Official Protocol Title:	Protocol/Amendment No.: 021-02 An Open-Label, Single-Dose Study to Investigate the Influence of Renal Impairment on the Pharmacokinetics of MK-6482
NCT number:	NCT04994522
Document Date:	17-Apr-2023

Title Page

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

Protocol Number: 021-03

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: 17 April 2023

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 03	17-Apr-2023	Protocol amended to widen the allowable range of body mass index (BMI) in the inclusion criterion to facilitate recruitment of participants with end stage renal disease (ESRD).
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 add the exclusion of UGT2B17 and CYP2C19 dual poor metabolizers.
Original Protocol	30-Jun-2021	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 03

Overall Rationale for the Amendment:

The upper limit of the BMI is being increased from 40 to 46 kg/m^2. This increase in the upper limit of the BMI is to facilitate recruitment. Based on review of the site database of eligible participants, the Sponsor was informed that many of the ESRD patients have BMIs that exceed 40 kg/m^2. The upper limit of the BMI for the Sponsor clinical database for MK-6482, that includes adult patients with von Hippel-Lindau (VHL) who require therapy for associated renal cell carcinoma (RCC), is 52 kg/m^2. Therefore, the Sponsor has clinical experience with the use of MK-6482 in patients with BMIs exceeding 40 kg/m^2. Based on a population pharmacokinetic (PK) model, body weight (which is highly correlated with BMI) does not have a clinically meaningful effect on the PK of MK-6482.

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

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
5.1.1 Inclusion Criteria for Participants With Healthy Renal Function	The BMI upper limit in criterion #3 was increased. **from**: Have a BMI 18.0-40.0 kg/m^2, inclusive, at prestudy (screening). 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 ESRD group. **to**: Have a BMI 18.0-46.0 kg/m^2, inclusive, at prestudy (screening). See Section 8.3.1 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height (m)^2. BMI must be	Inclusion criterion for BMI widened to facilitate recruitment of participants with ESRD. As the participants with healthy renal function are required to match the demographics of the participants with ESRD, the BMI of the healthy participants was also widened.

Section # and Name	Description of Change	Brief Rationale
	within ± 20% of the mean BMI in the ESRD group.	
5.1.2 Inclusion Criteria for Participants With ESRD	The BMI upper limit in criterion #3 was increased. **from**: Have a BMI 18.0-40.0 kg/m^2, inclusive, at prestudy (screening). See Section 8.3.1 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height $(m)^2$. **to**: Have a BMI 18.0-46.0 kg/m^2, inclusive, at prestudy (screening). See Section 8.3.1 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height $(m)^2$.	Inclusion criterion for BMI widened to facilitate recruitment of participants with ESRD.

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.
9.6.3 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 categorical effect for population (participants with ESRD before and after HD, control participants with normal renal function). **to**: Separately for each PK parameter, individual values of MK-6482 AUC0-inf, AUC0-24, and Cmax will be natural log-transformed and	Changes were made to correct details in the statistical analysis language.

Section # and Name	Description of Change	Brief Rationale
	evaluated with a mixed effects model containing a fixed effect for population (participants with ESRD before and after HD, control participants with normal renal function). **from**: To address the primary estimation objective and compare participants with ESRD before and after HD to participants with normal renal function, a two sided 90% CI for the difference in means (ESRD before HD – normal renal function, ESRD after HD – normal renal function) will be calculated for each PK parameter using the mean square error from the model and referencing a t-distribution. **to**: To address the primary estimation objective and compare participants with ESRD before and after HD to participants with normal renal function, a two sided 90% CI for the difference in least-squares means (ESRD before HD – normal renal function, ESRD after HD – normal renal 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, 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
1.1 Synopsis 3 Hypotheses, Objectives, and Endpoints	In the Objectives/Endpoints table, 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 of study intervention 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.
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	Information updated to be more current.

Section # and Name	Description of Change	Brief Rationale
	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.	
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).
4.1 Overall Design 5 Study Population 5.1.1 Inclusion Criteria for Participants With Healthy Renal Function	• 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 the time needed for MK-6482 to be eliminated.

Section # and Name	Description of Change	Brief Rationale
5.1.2 Inclusion Criteria for Participants With ESRD		
5.2.1 Exclusion Criteria for Participants with Healthy Renal Function 5.2.2 Exclusion Criteria for Participants With ESRD	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.
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.	CYP2C19 genotyping added for eligibility assessment.
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 abbreviation “CNS.”	Abbreviation added for completeness.

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 Renal Impairment on the Pharmacokinetics of MK-6482

Short Title: MK-6482 Renal Impairment Study

Acronym: Not Applicable

Hypotheses, Objectives, and Endpoints:

The following objectives will be evaluated in male and female participants with ESRD and matched control participants with normal renal function.

Objectives	Endpoints
Primary	
• To compare the plasma PK of MK-6482 following administration of a single oral 120 mg dose of MK-6482 to participants with ESRD before and after HD to each other and also to that of healthy matched control participants. • Estimation: The plasma PK (AUC0-inf and Cmax) of MK-6482 following a single oral 120 mg dose of MK-6482 to participants with ESRD before and after HD will be estimated and compared to each other and 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 120 mg dose of MK-6482 in participants with ESRD.	• AEs and discontinuation of study intervention due to AEs

• To investigate the extent of MK-6482 removed by HD. • Estimation: The extent to which MK-6482 is removed by HD from the plasma (eg, CLD, $_{plasma}$) will be estimated.	• CLD, $_{plasma}$ as a measure of the extent of MK-6482 removal by HD

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Renal Cell Carcinoma
Population	Adult male and female participants with ESRD and healthy adult male and female participants
Study Type	Interventional
Intervention Model	Parallel This is a single-site study.
Type of Control	Healthy matched control participants
Study Blinding	Unblinded Open-label
Blinding Roles	No Blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 12 participants will be allocated as described in Section 9.9.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name		Drug	Dose Level	Dose Frequency	Route of Administration	Treatment Period	Use
ESRD Group	Period 1	MK-6482	120 mg	Single Dose	Oral	1 day	Experimental
	Period 2	MK-6482	120 mg	Single Dose	Oral	1 day	Experimental
Healthy Matched Control Group		MK-6482	120 mg	Single Dose	Oral	1 day	Experimental

Other current or former name or alias for study intervention is as follows: PT2977.

Total Number of Intervention Groups/ Arms: 2

Duration of Participation: Each participant in the ESRD group will participate in the study for approximately 7 weeks from the time the participant provides documented informed consent through the final contact. Each participant in the healthy control group will participate in the study for approximately 6 weeks from the time the participant provides documented informed consent through the final contact.

Study Governance Committees:

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

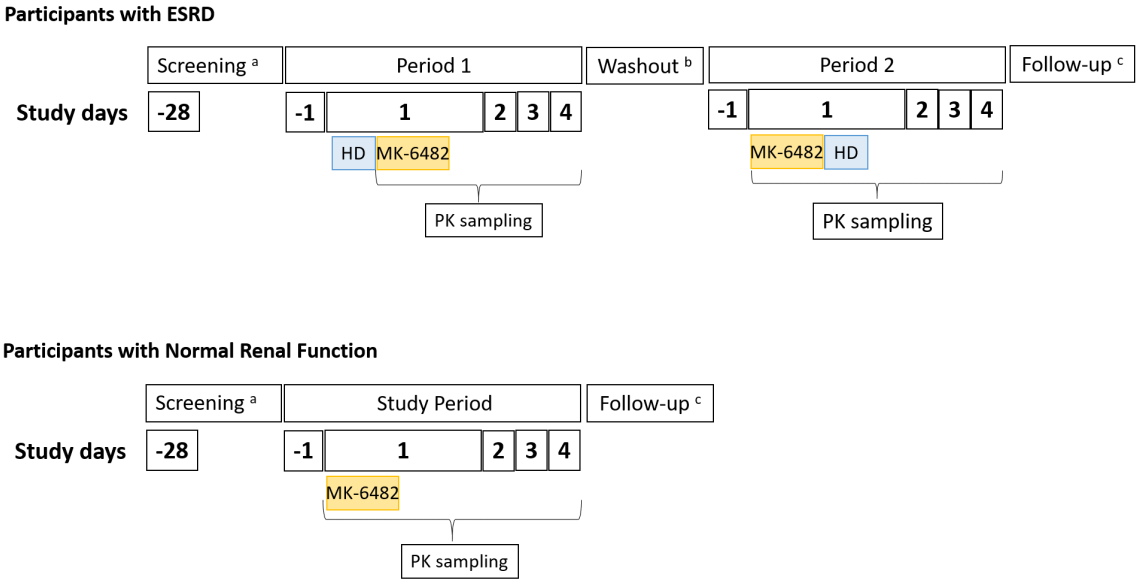
Study Accepts Healthy Volunteers: Yes

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 There will be a washout period of at least 7 days between study intervention administration in Periods 1 and 2.
c Follow-up will occur approximately 14 days after last dosing.

1.3 Schedule of Activities

1.3.1 ESRD Group

Period 1 for ESRD Group							
Study Period:	**Screening**	**Intervention**					**Notes**
Scheduled Day		**-1 (C-I)**	**1**	**2**	**3**	**4**	
Administrative Procedures							
Informed Consent	X						Screening will occur within 28 days prior to the first study intervention administration [Sec. 8.1.1.1].
Informed Consent for FBR	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 Sec. 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	Sec. 6.5
Assignment of Treatment/Allocation Number			X				Sec. 8.1.8
Domiciling		X	X	X	X	X	Sec. 8.1.12
Safety Procedures							
Complete Physical Examination	X						
Symptom-driven Physical Examination		X	X	X	X	X	Only to be conducted if the participant's symptoms warrant an examination or at the investigator's discretion.
Height	X						
Weight	X	X					BMI to be calculated only at the prestudy (screening) visit.
HR, BP, and RR	X	X	X	X	X	X	To be performed at Day -1, predose, and at 24, 48, and 72 hours postdose.
T	X	X	X	X	X	X	To be performed at Day -1, predose, and at 24, 48, and 72 hours postdose.
12-lead ECG	X	X		X		X	To be performed at Day -1, and at 24 and 72 hours postdose.
Pulse Oximetry	X	X	X	X	X	X	To be performed at Day -1, predose, and at 24, 48, and 72 hours postdose.

Period 1 for ESRD Group							
Study Period:	**Screening**	**Intervention**					**Notes**
Scheduled Day		**-1 (C-I)**	**1**	**2**	**3**	**4**	
Hem, Serum Chem, and UA	X	X		X		X	To be performed at Day -1, and at 24 and 72 hours postdose. Urine samples will be collected whenever possible, as some participants may not be able to produce urine. For participants who are anuric, urine samples for UA will not be collected.
Coagulation	X						
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					
AE/SAE Review	X	X	X	X	X	X	See Sec. 8.11.4 for poststudy contact details.
Study Intervention Administration							
MK-6482 Administration			X				To be administered immediately following the Friday or Saturday scheduled HD session. There will be a washout period of at least 7 days between study intervention administrations in each period.
Pharmacokinetics							
Blood for Plasma MK-6482 Assay			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, and 72 hours postdose.
Blood for Protein Binding			X				To be collected at predose.
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, CYP=cytochrome P450, ECG=electrocardiogram, EM=extensive metabolizer, ESRD=end stage renal disease, FBR=future biomedical research, FSH=follicle-stimulating hormone, HD=hemodialysis, Hem=hematology, HIV=human immunodeficiency virus, HR=heart rate, IM=intermediate metabolizer, RR=respiratory rate, SAE=serious adverse event(s), T=body temperature, UA=urinalysis, UGT=uridine 5'-diphospho-glucuronosyltransferase.

Period 2 for ESRD Group							
Study Period:	**Intervention**					**Poststudy or ET**	**Notes**
Scheduled Day	**-1 (C-I)**	**1**	**2**	**3**	**4**		Poststudy (follow-up) will occur approximately 14 days after the last study intervention administration [Sec. 8.11.4].
Administrative Procedures							
Prior/Concomitant Medication Review	X	X	X	X	X	X	Sec. 6.5
Domiciling	X	X	X	X	X		Sec. 8.1.12
Safety Procedures							
Complete Physical Examination						X	To be conducted also for participants who discontinue/withdraw from the study.
Symptom Driven Physical Examination	X	X	X	X	X		Only to be conducted if the participant's symptoms warrant an examination or at the investigator's discretion.
Weight						X	
HR, BP, and RR	X	X	X	X	X	X	To be performed at Day -1, predose, at 24, 48, and 72 hours postdose, and poststudy or prior to early termination from the study.
T	X	X	X	X	X	X	To be performed at Day -1, predose, at 24, 48, and 72 hours postdose, and poststudy or prior to early termination from the study. To be also performed at poststudy.
12-lead ECG	X		X		X	X	To be performed at Day -1, at 24 and 72 hours postdose, and poststudy or prior to early termination from the study.
Pulse Oximetry	X	X	X	X	X	X	To be performed at Day -1, predose, at 24, 48, and 72 hours postdose, and poststudy or prior to early termination from the study.
Hem, Serum Chem, and UA	X		X		X	X	To be performed at Day -1, at 24 and 72 hours postdose, and poststudy or prior to early termination from the study.
Coagulation						X	To be performed also for participants who discontinue/withdraw from the study.
Urine/Saliva Drug Screen	X						
Urine/Blood/Breathalyzer Alcohol Screen	X						
AE/SAE Review	X	X	X	X	X	X	See Sec. 8.11.4 for poststudy contact details.

Period 2 for ESRD Group							
Study Period:	**Intervention**					**Poststudy or ET**	**Notes**
Scheduled Day	**-1 (C-I)**	**1**	**2**	**3**	**4**		Poststudy (follow-up) will occur approximately 14 days after the last study intervention administration [Sec. 8.11.4].
Study Intervention Administration							
MK-6482 Administration		X					To be administered approximately 2 hours prior to the Friday or Saturday scheduled HD session. There will be a washout period of at least 7 days between study intervention administrations in each period.
HD		X					The 4-hour HD session will be initiated immediately following the 2-hour PK blood draw.
Pharmacokinetics							
Blood for Plasma MK-6482		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, and 72 hours postdose.
Dialyzer Samples for Plasma MK-6482		X					A pre-dialyzer plasma sample to be collected at the start of HD. Pre-dialyzer and post-dialyzer plasma samples to be collected at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, and 4 hours (immediately before HD completion) from the start of HD.
Abbreviations: AE=adverse event; BP=blood pressure, C-I=check-in, Chem=chemistry, ECG=electrocardiogram, ESRD=end stage renal disease, ET=early termination, HD=hemodialysis, Hem=hematology, HR=heart rate, PK=pharmacokinetic, RR=respiratory rate, SAE=serious adverse event(s), T=body temperature, UA=urinalysis.							

1.3.2 Healthy Control Group

Study Period in Healthy Control Group								
Study Period:	**Screening**	**Intervention**					**Poststudy or ET**	**Notes**
Scheduled Day		**-1 (C-I)**	**1**	**2**	**3**	**4**		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 FBR	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 Sec. 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	Sec. 6.5
Assignment of Treatment/Allocation Number			X					Sec. 8.1.8
Domiciling		X	X	X	X	X		Sec. 8.1.12
Safety Procedures								
Complete Physical Examination	X						X	
Symptom-driven Physical Examination		X	X	X	X	X		Only to be conducted if the participant's symptoms warrant an examination or at the investigator's discretion.
Height	X							
Weight	X	X					X	BMI to be calculated only at the prestudy (screening) visit.
HR, BP, and RR	X	X	X	X	X	X	X	To be performed at Day -1, predose, at 24, 48, and 72 hours postdose, and poststudy or prior to early termination from the study.
T	X	X	X	X	X	X	X	To be performed at Day -1, predose, at 24, 48, and 72 hours postdose, and poststudy or prior to early termination from the study.
12-lead ECG	X	X		X		X	X	To be performed at Day -1, at 24 and 72 hours postdose, and poststudy or prior to early termination from the study.

Study Period in Healthy Control Group								
Study Period:	**Screening**	**Intervention**					**Poststudy or ET**	**Notes**
Scheduled Day		**-1 (C-I)**	**1**	**2**	**3**	**4**		Poststudy (follow-up) will occur approximately 14 days after study intervention administration [Sec. 8.11.4].
Pulse Oximetry	X	X	X	X	X	X	X	To be performed at Day -1, predose, at 24, 48, and 72 hours postdose, and poststudy or prior to early termination from the study.
Hem, Serum Chem, and UA	X	X		X		X	X	To be performed at Day -1, at 24 and 72 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.
Renal Function Assessment	X							eGFR will be determined using the MDRD equation. All healthy control participants will also have a measured CLcr as determined by a 24-hour urine collection. This assessment can be done any time prior to Day -1 check-in.
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						
AE/SAE review	X	X	X	X	X	X	X	See Sec. 8.11.4 for poststudy contact details.
Study Intervention Administration								
MK-6482 Administration			X					
Pharmacokinetics								
Blood for Plasma MK-6482 Assay			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, and 72 hours postdose.
Blood for Protein Binding			X					To be collected at predose.

Study Period in Healthy Control Group								
Study Period:	**Screening**	**Intervention**					**Poststudy or ET**	**Notes**
Scheduled Day		**-1 (C-I)**	**1**	**2**	**3**	**4**		Poststudy (follow-up) will occur approximately 14 days after study intervention administration [Sec. 8.11.4].
Biomarkers								
Blood for Genetic Analysis			X					Collect 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, CLcr=creatinine clearance, CYP=cytochrome P450, ECG=electrocardiogram, eGFR=estimated glomerular filtration rate, EM=extensive metabolizer, FBR=future biomedical research, FSH=follicle-stimulating hormone, Hem=hematology, HIV=human immunodeficiency virus, HR=heart rate, IM=intermediate metabolizer, MDRD=Modification of Diet in Renal Disease, RR=respiratory rate, SAE=serious adverse event(s), 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 purpose of this study is to determine the impact of markedly impaired renal function on the single-dose PK of MK-6482.

In vitro, MK-6482 is a substrate of UGT2B17, CYP2C19 and CYP3A4. Both 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 approaches. The collective results of these analyses indicate that UGT2B17 is the major route of elimination in individuals who express this enzyme, while CYP2C19 is also a relevant clearance pathway. 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 is anticipated to confirm that hepatic metabolism represents a major elimination pathway (>20% of the absorbed drug) for MK-6482.

Renal excretion is not anticipated to represent a major clearance route for MK-6482. However, impaired renal function has been demonstrated to alter drug metabolism and transport pathways in the liver and gut, and these effects are more prominent in patients with severely impaired renal function (Dreisbach, 2009). As an example, CYP2C19 activity was reported to be reduced by 25% in patients with chronic renal impairment characterized by a GFR <50 mL/min (Dreisbach, 2009). There are no published reports on the impact of renal impairment on UGT2B17 activity. Furthermore, since nephron-sparing surgery is often the treatment of choice for amenable RCC lesions, VHL-RCC patients may undergo multiple sequential renal surgeries, which can lead to progressive worsening of renal function. In a retrospective analysis of 72 VHL patients with a median follow-up period of 61.5 months, 30% of patients who underwent RCC surgery developed chronic kidney disease while 5% of patients developed ESRD and required HD (Kwon et al., 2014).

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 blocks 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, HGB, and HCT 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.

2.2.3 Ongoing Clinical Studies

There are 14 ongoing clinical studies with MK-6482 which include: 5 Phase 1 studies, 1 Phase 1b/2 study, 5 Phase 2 studies, and 3 Phase 3 studies. The Phase 1 studies include an assessment of safety, tolerability, PK, pharmacodynamic properties, and anti-tumor activity of MK-6482 in participants with advanced solid tumors (MK-6482-001); investigation of absorption, metabolism, excretion, and mass balance of MK-6482 in healthy participants (MK-6482-008); evaluation of MK-6482 as monotherapy and in combination with lenvatinib with or without pembrolizumab in China participants with advanced RCC (MK-6482-010); evaluation of safety and tolerability of MK-6482 in participants with advanced ccRCC

(MK-6482-018); and evaluation of the impact of crystalline drug substance on MK-6482 PK in healthy participants (MK-6482-019). The Phase 1b/2 study is an evaluation of immune and targeted combination therapies in participants with RCC (MK-3475-U03). The Phase 2 studies include an evaluation of efficacy and safety of MK-6482 in patients with VHL-RCC an evaluation of efficacy and safety of MK-6482 in combination with cabozantinib in adult participants with advanced ccRCC (MK-6482-003); evaluation of efficacy and safety of MK-6482 in patients with VHL-RCC (MK-6482-004); evaluation of efficacy and safety of MK-6482 in patients with advanced RCC (MK-6482-013); evaluation of efficacy and safety of MK-6482 monotherapy in participants with advanced pheochromocytoma/paraganglioma or pancreatic neuroendocrine tumor (MK-6482-015); and evaluation of efficacy and safety of pembrolizumab plus lenvatinib in combination with MK-6482 in multiple solid tumors (MK-6482-016). The ongoing Phase 3 studies include an evaluation of the efficacy and safety of MK-6482 in patients with advanced RCC (MK-6482-005); evaluation of MK-6482 in combination with lenvatinib versus cabozantinib in participants with advanced RCC (MK-6482-011); and an evaluation of the efficacy and safety of pembrolizumab in combination with MK-6482 and lenvatinib, versus pembrolizumab and lenvatinib in participants with advanced ccRCC (MK-6482-012). 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.

One case of multiple organ dysfunction syndrome resulting in death was reported in MK-6482-005 for a participant with advanced RCC, who received MK-6482 120 mg daily for approximately 2 weeks. The participant was also reported as experiencing disseminated intravascular coagulation, hepatic failure, hypocalcemia and sepsis. 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, PPD 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 the prestudy (screening) visit 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 safety laboratory tests, AE questioning, and physical examinations) 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 males and females with ESRD and matched control participants with normal renal function:

Objectives	Endpoints
Primary	
• To compare the plasma PK of MK-6482 following administration of a single oral 120 mg dose of MK-6482 to participants with ESRD before and after HD to each other and also to that of healthy matched control participants. • Estimation: The plasma PK (AUC0-inf and Cmax) of MK-6482 following a single oral 120 mg dose of MK-6482 to participants with ESRD before and after HD will be estimated and compared to each other and 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 120 mg dose of MK-6482 in participants with ESRD.	• AEs and discontinuation of study intervention due to AEs

• To investigate the extent of MK-6482 removed by HD. • Estimation: The extent to which MK-6482 is removed by HD from the plasma (eg, CLD, $_{plasma}$) will be estimated.	• CLD, $_{plasma}$ as a measure of the extent of MK-6482 removal by HD
Tertiary/Exploratory	
• 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 UGT2B17 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, single-site, open-label study of MK-6482 in participants with ESRD and healthy matched control participants.

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

A total of approximately 12 adult male (vasectomized or surgically sterilized) and female (nonchildbearing potential only) participants will be enrolled: 6 participants with ESRD and 6 healthy matched control participants with normal renal function.

Assignment to renal function group will be as follows:

Group	N	eGFR (mL/min/1.73m^2)
ESRD	6 [a]	Require dialysis
Healthy matched control	6 [a]	≥ 90 [b]

a. At least 2 UGT2B17 IMs and at least 2 EMs will be enrolled per group.
b. The eGFR based on the MDRD equation will be calculated at screening. Baseline eGFR will be assessed during the screening period for study eligibility. If a repeat measurement is obtained, the mean of the two values will be used to assess study eligibility. At the discretion of the investigator, a measured CLcr as determined by a 24-hour urine collection may be used to determine eligibility for enrollment. Participants with an eGFR (using the MDRD equation) up to 10% below 90 mL/min/1.73 m^2 (ie, ≥81 mL/min/1.73 m^2) may be eligible for the study if their measured CLcr (based on a 24-hour urine collection) is ≥90 mL/min.

Following enrollment of the ESRD group, the healthy control group will be enrolled. Each healthy control participant will be matched to the mean age (± 15 years), BMI (± 20%), sex (with a similar male/female ratio in each group), and UGT2B17 genotype (at least 2 IMs and 2 EMs) of participants with ESRD. If a UGT2B17 PM ESRD participant is enrolled in the study, a UGT2B17 PM healthy matched control participant should be included in the control group. If after reasonable efforts, a UGT2B17 PM healthy matched control participant cannot be enrolled, an additional ESRD participant (ie, a 7th ESRD participant), who is not UGT2B17 PM, will be enrolled. This additional ESRD participant should be matched to the mean age (± 15 years) and BMI (± 20%) of the other 6 ESRD participants. The final healthy matched control participant (ie, the 6th 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 6 ESRD participants (ie, not including the 7th ESRD participant).

ESRD participants will receive a single oral dose of 120 mg MK-6482 on 2 separate occasions. In Period 1, ESRD participants will receive a single oral dose of 120 mg MK-6482 immediately following completion of their normally scheduled HD, followed by 72 hours of blood sampling for PK assessment of MK-6482. For participants following a Monday, Wednesday, Friday HD schedule, MK-6482 will be administered immediately following their Friday HD session. For participants following a Tuesday, Thursday, Saturday HD schedule, study intervention will be administered immediately following their Saturday HD session. The participant's next regularly scheduled HD session (either Monday or Tuesday) should initiate immediately following the 72-hour blood draw. If HD must be initiated before 72 hours postdose, a sample for MK-6482 analysis will be collected prior to HD. There will be a washout period of at least 7 days between MK-6482 administrations in each period.

In Period 2, ESRD participants will receive a single oral dose of 120 mg MK-6482 approximately 2 hours prior to their normally scheduled HD followed by 72 hours blood sampling for PK assessment of MK-6482. For participants following a Monday, Wednesday, Friday HD schedule, MK-6482 will be administered approximately 2 hours prior to their Friday HD session. For participants following a Tuesday, Thursday, Saturday HD schedule, MK-6482 will be administered approximately 2 hours prior to their Saturday HD session. The 4-hour HD session should initiate immediately following the 2-hour PK blood draw. A pre-dialyzer plasma sample will be collected at the start of HD. During this dialysis session, pre- and post-dialyzer plasma samples will be collected approximately every 30 minutes during HD for MK-6482 analysis.

Healthy matched control participants will receive a single oral dose of 120 mg MK-6482, followed by 72 hours of blood sampling for PK assessment of MK-6482.

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

The primary objective of this trial is to investigate the impact of markedly impaired renal function on MK-6482 PK. MK-6482 is anticipated to be eliminated predominantly by hepatic metabolism. Although renal excretion is not anticipated to represent a major clearance route for MK-6482, impaired renal function can alter drug metabolism and transport pathways in the liver and gut. Since these effects are more prominent in patients with severely compromised renal function, this study will evaluate and compare MK-6482 PK in ESRD patients requiring HD to healthy control participants with normal renal function that are reasonably matched to the mean demographic parameters of participants with ESRD to control for the influence of covariates. In addition, the impact of HD on MK-6482 PK will also be assessed.

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 ESRD before and after HD compared to participants with healthy renal function, using GMR and CI to assess differences between these two groups.

The secondary endpoint of this study is to evaluate the extent of MK-6482 removal by HD from plasma (CLD, $_{plasma}$). The plasma parameter included in this secondary endpoint will be evaluated and compared between participants with ESRD before and after HD compared to participants with healthy renal function.

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 in VHL-RCC and RCC patients of all available information include: hypoxia, anemia, fatigue, dyspnea, and dizziness. Therefore, the standard safety monitoring of AEs, physical examinations, 12-lead ECGs, pulse oximetry, vital signs, clinical safety laboratory tests (hematology, serum chemistry, and urinalysis), obtained throughout the study are appropriate to assess safety and tolerability of MK-6482 in this study.

4.2.1.3 Planned Exploratory Biomarker Research

4.2.1.3.1 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.

4.2.1.4 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 clinical dose for MK-6482 is 120 mg daily, which will be evaluated in this study. Single MK-6482 doses up to 200 mg, which was associated with a 1.6-fold increase in AUC compared to 120 mg, have been previously administered to healthy participants and were generally well tolerated. Furthermore, multiple daily doses of up to 240 mg daily and 120 mg twice daily have been administered to patients with advanced solid tumors.

Renal impairment was not identified as a significant covariate based on a population PK analysis using MK-6482 concentration data across multiple MK-6482 clinical studies, which was anticipated since renal clearance represents a minor elimination pathway for MK-6482 in humans.

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 renal function will match to the mean demographic parameters of the ESRD group. Healthy control participants will be matched for the mean age (± 15 years), mean BMI (± 20%), sex (with a similar male/female ratio in each group), and UGT2B17 genotype (at least 2 IMs and 2 EMs) of the ESRD group. If a UGT2B17 PM ESRD participant is enrolled in the study, a UGT2B17 PM healthy matched control participant should be included in the control group. If after reasonable efforts, a UGT2B17 PM healthy matched control participant cannot be enrolled, an additional ESRD participant (ie, a 7th ESRD participant), who is not UGT2B17 PM, will be enrolled. This additional ESRD participant should be matched to the mean age (± 15 years) and BMI (± 20%) of the other 6 ESRD participants. The final healthy matched control participant (ie, the 6th 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 6 ESRD participants (ie, not including the 7th ESRD 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 Renal 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 the study intervention.
2. Is in good health based on clinical laboratory safety tests obtained at the prestudy (screening) visit and before administration of study intervention. Appendix 2 provides a table of clinical laboratory safety tests to be performed. Appendix 9 provides an algorithm for the assessment of out-of-range laboratory values.
3. Have a BMI 18.0-46.0 kg/m^2, inclusive, at prestudy (screening). 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 ESRD 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 ESRD 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 ESRD

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 renal 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 the initial administration of the study intervention.
2. With exception of the renal impairment, is in good health, in the opinion of the investigator, based on clinical laboratory safety tests obtained at the prestudy (screening) visit and before the initial administration of study intervention. Appendix 2 provides a table of clinical laboratory safety tests to be performed.
3. Have a BMI 18.0-46.0 kg/m^2, inclusive, at prestudy (screening). See Section 8.3.1 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height $(m)^2$.
4. Participant has ESRD maintained on stable regimen of at least 3 times per week HD for at least 3 months prior to the initial administration of the study intervention.

Demographics

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

Male Participants

6. Male participants are eligible to participate if they have been vasectomized or undergone surgical sterilization at least 4 months or more prior to the initial 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 the last 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

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

Informed Consent

8. 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 Participants With Healthy Renal 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 prior to the prestudy [screening] visit, 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 in the last 5 years prior to the prestudy [screening] visit. 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. Participant has an estimated eGFR <90 mL/min/1.73 m^2 based on the MDRD equation. At the discretion of the investigator, a measured CLcr as determined by a 24-hour urine collection may be used to determine eligibility for enrollment. Participants with an eGFR (using the MDRD equation) up to 10% below 90 mL/min/1.73 m^2 (ie, ≥81 mL/min/1.73 m^2) may be eligible for the study if their measured CLcr (based on a 24-hour urine collection) is ≥90 mL/min.

   MDRD Equation:

   eGFR (mL/min/1.73 m^2) =
   175 x (serum creatinine)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 [if female]) x (1.212 [if Black or African American])

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 at the prestudy (screening) visit.
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 the initial 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 a history of anemia within 5 years prior to the prestudy (screening) visit.
13. Has a pulse oximetry reading <92% at rest at the prestudy (screening) visit or check-in.
14. Has a QTc interval >470 msec, 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 at the prestudy (screening) visit.
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 ESRD

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 the prestudy (screening) visit or expected during the conduct of the study or has a history of clinically significant psychiatric disorder in the last 5 years prior to the prestudy (screening) visit. 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 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.
4. Has required frequent emergent HD (≥3) within a year prior to the initial dose of study intervention.
5. Is positive for HBsAg, hepatitis C antibodies, or HIV at the prestudy (screening) visit.
6. 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

7. 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).
8. 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/Concomitant Clinical Study Experience

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

Diagnostic Assessments

10. Has a UGT2B17 and CYP2C19 genotype consistent with a dual poor metabolizer phenotype.
11. Has HGB level <9.5 g/dL at the prestudy (screening visit) or check-in. Participants with HGB ≥9.0 g/dL may be enrolled to the study at the discretion of the investigator and following consultation with the Sponsor.
12. Has a pulse oximetry reading <92% at rest at the prestudy (screening visit) or first check-in.
13. Has a QTc interval >480 msec, 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

14. Is under the age of legal consent at the prestudy (screening) visit.
15. Is a heavy smoker or heavy user of nicotine-containing products (>20 cigarettes or equivalent/day).
16. 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.
17. 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.
18. 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.
19. 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 first check-in, unless the positive drug screen is due to prescription drug use that is approved by the investigator and Sponsor.

20. 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.
21. Is unwilling to comply with the study restrictions (see Section 5.3 for a complete summary of study restrictions).
22. 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 clinical laboratory safety evaluations are specified in Appendix 2.

On Day 1 of each period (as applicable), 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 (initial) study intervention, throughout the study and until the last PK sample collection.

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

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

5.3.2.1 Caffeine Restrictions

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

5.3.2.2 Alcohol Restrictions

Participants will refrain from consumption of alcohol 24 hours before the prestudy (screening) and poststudy (follow-up) visits and from 48 hours before each study intervention administration and until last PK sample collection in each period. At all other times, alcohol consumption is limited to no more than approximately 3 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 study intervention, throughout the study (including washout intervals between treatment periods), and until the poststudy (follow-up) 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 discontinues from study intervention or 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 1.

Table 1 Study Intervention

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
ESRD Group (Period 1 and Period 2)	Experimental	MK-6482	Drug	Tablet	40 mg	120 mg	Oral	Period 1, Day 1 Period 2, Day 1	Experimental	IMP	Sponsor
Healthy Control Group	Experimental	MK-6482	Drug	Tablet	40 mg	120 mg	Oral	Period 1, Day 1	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 European Economic Area. 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 1 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 allocation number at the time of initial study intervention administration, different from the screening number, and will receive the study intervention.

Participants will receive the treatment(s) as depicted in Table 2.

Table 2 Allocation Schedule

Group	N	Period 1	Period 2 [a]
ESRD participants	6	120 mg MK-6482 (immediately after HD)	120 mg MK-6482 (approximately 2 hours prior to HD)
Healthy participants	6	120 mg MK-6482	Not applicable

[a] There will be at least 7 days of washout between study intervention administrations in each period.

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.

Interruptions from the protocol-specified treatment plan require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

Participants with ESRD only

Participants who are taking certain prescription medications to treat manifestations of renal disease or medications needed to treat stable diseases (eg, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers, diuretics) will be allowed to participate in the study at the discretion of the investigator and following consultation with the Sponsor. Participants must be on a stable regimen for at least 2 weeks (or 5 half-lives of the study drug, whichever is longer) prior to initial administration of the study intervention and is able to withhold the use within 4 hours prior to initial administration of the study intervention.

Any medication (including over-the-counter) that would significantly alter eGFR, which, by the determination of the investigator, might interfere with the study (eg, cimetidine) must be discontinued at least 2 weeks (or 5 half-lives of the compound, whichever is longer) prior to initial administration of the study intervention.

Phosphate binders containing aluminum, calcium, or lanthanum salts; iron supplements or other metal cations;H2-receptor antagonists (H2RAs [except cimetidine]); or multivitamins containing iron or zinc must be withheld at least 8 hours prior to each administration of the study intervention and at least 4 hours postdose.

Concurrent use of any prescription or nonprescription medication, or concurrent vaccination, must first be discussed between the investigator and Sponsor before administration, unless appropriate medical care necessitates that therapy or vaccination should begin before the investigator and Sponsor can consult. The participant will be allowed to continue in the study if both the Sponsor and the investigator agree.

Participants with Normal Renal 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, 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, 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 (initial) 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).

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

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, healthy matched control participants who receive a single-dose intervention cannot discontinue study intervention.

For ESRD participants only:

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.1.10, or if available, a PCL.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.10.

A participant must be discontinued from study intervention, but continue to be monitored in the study, for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a positive drug screen at any time during the course of the study (with the exception for positive drug screen due to prescription drug use that is approved by the investigator and Sponsor). The drug screen can be confirmed by a recheck at the discretion of the investigator after discussion with the Sponsor.

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 ESRD participant and healthy participant over the duration of the study will not exceed 313.5 mL and 148 mL, respectively (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 ICF 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.

If the investigator recommends continuation of study intervention beyond disease progression, the participant or their legally acceptable representative will be asked to provide documented informed consent.

Specifics about the study and the study population are to be included in the study ICF.

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 (initial) 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 allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

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

8.1.8 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. 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 and for each study period (as applicable), 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

ESRD Participants

On Day 1 of Period 1, 120 mg (3x40 mg tablets) MK-6482 will be administered at Hour 0, immediately following completion of their normally scheduled HD. On Day 1 of Period 2, 120 mg (3x40 mg tablets) MK-6482 will be administered at Hour 0, approximately 2 hours prior to their normally scheduled HD.

Healthy Participants

On Day 1, 120 mg (3x40 mg tablets) MK-6482 will be administered at Hour 0.

All Participants

The study intervention will be administered with 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

ESRD participants will be admitted to the CRU on Day -1 of each period, at the time indicated by the CRU, and will be housed until after the 72 hours postdose and/or study procedures on Day 4. As per CRU preference, participants may be confined throughout the study (ie, washout periods).

Healthy participants will be admitted to the CRU on Day -1 , at the time indicated by the CRU, and will be housed until after the 72 hours postdose and/or study procedures on Day 4.

All 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 to be drawn over the course of the study (from prestudy [screening] to poststudy [follow-up] visits), including approximate blood volumes drawn 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 or designee will be documented.

8.3.5 Hemodialysis (for ESRD Participants Only)

ESRD participants will receive HD as per their regular schedule.

Period 1: For participants following a Monday, Wednesday, Friday HD schedule, study intervention will be administered immediately following their Friday HD session. For participants following a Tuesday, Thursday, Saturday HD schedule, study intervention will be administered immediately following their Saturday HD session. The participant's next regularly scheduled HD session (either Monday or Tuesday) should initiate immediately following the 72-hour blood draw.

Period 2: For participants following a Monday, Wednesday, Friday HD schedule, study intervention will be administered approximately 2 hours prior to their Friday HD session. For participants following a Tuesday, Thursday, Saturday HD schedule, study intervention will

be administered approximately 2 hours prior to their Saturday HD session. The HD session should initiate immediately following the 2-hour PK blood draw. The HD period will be of approximately 4 hours. A pre-dialyzer plasma sample will be collected at the start of HD. Blood samples collected during HD will be collected from both the pre-dialyzer and post-dialyzer blood lines.

The blood flow, dialysate flow, and the make and model of the dialyzer will be recorded.

8.3.6 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 last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.7 Photograph of Rash

Photographs of any 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 relationship to the study intervention.

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.

AEs, 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 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 3.

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

Table 3 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
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

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 (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. 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 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

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

8.7 Pharmacodynamics

Not applicable.

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 (initial) 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 if there are Day -1 procedures planned per protocol.

8.11.2 Treatment Period

Refer to the SoA (Section 1.3).

8.11.3 Participants Discontinued From Study Intervention Continuing to be Monitored in the Study

At any point if a participant discontinues from study intervention or 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 at least one administration of study intervention (including participants who terminate the study early) will return to the CRU approximately 14 days after the last administration of study intervention 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 collection for MK-6482 is the critical procedure.

At any postdose time point, the blood sample for MK-6482 needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible. Study procedures can be performed before or after the prescribed/scheduled time.

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

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

The following variance in procedure collection times will be permitted.

- PK Collection as outlined in Table 4.

Table 4 Postdose Pharmacokinetic (Blood) Collection Windows

PK Collection (relative to dosing)	**PK Collection Window** (relative to scheduled time for collection)
0 to 2 hour	5 min
>2 to 12 hours	15 min
>12 to 48 hours	1 hour
>48 to 72 hours	2 hours

- Postdose standard safety evaluations: vital signs, ECG, pulse oximetry, and clinical 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 72-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 an 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 processed 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: The plasma PK (AUC0-inf and Cmax) of MK-6482 following a single oral 120 mg dose of MK-6482 to participants with ESRD before and after HD will be estimated and compared to each other and to those in healthy matched control participants.

Secondary Estimation:

Estimation: The extent to which MK-6482 is removed by HD from the plasma (eg, CLD, $_{plasma}$) will be estimated.

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 ESRD before and after HD to each other and to those in healthy matched control participants.

Additional PK endpoints will include AUC0-last, AUC0-24, AUC%extrap, Cmax, C24, Tmax, apparent terminal t½, λz, CL/F, and Vz/F.

For ESRD participants in Period 2, the secondary PK endpoint for plasma MK-6482 will include CLD_{plasma}. Additional PK endpoints for ESRD participants in Period 2 will include Ca, Cv, AUC(2-6)Ca, and AUC(2-6)Cv.

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 at least one dose of 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 plasma 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 Renal Function Assessment

The following renal function parameters will be calculated for each participant.

1. BSA normalized eGFR

   The MDRD (Modification of Diet in Renal Disease) equation will be used to estimate GFR standardized to a BSA of 1.73 m^2:

   eGFR (mL/min/1.73m^2) = 175 × standardized serum creatinine (mg/dL)$^{-1.154}$× age$^{-0.203}$ × (0.742 if female) × (1.212 if Black or African American).

2. BSA un-normalized eGFR

   The MDRD equation provides an estimate of GFR standardized to a BSA of 1.73 m^2, and it is therefore necessary to multiply this estimate by each participant's ratio of BSA/1.73 to determine the participant specific BSA un-normalized GFR:

   eGFR (mL/min) = eGFR (mL/min/1.73m^2) × [BSA (m^2) / 1.73].

   The BSA of an individual is calculated using the following equation:

   BSA (m^2) = [weight (kg)$^{0.425}$ × height (cm)$^{0.725}$] × 0.007184. (Dubois and Dubois, 1916, Wang et al., 1992)

   Note: The participants categorized into different renal categories based on BSA normalized eGFR may not fall into the same renal categories after re-categorization based on BSA un-normalized eGFR.

3. CLcr using the C-G Equation

   CLcr will be estimated using the following equation:

   CLcr = {[140 - age(yr)] × [body wt (kg)] × (0.85 if female)} / [72 × serum creat (mg/dL)]

   Note: The participants categorized into different renal categories based on eGFR using MDRD equation may not fall into the same renal categories after re-categorization based on CLcr by C-G equation.

9.6.3 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 (participants with ESRD before and after HD, control participants with normal renal function). An unstructured covariance matrix will be used to allow for unequal population variances and to model the correlation between repeated

measures (before and after HD) within each ESRD participant via the REPEATED and SUBJECT 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% confidence limits 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 subject;
model lnpk = population /ddfm=kr;
repeated population/ subject=subject type=UN;
lsmeans population /cl alpha=0.10;
lsmeans population/pdiff alpha=0.10;
run;
```

To address the primary estimation objective and compare participants with ESRD before and after HD to participants with normal renal function, a two sided 90% CI for the difference in least-squares means (ESRD before HD – normal renal function, ESRD after HD – normal renal function) will be calculated for each PK parameter using the aforementioned model. These confidence limits will be exponentiated to obtain the 90% CI for the ratio of geometric means (ESRD before HD/normal renal function, ESRD after HD/normal renal function) for each PK parameter. The same approach will be used to address the secondary estimation objective. The extent to which MK-6482 is removed from plasma by HD will be evaluated with the difference in means (ESRD before HD – ESRD after HD), the geometric mean ratio (ESRD before HD/ESRD after HD) and their 90% CIs. A sensitivity analysis may be performed without PMs at UGT2B17 or CYP2C19 if applicable as deemed clinically appropriate.

Figures showing summary plasma concentration-time profiles by population for MK-6482 (linear plot with arithmetic mean (±SD) for concentration and semi-log plot with arithmetic mean) will be provided. A table showing summary PK parameter values with GMs (%GCV) by population, will be provided for MK-6482 AUC0-inf, AUC0-24, Cmax, Tmax, and apparent terminal t½. A table showing the GMR (ESRD before HD /normal renal function, ESRD after HD/normal renal function, ESRD before HD/ESRD after HD) and corresponding 90% CI will be provided for PK parameters, AUC0-inf and Cmax.

Individual values will be listed for each PK parameter for MK-6482 (AUC0-inf, AUC0-last, AUC0-24, AUC%extrap ([percentage of AUC0-inf obtained by extrapolation from 24 hours to ∞], λz [terminal elimination rate constant], Cmax, Tmax, CL/F, Vz/F, λz, apparent terminal t½, CLD, $_{plasma}$ [dialysis clearance based on plasma], Ca [concentration in plasma samples from the pre-dialyzer line during the dialysis period], and Cv [concentration in plasma samples from the post-dialyzer line during the dialysis period]. 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). Descriptive statistics may be provided based on UGT2B17 and/or CYP2C19 phenotypes separately.

Individual participant PK parameter values will also be plotted against BSA normalized eGFR and against BSA un-normalized eGFR, using different symbols to identify participants from each population. For this analysis, eGFR may be calculated as the mean of the two values determined at the prestudy (screening) visit. Plots of PK parameters versus CLcr obtained from C-G equation may be provided. Additionally, plots of PK parameter values versus age and BMI may be provided. PK concentration listings for MK-6482 in plasma, including Ca and Cv concentrations, will be provided for each participant; AUC(2-6)Ca (plasma AUC values determined from Ca versus time profile during the dialysis period from 2 hours to 6 hours postdose using 'linear up, log down' calculation method option in WinNonlin), AUC(2-6)Cv (plasma AUC values determined from Cv versus time profile during the dialysis period from 2 hours to 6 hours postdose using 'linear up, log down' calculation method option in WinNonlin) for MK-6482 during HD in Period 2 will be provided for each ESRD participant.

9.6.4 Safety Analysis

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

9.7 Interim Analyses

Not applicable.

9.8 Multiplicity

Not applicable.

9.9 Sample Size and Power Calculations

The sample size selected to evaluate the effect of renal impairment on the PK of MK-6482 was not chosen to satisfy any a priori statistical requirement. This sample size (N=6 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 renal PK studies are presented below.

The precision of the estimated GMRs (ESRD before or after HD / normal renal 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 6 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 0.545. The lower and upper 90% confidence limits for the GMR will be given by OBS/1.72 and OBS*1.72 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 [0.87, 2.59].

Similarly, the observed between-participant coefficients of variation were 26.04% (~0.256 SD on the log scale) and 25.25% (~0.249 SD on the log scale) for Cmax from Protocol MK-6482-002 and Protocol MK-6482-006, respectively. Assuming a sample size of 6 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 0.243. The lower and upper 90% confidence limits for the GMR will be given by OBS/1.28 and OBS*1.28 for Cmax. Thus, for example, if the observed GMR for Cmax was 1.50, then the approximate 90% CI for the GMR would be [1.18, 1.91].

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/eCRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/eCRF 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 eCRF.

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/eCRFs.

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 eCRF 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 5 will be performed by the local laboratory with the exception of the UGT2B17 and CYP2C19 genotyping at 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 5 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	Magnesium
Coagulation	INR	PT		
Routine Urinalysis [b]	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• FSH (postmenopausal females only) • Urine [b]/breath alcohol and urine [b]/saliva drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Serology (HIV antibody, HBsAg, and hepatitis C virus antibody) • UGT2B17 genotyping • CYP2C19 genotyping			

[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 when the serum chemistry sample is taken
[b] For participants with ESRD, urine samples will be collected whenever possible, as they may not be able to produce urine. For participants who are anuric, urine samples for urinalysis will not be collected.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CYP=cytochrome P450; FSH=follicle-stimulating hormone; HBsAg=hepatitis B surface antigen; HCT=hematocrit; 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; 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 clinical 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 eCRFs/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 eCRF 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 eCRFs/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 eCRF.
- 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**

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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/
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10.7 Appendix 7: Country-specific Requirements

Not applicable

10.8 Appendix 8: Blood Volume Table

ESRD Participants Only	Prestudy	Treatment Periods	Poststudy	Total Collections	mL Per Collection	Total mL/ Test
Safety Clinical Laboratory Tests (including hematology, serum chemistry, FSH [if scheduled at the same time])	1	6 [b]	1	8	12.5	100
Coagulation	1	--	1	2	3.5	7
Blood for Planned Genetic Analysis	--	1	--	1	8.5	8.5
Blood for MK-6482	--	30	--	30	4	120
Blood for Protein Binding	--	1	--	1	4	4
Pre- and Post-dialyzer Plasma for MK-6482	--	17 [c]	--	17	4	68
Blood for UGT2B17 Genotyping	1	--	--	1	3	3
Blood for CYP2C19 Genotyping	1	--	--	1	3	3
Total Blood Volume per Participant [a]						**313.5 mL**

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

[b] If the CRU decides to confine the participants throughout the study (ie, washout period), some clinical laboratory assessments at the second check-in may not be performed at the investigator's discretion.

[c] Dialyzer samples collected in Period 2 only.

Healthy Participants Only	Prestudy	Treatment Period	Poststudy	Total Collections	mL Per Collection	Total mL/ Test
Safety Clinical Laboratory Tests (including hematology, serum chemistry, FSH [if scheduled at the same time])	1	3	1	5	12.5	62.5
Coagulation	1	--	1	2	3.5	7
Blood for Planned Genetic Analysis	--	1	--	1	8.5	8.5
Blood for MK-6482	--	15	--	15	4	60
Blood for Protein Binding	--	1	--	1	4	4
Blood for UGT2B17 Genotyping	1	--	--	1	3	3
Blood for CYP2C19 Genotyping	1	--	--	1	3	3
Total Blood Volume per Participant [a]						**148 mL**

[a] If additional PK 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
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase
ARNT	aryl hydrocarbon receptor nuclear translocator
AST	aspartate aminotransferase
AUC	area under the curve
BCS	Biopharmaceutical Classification System
bid	twice daily
BMI	body mass index
BP	blood pressure
BSA	body surface area
Ca	concentration in plasma samples from the pre-dialyzer line during the dialysis period
ccRCC	clear cell renal cell carcinoma
CCU	cardiac/coronary care unit
C-G	Cockcroft-Gault
CI	confidence interval
CL/F	apparent clearance
CLcr	creatinine clearance
CLD	HD clearance based on dialysate, calculated as: AED,total/AUCD
CLD, plasma	dialysis clearance based on plasma
Cmax	maximum plasma concentration
CNS	central nervous system
CRF	case report form
CRU	clinical research unit
CSR	clinical study report
Cv	concentration in plasma samples from the post-dialyzer line during the dialysis period
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic case report form
EDC	electronic data collection
eGFR	estimated glomerular filtration rate
EM	extensive metabolizer
EMA	European Medicines Agency

Abbreviation	Expanded Term
EPO	erythropoietin
ESRD	end stage renal disease
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FBR	future biomedical research
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
GMR	geometric mean ratio
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCT	hematocrit
HD	hemodialysis
HGB	hemoglobin
HIF-1α	hypoxia-inducible factor 1 alpha
HIF-1β	hypoxia-inducible factor 1 beta
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
ICU	intensive care unit
IEC	Independent Ethics Committee
IM	intermediate metabolizer
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IRB	Institutional Review Board
MDRD	Modification of Diet in Renal Disease
NCS	not clinically significant
NIMP	noninvestigational medicinal product
PAS	Per-ARNT-Sim
PCL	protocol clarification letter
PK	pharmacokinetic
PM	poor metabolizer

Abbreviation	Expanded Term
PP	per-protocol
PR	PR interval of ECG
PRO	patient-reported outcome
PT	prothrombin time
QRS	QRS interval of the ECG
QT	QT interval of the ECG
QTc	corrected QT interval
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
SLC2A1	glucose transporter solute carrier family 2 member 1
SoA	schedule of activities
SOP	standard operating procedures
SUSAR	suspected unexpected serious adverse reaction
T	body temperature
Tmax	time to maximum plasma concentration
t½	half life
UA	urinalysis
UGT	uridine 5′-diphospho-glucuronosyltransferase
ULN	upper limit of normal
VEGF-A	vascular endothelial growth factor A
VHL	von Hippel-Lindau disease
VHL-RCC	von Hippel-Lindau disease-associated renal cell carcinoma
WBC	white blood cell
WONCBP	woman/women of nonchildbearing potential

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