for MK-6482 120 mg daily is estimated to be ~2.13-fold for participants categorized as having moderate hepatic impairment (Child-Pugh B) compared to participants with normal hepatic function (36.29 µg*h/mL versus 17.06 µg*h/mL). To minimize the possibility of exposing participants with moderate hepatic impairment to

unanticipated higher exposures, a lower dose (80 mg) than the clinical dose for MK-6482 (120 mg) will be evaluated in this trial.

Multiple daily doses of 240 mg daily and 120 mg twice daily of MK-6482 have been administered to patients with advanced solid tumors, which were associated with 1.5 and 2.3-fold increases in AUC compared to 120 mg, respectively. The predicted higher exposures following a single 80 mg dose in patients with moderate hepatic impairment are within the range of observed exposures in the MK-6482 clinical development program.

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).

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

Vasectomized or surgically sterilized male participants and female participants of nonchildbearing potential between the ages of 18 and 75 years (inclusive) will be enrolled in this study.

Participants with normal hepatic function will match to the mean demographic parameters of the moderate hepatic impairment group. Healthy control participants will be matched for the mean age (± 15 years), mean BMI (±20%), sex (similar males/female ratio in each group), and UGT2B17 genotype (at least 2 IMs and 2 EMs in each group). If a UGT2B17 PM moderate hepatic impairment participant is enrolled in the study, a UGT2B17 PM healthy matched control participant will be included. If after reasonable efforts, a UGT2B17 PM healthy matched control participant is not enrolled, an additional participant with moderate hepatic impairment (ie, a 9th moderate hepatic impairment participant), who is not UGT2B17 PM, will be enrolled. This additional moderate hepatic impairment participant should be

matched to the mean age (± 15 years) and BMI (± 20%) of the other 8 hepatically impaired participants. The final healthy matched control participant (ie, the 8th healthy control participant), who is also not UGT2B17 PM, should also be matched to the mean age (± 15 years), BMI (± 20%), and sex (with a similar male/female ratio in each group) of the 8 moderate hepatic impairment participants (ie, not including the 9th hepatically impaired participant).

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

5.1 Inclusion Criteria

5.1.1 Inclusion Criteria for Participants With Healthy Hepatic Function

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

1. Is in good health based on medical history, physical examination, vital sign measurements, and ECGs performed at the prestudy (screening) visit and before administration of study intervention.
2. Is in good health based on laboratory safety tests obtained at the prestudy (screening) visit and before administration 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.
3. Has a BMI 18.0-40.0 kg/m^2, inclusive. See Section 8.3.1 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height $(m)^2$. BMI must be within ± 20% of the mean BMI in the hepatic impairment group.

Demographics

4. Is male or female, from 18 years to 75 years of age inclusive, at the time of signing the informed consent. Age must be within ± 15 years of the mean age in the hepatic impairment group.

Male Participants

5. Male participants are eligible to participate if they have been vasectomized or undergone surgical sterilization for at least 4 months or more prior to study intervention administration and agree to the following during the intervention period and for at least 7 days (time needed for MK-6482 to be eliminated) after administration of study intervention:

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

OR

- Must agree to use contraception as detailed below:
  - Agree to use 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

6. A female participant is eligible to participate if:
   - She is a WONCBP, as defined in Appendix 5.

Informed Consent

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

5.1.2 Inclusion Criteria for Participants With Moderate Hepatic Impairment

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

1. With exception of the hepatic impairment, is in good health, in the opinion of the investigator, based on medical history, physical examination, vital sign measurements, and ECGs performed at the prestudy (screening) visit and before administration of the study intervention.
2. With exception of the hepatic impairment, is in good health, in the opinion of the investigator, based on laboratory safety tests obtained at the prestudy (screening) visit and before administration 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.
3. Has a BMI 18.0-40.0 kg/m^2, inclusive. See Section 8.3.1 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height $(m)^2$.
4. Has a score on the Child-Pugh scale of B (a score of 7-9 on Child-Pugh Score) at the prestudy (screening) visit. At least five (5) participants with moderate hepatic impairment will be required to have total bilirubin range within >1.5X ULN and ≤3X ULN.

5. Has a diagnosis of chronic (>6 months), stable (no acute episodes of illness within the previous 30 days from administration of study intervention due to deterioration in hepatic function) hepatic impairment.

Demographics

6. Is male or female, from 18 years to 75 years of age inclusive, at the time of signing the informed consent.

Male Participants

7. Male participants are eligible to participate if they have been vasectomized or undergone surgical sterilization for at least 4 months or more prior to study intervention administration and agree to the following during the intervention period and for at least 7 days (time needed for MK-6482 to be eliminated) after administration of study intervention:
   - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

     OR

   - Must agree to use contraception as detailed below:
     - Agree to use 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

8. A female participant is eligible to participate if:
   - She is a WONCBP, as defined in Appendix 5.

Informed Consent

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

5.2 Exclusion Criteria

5.2.1 Exclusion Criteria for Participants with Healthy Hepatic Function

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

Medical Conditions

1. Has a history of clinically significant endocrine, GI, 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 from administration of study intervention, or childhood asthma) may be enrolled in the study at the discretion of the investigator.
2. 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 from administration of study intervention. Participants who have had situational depression may be enrolled in the study at the discretion of the investigator.
3. 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).

4. Has an estimated CrCl ≤70 mL/min based on the CG Equation.

   Cockcroft-Gault Equation:

   $$\text{CrCl} = \frac{(140 - \text{age[yr]})(\text{body wt [kg]})}{(72)(\text{serum creatinine [mg/dL]})}$$

   [When creatinine is measured in µmol/L, use this formula]

   $$\text{CrCl} = \frac{(140 - \text{age[yr]})(\text{body wt[kg]})}{(72)(\text{serum creatinine [µmol/L]} \times 0.0113)}$$

   For females, multiply the result by 0.85.

   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 CrCl.

5. 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 nonprescription drugs or food.
6. Is positive for HBsAg, hepatitis C antibodies, or HIV.
7. Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the prestudy (screening) visit.

Prior/Concomitant Therapy

8. Is unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs (with the exception of prescription drugs that are approved by the investigator and Sponsor) or herbal remedies as indicated in Section 6.5 for the prohibited period of time. There may be certain medications that are permitted (see Section 6.5).
9. Has received any nonlive vaccine starting from 14 days prior to study intervention or is scheduled to receive any nonlive vaccine through 30 days following study intervention.

   Exception: 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.

Prior/Concurrent Clinical Study Experience

10. Has participated in another investigational study within 4 weeks (or 5 half-lives, whichever is greater) prior to study intervention administration. The window will be derived from the date of the last study intervention administration in the previous study.

Diagnostic Assessments

11. Has a UGT2B17 and CYP2C19 genotype consistent with a dual poor metabolizer phenotype.
12. Has hemoglobin level below the lower limit of the normal range at the prestudy (screening visit) or check-in.
13. Has a pulse oximetry reading <92% at rest at the prestudy (screening visit) or check-in.
14. Has a QTc interval >470 msec at the prestudy (screening visit) or check-in, has a history of risk factors for Torsades de Pointes (eg, heart failure/cardiomyopathy or family history of long QT syndrome), has uncorrected hypokalemia or hypomagnesemia, is taking concomitant medications that prolong the QT/QTc interval.

Other Exclusions

15. Is under the age of legal consent.
16. Is a heavy smoker or heavy user of nicotine-containing products (>20 cigarettes or equivalent/day).
17. Smokers who do not agree to consume ≤10 cigarettes or equivalent/day from the time of the prestudy (screening) visit and until the last PK sample collection.

18. Consumes greater than 3 glasses of alcoholic beverages (1 glass 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 glasses of alcoholic beverages per day may be enrolled at the discretion of the investigator.
19. 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.
20. Is a regular user of cannabis, any illicit drugs or has a history of drug (including alcohol) abuse within approximately 2 years prior to the prestudy (screening) visit. Participants must have a negative drug screen at the prestudy (screening) visit or before administration of study intervention.
21. Presents any concern by the investigator regarding safe participation in the study or for any other reason the investigator considers the participant inappropriate for participation in the study.
22. Is unwilling to comply with the study restrictions (see Section 5.3 for a complete summary of study restrictions).
23. 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.

5.2.2 Exclusion Criteria for Participants With Moderate Hepatic Impairment

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

Medical Conditions

1. 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 from administration of study intervention. Participants who have had situational depression may be enrolled in the study at the discretion of the investigator.
2. 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).

3. Has an estimated CrCl ≤60 mL/min based on the CG Equation.

   Cockcroft-Gault Equation:

   $$\text{CrCl} = \frac{(140-\text{age[yr]})(\text{body wt [kg]})}{(72)(\text{serum creatinine [mg/dL]})}$$

[When creatinine is measured in µmol/L, use this formula]

$$CrCl = \frac{(140-age[yr])(body\ wt[kg])}{(72)(serum\ creatinine\ [\mu mol/L] \times 0.0113)}$$

For females, multiply the result by 0.85.

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 CrCl.

4. 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 nonprescription drugs or food.
5. Has fluctuating or rapidly deteriorating hepatic function within the prestudy (screening) period, in the opinion of the investigator.
6. History of liver or other solid organ transplantation.
7. Has transjugular intrahepatic portosystemic shunt and/or has undergone portacaval shunting.
8. Has encephalopathy Grade 3 or worse within 28 days before administration of study intervention.
9. Is positive for HIV. HBsAg positive participants are allowed to enroll if HBV DNA is below 1000 copies/mL in the plasma. Participants who are positive for HCVAb can be enrolled but must not have detectable HCV RNA in the plasma.
10. Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the prestudy (screening) visit.

Prior/Concomitant Therapy

11. Is unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs (with the exception of prescription drugs that are approved by the investigator and Sponsor) or herbal remedies as indicated in Section 6.5 for the prohibited period of time. There may be certain medications that are permitted (see Section 6.5).
12. Has received any nonlive vaccine starting from 14 days prior to study intervention or is scheduled to receive any nonlive vaccine through 30 days following study intervention.

    Exception: 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.

Prior/Concurrent Clinical Study Experience

13. Has participated in another investigational study within 4 weeks (or 5 half-lives, whichever is greater) prior to study intervention administration. The window will be derived from the date of the last study intervention administration in the previous study.

Diagnostic Assessments

14. Has a UGT2B17 and CYP2C19 genotype consistent with a dual poor metabolizer phenotype.
15. Has hemoglobin level below 9.5 g/dL at the prestudy (screening visit) or check-in. Participants with hemoglobin ≥9.0g/dL may be enrolled to the study at discretion of the investigator and following consultation with the Sponsor.
16. Has a pulse oximetry reading <92% at rest at the prestudy (screening visit) or check-in.
17. Has a QTc interval >480 msec at the prestudy (screening visit) or check-in, has a history of risk factors for Torsades de Pointes (eg, heart failure/cardiomyopathy or family history of long QT syndrome), has uncorrected hypokalemia or hypomagnesemia, is taking concomitant medications that prolong the QT/QTc interval.

Other Exclusions

18. Is under the age of legal consent.
19. Is a heavy smoker or heavy user of nicotine-containing products (>20 cigarettes or equivalent/day).
20. Smokers who do not agree to consume ≤10 cigarettes or equivalent/day from the time of the prestudy (screening) visit and until the last PK sample collection.
21. Consumes greater than 3 glasses of alcoholic beverages or equivalent (1 glass 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 glasses of alcoholic beverages per day may be enrolled at the discretion of the investigator.
22. 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. Is a regular user of cannabis, any illicit drugs or has a history of drug (including alcohol) abuse within approximately 2 years prior to the prestudy (screening) visit. Participants must have a negative drug screen at the prestudy (screening) visit or before administration of study intervention.
24. Presents any concern by the investigator regarding safe participation in the study or for any other reason the investigator considers the participant inappropriate for participation in the study.
25. Is unwilling to comply with the study restrictions (see Section 5.3 for a complete summary of study restrictions).
26. 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

Fasting requirements for study procedures, such as but not limited to laboratory safety evaluations are specified in Appendix 2.

On Day 1, participants will fast from all food and drinks, except water, for at least 10 hours before study intervention administration and until at least 4 hours postdose. Thereafter, there will be no restrictions (other than those provided in Section 5.3.1) regarding meals and snack(s). While in the CRU, participants will fast from all food and drinks except water between meals and snacks. Otherwise, there are no dietary restrictions other than those defined below.

After study intervention administration, if a participant exhibits symptom(s) of hypoglycemia, a sugary beverage may be provided at the discretion of the investigator, and must be documented.

Water will be provided during study intervention administration. Water will be restricted 1 hour before and 1 hour after study intervention administration.

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 study intervention, throughout the study and until the last PK sample collection.

Participants also will refrain from the consumption of all fruit juices at least 24 hours before and after study intervention administration. On all other days during the study, consumption of fruits and fruit juices (except for grapefruit juice, grapefruits, 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 at least 12 hours before the prestudy and poststudy visits and from at least 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 servings per day (1 unit = 120 mg of caffeine).

5.3.2.2 Alcohol Restrictions

Participants will refrain from consumption of alcohol at least 24 hours before the prestudy and poststudy visits and from at least 48 hours before study intervention administration and until last PK sample collection. At all other times, alcohol consumption is limited to no more than approximately 3 glasses of alcoholic beverages or equivalent (1 glass 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

Participants will follow the smoking restrictions (and if applicable, the use of nicotine/nicotine-containing products) defined by the CRU.

5.3.3 Activity Restrictions

Participants will avoid unaccustomed strenuous physical activity (ie, weight lifting, running, bicycling, etc) from the prestudy (screening) visit until administration of the of study intervention, throughout the study (including washout intervals between treatment periods) and 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/allocation 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 (eg, MK-6482) 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.

Table 3 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength	Dosage Level	Route of Administration	Treatment Period	Use	IMP/ NIMP	Sourcing
Moderate Hepatic Impairment Group	Experimental	MK-6482	Drug	Tablet	40 mg	80 mg	Oral	1 day	Experimental	IMP	Sponsor
Healthy Control Group	Experimental	MK-6482	Drug	Tablet	40 mg	80 mg	Oral	1 day	Experimental	IMP	Sponsor

IMP=investigational medicinal product; NIMP=noninvestigational medicinal product.

The classification of IMP 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/NIMP 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 8.1.9 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

Each participant will be assigned a unique identification number upon screening. Participants who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique treatment/allocation number at the time of dosing, different from the screening number, and will receive the study intervention.

Participants will receive the treatment on one occasion, as depicted in Table 4.

Table 4 Allocation Schedule

Group	N	Treatment
Moderate hepatic impairment participants	8	80 mg MK-6482
Healthy participants	8	80 mg MK-6482

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

A qualified designee will be responsible for monitoring the administration of the timed oral doses. A mouth check will be performed by the qualified designee to ensure that the participants have swallowed the study intervention. Once a participant has finished the dosing water, the qualified designee will use a flashlight and a tongue depressor to check the participant's mouth. Participants' hands will also be verified to ensure that the study intervention was ingested.

6.5 Concomitant Therapy

Participants with Hepatic Impairment Only

Participants with moderate hepatic impairment, who are taking medications to treat manifestations of hepatic disease or medications needed to treat stable diseases (eg, diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers, lactulose, or rifaximin or antibiotics used for spontaneous bacterial peritonitis like fluoroquinolones) may be allowed to participate in the study at the discretion of the investigator and following consultation with the Sponsor. Participants are required to be on stable medication regimen (steady-dose, drug, and regimen) for at least 14 days before administration of study intervention and be able to withhold the use of their maintenance

medication until after at least 4 hours postdose. Phosphate binders containing aluminum, calcium, or lanthanum salts; iron supplements or other metal cations; or multivitamins containing iron or zinc must be withheld for at least 8 hours before administration of study intervention and for at least 6 hours postdose.

Concurrent use of any prescription or nonprescription medication, or concurrent vaccination, during the ongoing study (ie, after intervention allocation)] 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.

Participants with Normal Hepatic Function Only

If a participant does not discontinue all prior medications within 14 days or 5 half-lives of study intervention administration, 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 intervention allocation)] 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.

All Participants

Any drugs known to be inhibitors or inducers of UGT2B17 or CYP2C19, and any drugs known to be strong or moderate inhibitors or inducers of CYP3A4 enzymes will be restricted for at least 28 days before administration of study intervention and until the last PK sample collection. Drugs known to be weak inhibitors or inducers of CYP3A may be allowed as per investigator discretion following consultation with the Sponsor. Appropriate sources (eg, Flockhart Table™) will be consulted to confirm lack of PK/pharmacodynamic interaction with study intervention.

Following administration of study intervention, acetaminophen (up to 2 g per 24 hours) may be administered for minor ailments at the discretion of the intervention or designee.

Participants must not have received another investigational agent within 4 weeks (or 5 half-lives, whichever is greater) before administration of study intervention.

All medications taken by participants during the course of the study will be recorded.

Nonlive vaccines may only be administered in consultation with the Sponsor prior to or following the receipt of study intervention according to the time frames specified in Exclusion Criteria (Section 5.2).

Exception: 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.

6.5.1 Rescue Medications and Supportive Care

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

6.6 Dose Modification (Escalation/Titration/Other)

The dose and administration of the study intervention to any participant may not be modified. If necessary, a participant must be discontinued for the reasons described in Section 7.

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.

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

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

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 8.1.10. 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 193 or 228 mL (Appendix 8).

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 their 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 their 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 their 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 Genotyping of UGT2B17 and CYP2C19

After the participant provides written informed consent using IRB-approved study ICF, CYP2C19 genotype and UGT2B17 polymorphisms will be investigated as a genetic screening.

8.1.4 Participant Identification Card

Not applicable as the study site will use its SOP for participant identification.

8.1.5 Medical History

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

8.1.6 Prior and Concomitant Medications Review

8.1.6.1 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 28 days before administration of study intervention.

8.1.6.2 Concomitant Medications

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

8.1.7 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. 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.

8.1.8 Assignment of Treatment/Allocation Number

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

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

8.1.9 Study Intervention Administration

Administration of study intervention will be monitored by the investigator and/or study staff.

The pharmacy at the CRU will provide each dose in individual unit dose containers for each participant, as per the allocation scheme.

Participants will be instructed not to crush, split, or chew the study intervention.

8.1.9.1 Timing of Dose Administration

On Day 1, 80 mg (2x40 mg tablets) MK-6482 will be administered at Hour 0.

The study intervention will be administered with approximately 240 mL of water following at least a 10-hour fast and participants will continue to fast for at least 4 hours postdose. See Section 5.3.1 for additional information on meal restrictions throughout the study.

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

8.1.10 Discontinuation and Withdrawal

The investigator or study coordinator must notify the Sponsor when a participant has been discontinued/withdrawn from the study and/or intervention. If a participant discontinues for any reason at any time during the course of the study and/or intervention, 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 8.11.4] 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.

8.1.10.1 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.

8.1.11 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study.

8.1.12 Domiciling

Participants will be admitted to the CRU on Day -1, at the time indicated by the CRU, and will be housed until 120 hours postdose on Day 6. Participants may be admitted earlier than Day -1 for testing not related to study protocol as per CRU requirements (eg, COVID-19 testing).

At all times, a participant may be required to remain at the CRU for longer at the discretion of the investigator or designee.

8.1.13 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 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/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in Section 10.8 (Appendix 8).

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.

Symptom-driven physical examinations may be performed at other times, if deemed necessary by the investigator or designee.

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

Single measurements of T, RR, BP, and HR, will be measured as outlined in SoA (Section 1.3). Additional vital signs may be taken at any other times, if deemed necessary.

BP and HR measurements will be performed with participants in a seated position for at least 5 minutes before assessing vital signs, except when they are supine or semi-reclined because of study procedures and/or AEs (eg, nausea, dizziness) or if deemed necessary by the investigator or designee.

8.3.3 Electrocardiograms

- Single 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. Additional ECGs may be taken at any other times, if deemed necessary by the investigator or designee.
- ECGs will be performed with participants in a supine position, for at least 5 minutes before the measurement. All ECG tracings will be reviewed by the investigator or designee.
- 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.
- The correction formula to be used for QTc is Fridericia.
- If a participant demonstrates an increase in QTc interval ≥60 msec compared with the 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.
- 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 may be consulted by the investigator as needed to review ECG tracings with significant abnormalities.

8.3.4 Pulse Oximetry

Pulse oximetry will be obtained as outlined in the SoA (Section 1.3). Each participant will have a baseline pulse oximetry (oxygen levels as saturation [%] and HR) reading done at check-in.

Readings may be taken at other times, if deemed necessary by the investigator or designee. Any oxygen saturation reading deemed clinically significant by the investigator will be documented.

8.3.5 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 eCRF. 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 eCRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 1 day after the 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.

8.3.6 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 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 for randomized participants only if the event causes the participant to be excluded from the study, or 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 approximately 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 Table 5.

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 (Randomized participants only)	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
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

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation (Randomized participants only)	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:
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), including the pregnancy of a male participant's female partner, 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.

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. For healthy control participants only:

   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.

3. An AE of anemia.
4. An AE of hypoxia.
5. An AE of dyspnea.

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.

8.6 Pharmacokinetics

Plasma samples for evaluation of MK-6482 and PT3317 PK will be collected at scheduled time points as delineated in the SoA.

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.

8.6.1 Blood Collection for Plasma MK-6482 and PT3317

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

8.7 Pharmacodynamics

Blood samples for erythropoietin analysis will be collected at scheduled time points as delineated in the SoA.

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 will be drawn for UGT2B17 and CYP2C19 genotyping and for planned analysis of the association between genetic variants in DNA and drug response. If the IRB/IEC does not approve of the planned analysis of the association between DNA variation and drug response, or if there is a local law or regulation prohibiting the same, data analysis will be limited to UGT2B17 and CYP2C19. Leftover extracted DNA will be stored for FBR if the participant provides documented informed consent for 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 Health Economics Medical Resource Utilization and Health Economics

Not applicable

8.11 Visit Requirements

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

8.11.1 Screening

Approximately 28 days before administration of study intervention, 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/randomization if there are Day -1 procedures planned per protocol.

8.11.2 Treatment Period

Refer to the SoA (Section 1.3).

8.11.3 Discontinued Participants Continuing to be Monitored in the Study

At any point if a participant discontinues from the study but continues to be monitored in the study, all study procedures specified in the SoA may be completed at the discretion of the investigator and with Sponsor agreement.

8.11.4 Poststudy (Follow-up)

All participants who received the study intervention (including participants who terminate the study early) will return to the CRU approximately 14 days after study intervention administration for poststudy (follow-up) procedures, and to determine if any AE has occurred since the last study visit. If the poststudy visit occurs less than 14 days after administration of study intervention, a subsequent follow-up telephone call should be made at 14 days post administration of study intervention to determine if any AEs have occurred since the poststudy clinic visit.

8.11.5 Critical Procedures Based on Study Objectives: Timing of Procedure

For this study, the blood sample for MK-6482 and PT3317 is the critical procedure.

At any postdose time point, the blood sample for MK-6482 and PT3317 need 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 Postdose Pharmacokinetic (Blood) Collection Windows

PK Collection (relative to dosing)	**PK Collection Window** (relative to scheduled time for collection)
0 to 2 hours	5 min
>2 to 12 hours	15 min
>12 to 48 hours	1 hour
>48 to 120 hours	2 hours

- Postdose standard safety evaluations: vital signs, ECG, pulse oximetry, and laboratory safety tests
  - Prior to 24-hours postdose may be obtained within 15 minutes of the theoretical sampling time
  - Between 24-hours and 48-hours postdose may be obtained within 1 hour of the theoretical sampling time
  - From 48-hours to 120-hours postdose may be obtained within 2 hours of the theoretical sampling time.

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

This is a Phase 1 assessment of MK-6482 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 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.

- Instructions to take study intervention with or without food or drink may also be modified based on newly available data
- Modification of the PK/pharmacodynamic 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 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 their participation in the entire study (Appendix 8).

The timing of procedures for assessment of safety procedures (eg, vital signs, ECG, safety laboratory tests, pulse oximetry, etc) may be modified during the study based on newly available data. Additional safety laboratory 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 their 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

Data will be handled and process according to Celerion SOPs, which are written based on the principles of GCP.

9.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this study. Full detail is in the SAP to be provided separately.

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in an SAP. The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate.

9.2 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be conducted by the Data Management and Biometrics department at Celerion.

If, after the study has begun, changes are made to the statistical analysis 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

Primary Estimation:

Estimation 1: The plasma PK (AUC0-inf and Cmax) of MK-6482 following a single oral 80 mg dose of MK-6482 to participants with moderate hepatic impairment will be estimated and compared to those in healthy matched control participants.

9.4 Analysis Endpoints

The primary PK endpoints will be AUC0-inf and Cmax of MK-6482 following a single oral dose of MK-6482 to participants with moderate hepatic impairment compared to those in healthy matched control participants.

Additional PK endpoints will be other PK parameters of MK-6482 including AUC0-last, AUC0-24, AUC%extrap, C24, Tmax, apparent terminal t½, λz, CL/F and Vz/F. Relevant PK parameters for PT3317 will also be presented.

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 study intervention(s) they actually received.

All Participants as Treated (APaT): The All Participants as Treated Population consists of all participants who received the study intervention. This population will be used for assessments of safety and tolerability.

Per-Protocol (PP): The Per-Protocol Population consists of the subset of participants who comply with the protocol sufficiently to ensure that generated data will be likely to 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 prior to unblinding 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

9.6.1 PK Descriptive Statistics

Individual values will be listed for each PK parameter by group and analyte, and the following (non-model-based) descriptive statistics will be provided: N (number of participants with non-missing data), arithmetic mean, standard deviation, arithmetic percent

CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s^2) - 1), where s^2 is the observed variance on the natural log-scale.

9.6.2 PK Statistical Analysis

Separately for each PK parameter, individual values of MK-6482 AUC0-inf, AUC0-24, and Cmax will be natural log-transformed and evaluated with a linear mixed effects model containing a fixed effect for population (hepatic impairment group and normal hepatic function group). 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). Ninety percent (90%) CIs for the least squares means for each population will be constructed on the natural log scale and will reference the t-distribution. Exponentiating the least-squares means and their corresponding 90% CIs will yield estimates for the population geometric means and confidence intervals about the geometric means 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=0.1;
run;
```

To compare participants with hepatic impairment to participants with normal hepatic function, a two sided 90% CI for the difference in least-squares means (hepatic impairment – normal hepatic function) will be calculated for each PK parameter using the aforementioned model. These confidence limits will be exponentiated to obtain the 90% confidence interval for the ratio of geometric means (hepatic impairment/normal hepatic function) for each PK parameter. A sensitivity analysis may be performed without poor metabolizers at UGT2B17 or CYP2C19 if applicable as deemed clinically appropriate.

Figures showing summary concentration-time profiles by hepatic impairment category for both MK-6482 and PT3317 (linear plot with arithmetic mean (±SD) for concentration and semi-log plot with arithmetic mean) will be provided. Individual participant concentration-time profiles may also be provided in the appendix separately and/or as overlays using hepatic impairment category as grouping variable. A table showing summary PK parameter values with GMs (%GCV) by population, will be provided for PK parameters, AUC0-inf, AUC0-last, AUC0-24, Cmax, C24, Tmax, apparent terminal t½, CL/F (parent only), and Vz/F (parent only). A table showing the GMR (hepatic impairment/normal hepatic function) and corresponding 90% CI will be provided for PK parameters, AUC0-inf, AUC0-24, and Cmax.

Individual values will be listed for each PK parameter for MK-6482 (AUC0-inf, AUC0-last, AUC0-24, Cmax, C24, Tmax, apparent terminal t½, CL/F, Vz/F, AUC%extrap[percentage of AUC0-inf obtained by extrapolation], λz [terminal elimination rate constant]) and PT3317 (AUC0-inf, AUC0-last, AUC0-24, Cmax, C24, Tmax, apparent terminal t½, MPR for Cmax [metabolite to parent ratio for Cmax] and MPR for AUC0-inf [metabolite to parent ratio for AUC0-inf]) by group, and the following (non-model-based) descriptive statistics will be provided: N (number of participants with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s^2) - 1), where s^2 is the observed variance on the natural log-scale). PK concentration listings for MK-6482 in plasma and PT3317 will also be provided for each participant. Descriptive statistics may be provided based on UGT2B17 and/or CYP2C19 phenotypes separately.

The relationship between MK-6482 PK and hepatic impairment will be examined in an exploratory manner via a scatter plot of PK values (AUC0-inf, AUC0-24, Cmax, Tmax, and apparent terminal t½) versus the Child-Pugh score. Plots of PK values (AUC0-inf, AUC0-24, Cmax, Tmax, and apparent terminal t½) and the baseline laboratory components of the Child-Pugh score (ie, bilirubin, albumin levels, and prothrombin time) will be provided. Plots of PK parameter values (AUC0-inf, AUC0-24, Cmax, Tmax, and apparent t½) versus age and BMI will also be provided.

Descriptive statistics for aforementioned PK parameters will also be provided by NCI classification.

9.6.3 Safety Analysis

For safety, all AEs, vital signs, ECGs, pulse oximetry, and safety laboratory values will be listed for each participant and tabulated by group. Summary statistics for the safety laboratory tests, vital signs, and/or ECGs may also be computed and provided, as deemed clinically appropriate.

9.7 Pharmacodynamics Analysis

Summary statistics by time point and plots may be generated for erythropoietin as well as for change from baseline, as deemed clinically appropriate.

9.8 Interim Analyses

Not applicable

9.9 Multiplicity

Not applicable

9.10 Sample Size and Power Calculations

The sample size selected for each population to evaluate the effect of hepatic impairment on the PK of MK-6482 was not chosen to satisfy any a priori statistical requirement. This sample size (N=8 per group) has historically been shown to be sufficient for studies of this type and should provide adequate data to support the planned analyses. Nevertheless, estimates of the expected precision of the estimates, based on these sample sizes and the known variability obtained from hepatic PK studies are presented below.

The precision of the estimated GMRs (hepatic impairment / normal hepatic function) of PK parameters obtained from this study can be assessed by calculating the half-width of the 90% CIs expected for the given sample size and assumed variability. The observed between-participant coefficients of variation were 62.44% (~0.574 standard deviation on the log scale) and 56.29% (~0.525 standard deviation on the log scale) for AUC0-inf from food-effect study (Protocol MK-6482-002) and comparative bioavailability study (Protocol MK-6482-006), respectively. Assuming a sample size of 8 participants per population and observed between-participant SD is 0.574 on the log scale, then the half width of the 90% CI of GMR for MK-6482 AUC0-inf on the log scale will be 0.472. The lower and upper 90% confidence limits for the GMR will be given by OBS/1.60 and OBS*1.60 for AUC0-inf, where OBS is the observed GMR. Thus, for example, if the observed GMR for AUC0-inf was 1.50, then the approximate 90% CI for the GMR would be [0.94 to 2.40].

Similarly, the observed between-participant coefficients of variation were 26.04% (~0.256 standard deviation on the log scale) and 25.25% (~0.249 standard deviation on the log scale) for Cmax from Protocols 002 and 006, respectively. Assuming a sample size of 8 participants per population and observed between-participant SD is 0.256 on the log scale, then the half width of the 90% CI of GMR for MK-6482 Cmax on the log scale will be 0.211. The lower and upper 90% confidence limits for the GMR will be given by OBS/1.23 and OBS*1.23 for Cmax. Thus, for example, if the observed GMR for Cmax was 1.50, then the approximate 90% CI for the GMR would be [1.22 to 1.85].

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 & 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 (eg, 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 (ie, 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 (eg, 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 their 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 their 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 their 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 with the exception of the UGT2B17 and CYP2C19 genotyping screening which will be performed by a central laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 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 HGB HCT	RBC Indices: MCV MCH Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry [a]	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	
Coagulation	INR	PT		
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (if protein, blood, nitrite and/or leukocyte esterase are abnormal)			
Other Tests	• FSH (postmenopausal females only) • Urine/blood/breath alcohol and urine/saliva drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Serology (HIV antibody, HBsAg, and hepatitis C virus antibody) [b] • UGT2B17 genotyping • CYP2C19 genotyping • Erythropoietin			

Laboratory Assessments	Parameters
[a] Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of dropouts or rechecks, participants may not have fasted for 8 hours prior to the serum chemistry sample is taken. [b] For participants with moderate hepatic impairment only: HBsAg positive participants are allowed to enroll if HBV DNA is below 1000 copies/mL in the plasma. Participants who are positive for HCVAb can be enrolled but must not have detectable HCV RNA in the plasma. ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CYP=cytochrome P450; DNA=deoxynucleic acid; FSH=follicle-stimulating hormone; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCT=hematocrit; HCV=hepatitis C virus; HGB=hemoglobin; HIV=human immunodeficiency virus; INR=International Normalized Ratio; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PT=prothrombin time; RBC=red blood cell; RNA=ribonucleic acid; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; UGT=uridine 5'-diphospho-glucuronosyltransferase; ULN=upper limit of normal; WBC=white blood cell.	

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 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.

10.3.2 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.

10.3.3 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

10.3.4 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 /toxicity

- 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.

10.3.5 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 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.

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 their 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: Blood Volume Table

All Participants	Prestudy	Treatment Period	Poststudy	Total Collections	mL Per Collection	Total mL/ Test
Safety Laboratory Safety Tests (including hematology, serum chemistry, FSH)	1	4	1	6	12.5	75
INR/PT	1	--	1	2	3.5	7
Blood for Planned Genetic Analysis	--	1	--	1	8.5	8.5
Blood for MK-6482 and PT3317 PK	--	17	--	17	4	68
Blood for Protein Binding	--	1	--	1	4	4
Blood for UGT2B17 Genotyping	1	--	--	1	3	3
Blood for CYP2C19 Genotyping	1	--	--	1	3	3
Blood for Serum Erythropoietin	--	6	1	7	3.5/8.5 [a]	24.5/59.5
Total Blood Volume per Participant [b]						**193/228 mL**

[a] Blood for serum erythropoietin samples may be collected in either 3.5 mL or 8.5 mL collection tubes.

[b] If additional PK/pharmacodynamic and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained.

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:

    a. The participant may be excluded from the study.
    b. 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).
    c. 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

    d. 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
AE	adverse event
ALT	alanine aminotransferase
ARNT	aryl hydrocarbon receptor nuclear translocator
AST	aspartate aminotransferase
AUC	area under the curve
BCS	Biopharmaceutics Classification System
bid	twice daily
BMI	body mass index
BP	blood pressure
ccRCC	clear cell renal cell carcinoma
CG	Cockcroft-Gault
CI	confidence interval
CL	clearance
Cmax	maximum plasma concentration
CNS	central nervous system
CRF	case report form
CRU	clinical research unit
CSR	clinical study report
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic case report form
EDC	electronic data collection
EM	extensive metabolizer
EMA	European Medicines Agency
EPO	erythropoietin
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCT	hematocrit
HCV	hepatitis C virus

Abbreviation	Expanded Term
HGB	hemoglobin
HIF-1α	hypoxia-inducible factor 1 alpha
HIF-2α	hypoxia-inducible factor 2 alpha
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
IEC	Independent Ethics Committee
IM	intermediate metabolizer
IND	investigational new drug
INR	international normalized ratio
IRB	Institutional Review Board
NCI	National Cancer Institute
NCS	not clinically significant
PK	pharmacokinetic
PM	poor metabolizer
PP	per-protocol
RBC	red blood cell
RCC	renal cell carcinoma
RNA	ribonucleic acid
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SLAB	supplemental laboratory test(s)
SoA	schedule of activities
SOP	standard operating procedures
SUSARs	suspected unexpected serious adverse reaction
T	body temperature
Tmax	time to maximum plasma concentration
t½	half life
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
Vd/F	apparent volume of distribution
VHL-RCC	von Hippel-Lindau disease-associated renal cell carcinoma
WBC	white blood cell

Abbreviation	Expanded Term
WONCBP	woman/women of nonchildbearing potential

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