Official Protocol Title:	A Single-and Multiple Dose Study to Assess the Safety, Pharmacokinetics and Pharmacodynamics of Subcutaneous MK-2060 in Participants with Chronic and/or End-Stage Kidney Disease
NCT number:	NCT05656040
Document Date:	31-Oct-2023

TITLE PAGE

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Protocol Title: A Single-and Multiple Dose Study to Assess the Safety, Pharmacokinetics and Pharmacodynamics of Subcutaneous MK-2060 in Participants with Chronic and/or End-Stage Kidney Disease

Protocol Number: 011-01

Compound Number: MK-2060

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

Legal Registered Address:

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

NCT	Not applicable
EU CT	Not applicable
EudraCT	Not applicable
JRCT	Not applicable
WHO	Not applicable
UTN	Not applicable
IND	142,237

Approval Date: 31 October 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 1	31-OCT-2023	This amendment is issued to include the addition of a multiple dose panel in participants with CKD 4 or 5 and a single dose panel in participants with ESKD on peritoneal dialysis.
Original Protocol	31-OCT-2022	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 01

Overall Rationale for the Amendment:

This amendment is primarily issued to include the addition of a multiple dose panel in participants with CKD 4 or 5 and a single dose panel in participants with ESKD on peritoneal dialysis.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 4.1, Overall Design	Addition of a multiple dose panel in participants with CKD 4 or 5 and a single dose panel in participants with ESKD on peritoneal dialysis.	These changes were made in order to include some participants with CKD5 and to enable enrollment of ESKD-on peritoneal dialysis participants in Phase 3 studies.

Section Number and Name	Description of Change	Brief Rationale
Other Changes in Amendment		
	The structure of the protocol has been updated.	To comply with current industry regulations and guidelines. This restructuring does not affect the clinical or regulatory integrity of the protocol. All other relevant changes and their primary reasons are included for completeness.
Section 1.1, Synopsis	Change of the hypothesized geometric mean AUC0-∞ from 1130nM*hr to 11300 nM*hr.	This change was made to correct a typographical error and to align with a previously issues 19-DEC-2022 PCL #2.
Section 1.2, Schema	Added Figures for study design in the multiple dose panel and the single dose panel in peritoneal dialysis patients.	This change was made due to the addition of a multiple-dose panel in CKD 4 or 5 participants and a single-dose panel in ESKD on peritoneal dialysis participants.

Section Number and Name	Description of Change	Brief Rationale
Section 1.3, Schedule of Activities	Addition of footnote “d” to clarify wording regarding the Screening 2 visit Hematology, Chemistry, Urinalysis (Lab Safety Tests).	This change was made to align with a previously issued 09-FEB-2023 PCL #4.
Section 1.3, Schedule of Activities	Addition of footnote “e” to clarify wording regarding the Screening 1 visit Hemoccult test.	This change was made to align with a previously issued 15-FEB-2023 PCL #5.
Section 1.3, Schedule of Activities	Addition of Part 2 and Part 3 SoA.	Refer to Section 1.2 rationale.
Section 2.1	Addition of text to support study rationale.	This change was made to provide more context in support of the study and the amendment.
Section 2.2.2, Completed Clinical Studies	MK-2060-011-01 and MK-2060-08 were added to list of completed clinical studies.	This change was made to include new data from completed clinical studies.
Section 2.2.3, Ongoing Clinical Studies	Addition of study data/information for MK-2060-007, MK-2060-009, MK-2060-012, and MK-2060-013.	This change was made to include new data from ongoing clinical studies.
Section 3, Hypotheses, Objectives and Endpoints	Change of the hypothesized geometric mean AUC0-∞ from 1130nM*hr to 11300 nM*hr.	Refer to Section 1.1 rationale.
Section 4.2, Scientific Rationale for Study Design	Clarifying wording due to addition of a multiple dose panel in participants with CKD 4 or 5 and a single dose panel in participants with ESKD on peritoneal dialysis.	Refer to Section 1.2 rationale.
Section 4.2.1.2, Pharmacokinetic Endpoints	Clarifying wording due to addition of a multiple dose panel in participants with CKD 4 or 5 and a single dose panel in participants with ESKD on peritoneal dialysis.	Refer to Section 1.2 rationale.
Section 4.2.2, Rationale for the Use of Placebo	Clarifying wording due to addition of a multiple dose panel in participants with CKD 4 or 5 and a single dose panel in participants with ESKD on peritoneal dialysis.	Refer to Section 1.2 rationale.
Section 4.3, Justification for Dose	Added dose justification for Part 2 and Part 3.	Refer to Section 1.2 rationale.
Section 5.1, Inclusion Criteria	Changed inclusion criteria to clarify that the eGFR value used to determine eligibility would be the mean of 2 values taken at least 72 hours apart.	This change was made to remove ambiguity about eGFR inclusion criteria as it was stated as value at screening visit, but there are 2 screening visits per Section 1.2.
Section 5.1, Inclusion Criteria	Reduced the lower limit eGFR value from 15 to 10.	This change was made to reduce screen failure in otherwise stable individuals with CKD and thereby also include some participants with CKD5. The eGFR lower limit of 10 was selected as participants with eGFR above this level would be less likely to transition to dialysis during the time frame of the study.

Section Number and Name	Description of Change	Brief Rationale
Section 5.2, Exclusion Criteria	Removed clopidogrel use as an exclusion for the study.	This change was made due to new data showing coadministration of clopidogrel with MK-2060 in P008 did not impact time to hemostasis or lead to any bleeding related AEs.
Section 5.2, Exclusion Criteria	Added an exclusion criterion surrounding 2 measurements of eGFR (taken at least 72 hours apart) are different by more than 30%.	This change was made to ensure participants with rapidly fluctuating renal function are not enrolled and that eGFR is at or near steady state.
Section 5.3.2.1, Caffeine Restrictions	Added caffeine restrictions for Part 2 and Part 3 and clarified restrictions for Part 1.	Refer to Section 1.2 rationale.
Section 6.1, Study Intervention(s) Administered	Updated Table°1 to include information for Part 2 and Part 3.	Refer to Section 1.2 rationale.
Section 6.3.1, Intervention Assignment	Added intervention assignment information for Part 2 and Part 3.	Refer to Section 1.2 rationale.
Section 6.5, Concomitant Therapy	Removed clopidogrel use as prohibited for the study.	See rationale for Section 5.2.
Section 8.1.7, Assignment of Treatment/Randomization Number	Updated to include information and/or wording regarding the addition of Part 2 and Part 3.	Refer to Section 1.2 rationale.
Section 8.1.8.1, Timing of Dose Administration	Reduced total dosing time from 2 minutes to 1 minute.	This change was made to decrease the allowable study medication administration window.
Section 8.1.9, Discontinuation and Withdrawal	Updated to include information and/or wording regarding the addition of Part 2 and Part 3.	Refer to Section 1.2 rationale.
Section 8.1.11, Domiciling	Updated to include information and/or wording regarding the addition of Part 2 and Part 3.	Refer to Section 1.2 rationale.
Section 8.3.2.1, Resting Vital Signs	Updated to include information and/or wording regarding the addition of Part 2 and Part 3.	Refer to Section 1.2 rationale.
Section 8.3.3, Electrocardiogram	Updated to include information and/or wording regarding the addition of Part 2 and Part 3.	Refer to Section 1.2 rationale.
Section 8.3.3, Electrocardiogram	Change of allowable procedure window for Day 1 predose ECGs from within 24 hours prior to dosing MK-2060/placebo to within 3 hours prior to dosing MK-2060/placebo.	This change was made to correct a typographical error and to align with a previously issued 01-FEB-2023 PCL #3.
Section 8.3.6, Hemoccult Test	Clarifying wording surrounding when to provide and return hemoccult tests.	Refer to Section 8.3.3 rationale.
Section 8.3.8.1, Systemic Injection Reaction Assessment	Clarified wording surrounding how long participants will be monitored during the administration of MK-2060/placebo – now participants will be monitored for at least 4 hours up to 24 to 48 hours postdose at the CRU after the initiation of administration.	This change was made following investigator/site feedback.

Section Number and Name	Description of Change	Brief Rationale
Section 8.6.1, Blood Collection for Plasma MK-2060	Removal of statement "Samples taken on the day of infusion will be collected in the opposite arm from the infusion site."	This change was made to correct a typographical error.
Section 8.7, Pharmacodynamics	Clarified wording that sample collection, storage, and shipment instructions for pharmacodynamic samples will be provided in the Study Operations Manual.	This change was made to correct a typographical error.
Section 8.9, Future Biomedical Research Sample Collection	Clarified what specimens be obtained as part of FBR.	This change was made to correct a typographical error.
Section 8.11.3, Poststudy	Updated to include information and/or wording regarding the addition of Part 2 and Part 3.	Refer to Section 1.2 rationale.
Section 8.11.4, Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study	Addition of CKD5 as a possible group of participants that may progress to ESKD during the study.	Refer to Section 5.1 rationale.
Section 8.11.6, Critical Procedures Based on Study Objectives: Timing of Procedure	Updated to include information and/or wording regarding the addition of Part 2 and Part 3.	Refer to Section 1.2 rationale.
Section 8.11.7, Study Design/Procedures Modifications Permitted Within Protocol Parameters	Updated to include information and/or wording regarding the addition of Part 2 and Part 3.	Refer to Section 1.2 rationale.
Section 9.4, Analysis Endpoints	Change of the hypothesized geometric mean AUC0-∞ from 11345 nM*hr to 11300 nM*hr.	Refer to Section 1.1 rationale.
Section 9.9, Sample Size and Power Calculations	Change of protocol number from MK-6194 to MK-2060.	This change was made to correct a typographical error and to align with a previously issued 11-NOV-2022 PCL #1.
Section 10.3, Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Replacement of "Sponsor's product" with "Study intervention" throughout the section.	This change was made due to incorrect standard text.
Section 10.8 Appendix 8, Blood Volume Tables	Addition of Part 2 and Part 3 blood volume tables.	Refer to Section 1.2 rationale.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Single-and Multiple Dose Study to Assess the Safety, Pharmacokinetics and Pharmacodynamics of Subcutaneous MK-2060 in Participants with Chronic and/or End-Stage Kidney Disease

Short Title: MK-2060 PK Study

Acronym: N/A

Hypotheses, Objectives, and Endpoints:

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

This study is to be conducted in adult participants with chronic and/or end-stage kidney disease.

Primary Objectives	**Primary Endpoints**
Part 1: To evaluate the safety and tolerability of MK-2060 following single-dose SC administration in adult participants with Stage 4 or 5 Chronic Kidney Disease. Part 2: To evaluate the safety and tolerability of MK-2060 following multiple-dose SC administration in adult participants with Stage 4 or 5 Chronic Kidney Disease. Part 3: To evaluate the safety and tolerability of MK-2060 following single-dose SC administration in adult participants with End-Stage Kidney Disease on Peritoneal Dialysis.	Bleeding related AEs, AEs, and discontinuations due to AEs
Part 1: To evaluate plasma pharmacokinetics of MK-2060 following single-dose SC administration in adult participants with Stage 4 or 5 Chronic Kidney Disease. <u>Hypothesis:</u> The true geometric mean of AUC0-∞ after a single well tolerated dose of MK-2060 in adult participants with Stage 4 or 5 Chronic Kidney Disease is at least 11300 nM*hr.	Measurement of MK-2060 plasma AUC0-∞, AUC0-168, Cmax, C168, Tmax, terminal t1/2, CL/F and Vz/F

Part 2: To evaluate plasma pharmacokinetics of MK-2060 following multiple-dose SC administration in adult participants with Stage 4 or 5 Chronic Kidney Disease. Estimation: The effect of multiple-dose SC administration of MK-2060 in adult participants with Stage 4 or 5 Chronic Kidney Disease will be estimated. Part 3: To evaluate plasma pharmacokinetics of MK-2060 following single-dose SC administration in adult participants with End-Stage Kidney Disease on Peritoneal Dialysis. Estimation: The effect of single-dose SC administration of MK-2060 in adult participants with End Stage Kidney Disease on Peritoneal Dialysis will be estimated.	
Secondary Objective	**Secondary Endpoint**
Part 1: To evaluate the effect of MK-2060 on aPTT following single dose SC administration in adult participants with Stage 4 or 5 Chronic Kidney Disease. Part 2: To evaluate the effect of MK-2060 on aPTT following multiple-dose SC administration in adult participants with Stage 4 or 5 Chronic Kidney Disease. Part 3: To evaluate the effect of MK-2060 on aPTT following single dose SC administration in adult participants with End-Stage Kidney Disease on Peritoneal Dialysis.	aPTT fold change from baseline

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Thrombosis
Population	Patient: Adult participants with CKD
Study Type	Interventional
Intervention Model	Single Group This is a multi site study.
Type of Control	Placebo
Study Blinding	Double-blind
Blinding Roles	Participants or Subjects
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 16 to 18 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 randomized to receive MK-2060 or placebo in a 3:1 ratio (9 active and 3 placebo) in both Part 1 and Part 2 and approximately 9 participants will be allocated to receive MK-2060 in Part 3.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
MK-2060	MK-2060	15 mg/mL	30 mg	SC	Part 1: Day 1 Part 2: Days 1, 2, 3, 4, 8, 15, and 22 Part 3: Day 1	Test Product
Placebo	Placebo	Saline	0 mg	SC	Part 1: Day 1 Part 2: Days 1, 2, 3, 4, 8, 15, and 22	Placebo

SC=subcutaneous; USP=United States Pharmacopeia
Placebo SC (0.9% sodium chloride infusion, USP sterile saline)

Total Number of Intervention Groups/Arms	There will be 3 intervention groups.
Duration of Participation	Part 1: Each participant will participate in the study for approximately 19 weeks from the time the participant provides documented informed consent through the final contact. After a screening phase of 4 weeks, each participant will receive assigned intervention for approximately 1 day. After the end-of-treatment each participant will be followed for approximately 13 weeks. Part 2: Each participant will participate in the study for approximately 20 weeks from the time the participant provides documented informed consent through the final contact. After a screening phase of 4 weeks, each participant will receive assigned intervention for approximately 4 weeks (4 consecutive days of loading doses followed by weekly single dose x 3). After the end-of-treatment each participant will be followed for approximately 13 weeks. Part 3: Each participant will participate in the study for approximately 23 weeks from the time the participant provides documented informed consent through the final contact. After a screening phase of 4 weeks, each participant will receive assigned intervention for approximately 1 day. After the end-of-treatment each participant will be followed for approximately 17 weeks.

Study Governance Committees:

Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No

There are no governance committees in this study. Regulatory, ethical, and study oversight considerations are outlined in Appendix 1.

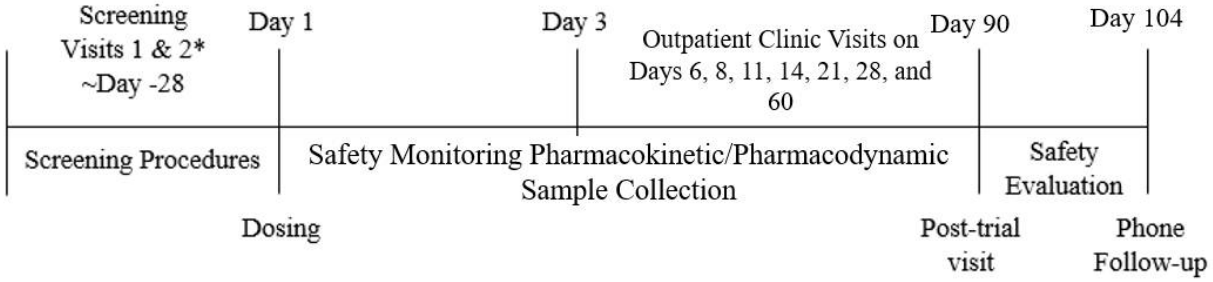
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 10.

1.2 Schema

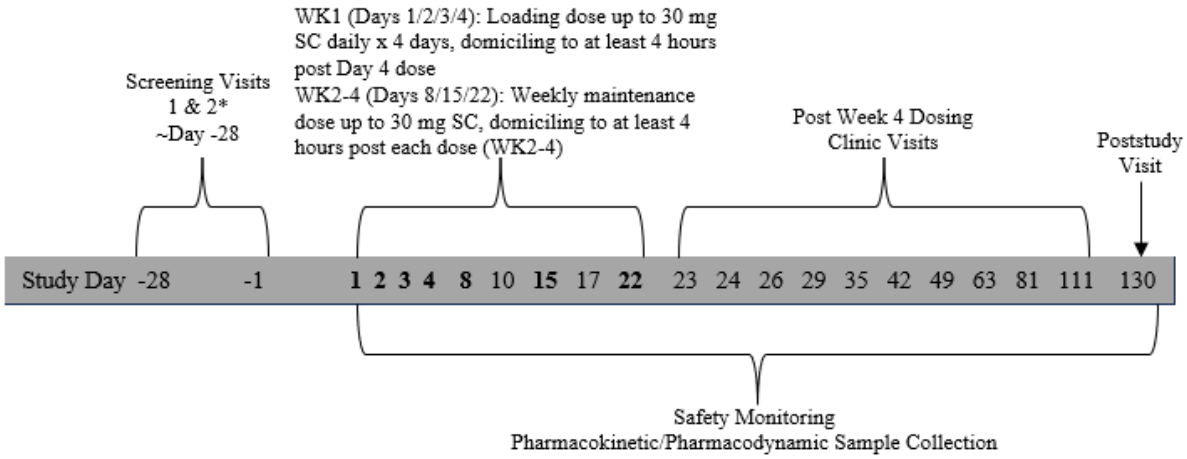
The study design is depicted in Figure 1, Figure 2, and Figure 3.

Figure 1 Study Design for Part 1



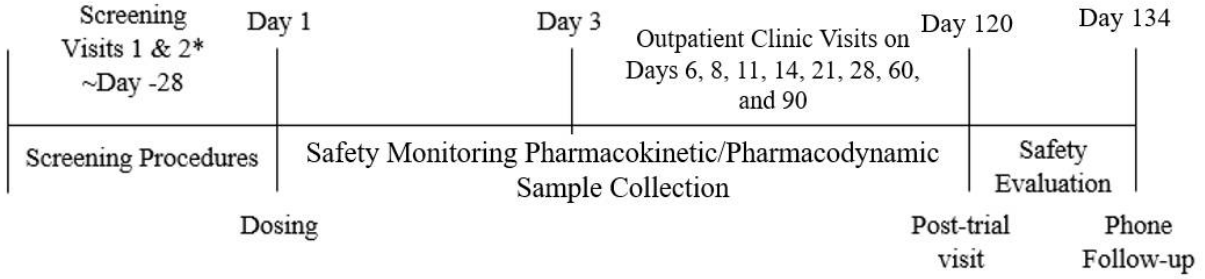
* Screening Visit 2: not required if screening visit 1 occurs within **96** hrs prior to Day 1

Figure 2 Study Design for Part 2



*Screening Visit 2: not required if Screening Visit 1 occurs within 96 hrs prior to Day 1
SC=subcutaneous; WK=week

Figure 3 Study Design for Part 3



* Screening Visit 2: not required if screening visit 1 occurs within **96** hrs prior to Day 1

1.3 Schedule of Activities

1.3.1 Part 1

Part 1																				
	Scheduled Time																			
			Day 1 (hours post-dose)						**Days**											
Scheduled Timing	**Screening 1**	**Screening 2[a]**	**Predose**	**0**	**1**	**4**	**8**	**12**	**2 (D1 24 hrs)**	**3 (D1 48 hrs)**	**6 (D1 120 hrs) (±1 Day)**	**8 (D1 168 hrs)**	**11 (±1 Day)**	**14 (±1 Day)**	**21 (±2 Days)**	**28 (±3 Days)**	**60 (±5 Days)**	**90 Poststudy[b] (±5 Days)**	**104 Phone Follow-up[c] (±5 Days)**	**Notes**
Administrative Procedures																				
Informed Consent	X																			Sec. 5.1, 8.1.1.1
Informed Consent for FBR	X																			Sec. 5.1, 8.1.1.2
Inclusion/Exclusion Criteria	X	X	X																	Sec. 5.1, 5.2, 8.1.2
Participant ID Card	X																			Sec. 8.1.3
Participant ID Bracelet			X																	Sec. 8.11.2
Medical History	X	X	X																	Sec. 8.1.4
Assignment of Screening Number	X																			Sec. 8.1.6
Assignment of Randomization Number				X																The randomization number is assigned at the time of study drug administration. Sec. 5.5, 8.1.7
Prior/Concomitant Medication Review	X----------X																			Sec. 5.2, 6.5, 8.1.5
Safety/Clinic Procedures																				
Full physical examination	X		X						X	X								X		Sec. 8.3.1, 8.3.7

Part 1																				
	Scheduled Time																			
			Day 1 (hours post-dose)						**Days**											
Scheduled Timing	**Screening 1**	**Screening 2[a]**	**Predose**	**0**	**1**	**4**	**8**	**12**	**2 (D1 24 hrs)**	**3 (D1 48 hrs)**	**6 (D1 120 hrs) (±1 Day)**	**8 (D1 168 hrs)**	**11 (±1 Day)**	**14 (±1 Day)**	**21 (±2 Days)**	**28 (±3 Days)**	**60 (±5 Days)**	**90 Poststudy[b] (±5 Days)**	**104 Phone Follow-up[c] (±5 Days)**	**Notes**
Targeted physical examination																X	X			Sec. 8.3.1, Sec. 8.3.7
Height	X																			Sec. 8.3.1
Weight	X																	X		BMI to be taken only at Screening 1. Sec. 8.3.1
Orthostatic VS (HR, BP)	X		X								X									Sec. 8.3.2.2.
Semi-recumbent VS (HR, BP)	X		X----------X							X	X		X			X	X	X		Day 1 measurements will be at predose, 1- and 12-hours postdose. Sec. 8.3.2
RR and body temperature	X		X		X			X		X	X		X					X		Sec. 8.3.2.
12-lead ECG	X		X					X		X	X		X					X		Sec. 8.3.3.
Standard Meals					X----------X															Sec. 5.3.1.
Domiciling			X----------X																	Sec. 8.1.11
MK-2060/Placebo Administration				X																MK-2060/Placebo will be administered SC at Time 0. Refer to Sec. 6.2, 8.1.8 and the Study Pharmacy Manual for additional information on the preparation and administration of the study drug.

Part 1																				
	Scheduled Time																			
			Day 1 (hours post-dose)						**Days**											
Scheduled Timing	**Screening 1**	**Screening 2[a]**	**Predose**	**0**	**1**	**4**	**8**	**12**	**2 (D1 24 hrs)**	**3 (D1 48 hrs)**	**6 (D1 120 hrs) (±1 Day)**	**8 (D1 168 hrs)**	**11 (±1 Day)**	**14 (±1 Day)**	**21 (±2 Days)**	**28 (±3 Days)**	**60 (±5 Days)**	**90 Poststudy[b] (±5 Days)**	**104 Phone Follow-up[c] (±5 Days)**	**Notes**
Local Injection Site Reaction					X	X	X		X	X	X	X								Note: Participants who call the CRU to report an injection site reaction on Days 4, 5, and/or 7 may be asked to return to the CRU as soon as possible for an additional assessment. Sec. 8.3.7.
AE/SAE Review	X----------X																			All NSAEs and SAEs will be recorded up to 104-days postdose (inclusive). Sec. 8.4
Laboratory Procedures																				
Serum hCG (WOCBP only)	X		X															X		Appendices 2 and 8
Serum FSH - (WONCBP only)	X																			Appendices 2, 5, and 8
HIV, hepatitis B and C screen (per site SOP)	X																			Sec. 5.2, Appendices 2 and 8

Part 1																				
	Scheduled Time																			
			Day 1 (hours post-dose)						**Days**											
Scheduled Timing	**Screening 1**	**Screening 2[a]**	**Predose**	**0**	**1**	**4**	**8**	**12**	**2 (D1 24 hrs)**	**3 (D1 48 hrs)**	**6 (D1 120 hrs) (±1 Day)**	**8 (D1 168 hrs)**	**11 (±1 Day)**	**14 (±1 Day)**	**21 (±2 Days)**	**28 (±3 Days)**	**60 (±5 Days)**	**90 Poststudy[b] (±5 Days)**	**104 Phone Follow-up[c] (±5 Days)**	**Notes**
Drug and Alcohol Screen (per site SOP)	X		X																	Screening and predose drug/alcohol screen are mandatory (predose drug screen may occur in the evening prior to Day 1 at the time of admission); any additional drug/alcohol screen is conducted per site SOP. Sec. 8.3.5 and Appendix 2
24-Hour Urine Protein Collection			X																	The 24-hour urine collection will begin the evening before dosing. Sec. 8.3.4, Appendix 2.
24-Hour Urine Creatinine Collection			X																	The 24-hour urine collection will begin the evening before dosing. Sec. 8.3.4, Appendix 2.
Spot Urine Collection for Urine Protein: Urine Creatinine Ratio								X								X		X		If a participant is unable to produce a urine sample 12-hours postdose, this spot urine can be collected the next time the participant is able to void. Sec. 8.3.4, Appendix 2

Part 1																				
	Scheduled Time																			
			Day 1 (hours post-dose)						**Days**											
Scheduled Timing	**Screening 1**	**Screening 2[a]**	**Predose**	**0**	**1**	**4**	**8**	**12**	**2 (D1 24 hrs)**	**3 (D1 48 hrs)**	**6 (D1 120 hrs) (±1 Day)**	**8 (D1 168 hrs)**	**11 (±1 Day)**	**14 (±1 Day)**	**21 (±2 Days)**	**28 (±3 Days)**	**60 (±5 Days)**	**90 Poststudy[b] (±5 Days)**	**104 Phone Follow-up[c] (±5 Days)**	**Notes**
Hematology, Chemistry, Urinalysis	X	X[d]	X							X		X				X		X		Hematology/Chemistry/Urinalysis will be obtained after an 8-hour fast. Predose tests can be conducted up to 24 hours prior to dosing. Sec. 8.3.5, Appendices 2 and 8
aPTT and PT at local lab	X							X		X	X	X	X			X				Sec. 5.2, 8.3.5, Appendices 2 and 8
Hemoccult test	X[e]									X	X	X	X	X	X	X	X			Sec. 8.3.6
Biomarkers																				
Blood for Genetic Analysis[f]			X																	Collected predose from enrolled participants only. Sec. 8.8.1, Appendix 8
Pharmacokinetics																				
Blood for Plasma MK-2060			X		X			X	X	X	X	X	X	X	X	X	X	X		Sec. 8.6.1, Appendix 8, and Study Operations Manual
Pharmacodynamics																				
Blood for PT/aPTT/FXI activity by central lab			X		X			X	X	X	X	X	X	X	X	X	X	X		Sec. 8.7.1, Appendix 8, and Study Operations Manual
Blood for plasma ADA			X											X	X	X	X	X		Sec. 8.7.2, Appendix 8, and Study Operations Manual

Part 1																				
	Scheduled Time																			
			Day 1 (hours post-dose)						**Days**											
Scheduled Timing	**Screening 1**	**Screening 2[a]**	**Predose**	**0**	**1**	**4**	**8**	**12**	**2 (D1 24 hrs)**	**3 (D1 48 hrs)**	**6 (D1 120 hrs) (±1 Day)**	**8 (D1 168 hrs)**	**11 (±1 Day)**	**14 (±1 Day)**	**21 (±2 Days)**	**28 (±3 Days)**	**60 (±5 Days)**	**90 Poststudy[b] (±5 Days)**	**104 Phone Follow-up[c] (±5 Days)**	**Notes**

ADA=antidrug antibody; aPTT=activated partial thromboplastin time; AE=adverse event; BMI=body mass index; BP=blood pressure; CRU=clinical research unit; D=Day; DNA=deoxyribonucleic acid, ECG=electrocardiogram; FBR=future biomedical research, FSH=follicle stimulating hormone; FXI=factor XI; HIV=human immunodeficiency virus; hCG=human chorionic gonadotropin; HR=heart rate; ID=identification; IEC=Independent Ethics Committee; IRB=Institutional Review Board; NSAE=nonserious adverse event; PT=prothrombin time; RR=respiratory rate; SAE=serious adverse event; SC=subcutaneous; SOP=standard operating procedure; VS=vital signs; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential

a. Screening 2 should occur within 96 hours prior to Day 1. If Screening 1 occurs within 96 hrs prior to administration of the dose of study drug, Screening 2 is not required.

b. The poststudy visit will occur approximately 90 days following administration of study drug. Procedures outlined in the poststudy visit may obtained on Day 90 (±5 days) Follow up on any clinical or laboratory AEs should occur in person if the poststudy visit occurs prior to 90 days following administration of study drug. If a participant discontinues for any reason at any time during the course of the study the participant may be asked to return to the clinic to complete the poststudy visit. The investigator may decide to perform the poststudy visit at the time of discontinuation or as soon as possible after discontinuation as outlined in Sections 7.1 and 8.1.9.

c. At the discretion of the investigator an in-person follow-up may be performed.

d. If Screening 2 occurs on Day -1, only obtain predose Hematology, Chemistry, Unrinalysis lab safety tests (these results will be used to satisfy both the Screening 2 and predose safety lab tests).

e. Hemoccult test will be provided to a participant at Screening 1 visit and returned at Screening 2 visit or prior to dosing at the time scheduled by the investigator, if Screening 2 visit does not occur.

f. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for this purpose. If the sample is collected, leftover extracted DNA will be stored for future biomedical research once the participant signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR. Blood for genetic analysis should be collected only once per participant after randomization.

1.3.2 Part 2

Part 2																						
	Screening ≤28 days to Day 1		**Intervention**																		**Post-study**	**Notes**
Scheduled Timing (Week)	**Screening 1**	**Screening 2[a]**	**Week 1**				**Week 2**		**Week 3**		**Week 4**			**Post Week 4**								
Scheduled Timing (Day)			**1**	**2**	**3**	**4**	**8**	**10**	**15**	**17**	**22**	**23**	**26**	**29**	**35**	**42**	**49**	**63**	**81**	**111**	**130**	
Visit Window (Day)			**NA**	**NA**	**NA**	**NA**	**NA**	**±1**	**NA**	**±1**	**NA**	**NA**	**±1**	**NA**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±7**	
Administrative Procedures																						
Informed Consent	X																					Sec. 5.1, 8.1.1.1
Informed Consent for FBR	X																					Sec. 5.1, 8.1.1.2
Inclusion/Exclusion Criteria	X	X	X																			Sec. 5.1, 5.2, 8.1.2
Participant ID Card	X																					Sec. 8.1.3
Participant ID Bracelet			X																			Sec. 8.11.2
Medical History	X	X	X																			Sec. 8.1.4
Assignment of Screening Number	X																					Sec. 8.1.6
Assignment of Randomization Number			X																			The randomization number is assigned at the time of study drug administration. Sec. 5.5, 8.1.7

Part 2																						
	Screening ≤28 days to Day 1		**Intervention**																		**Post-study**	**Notes**
Scheduled Timing (Week)	**Screening 1**	**Screening 2[a]**	**Week 1**				**Week 2**		**Week 3**		**Week 4**			**Post Week 4**								
Scheduled Timing (Day)			**1**	**2**	**3**	**4**	**8**	**10**	**15**	**17**	**22**	**23**	**26**	**29**	**35**	**42**	**49**	**63**	**81**	**111**	**130**	
Visit Window (Day)			**NA**	**NA**	**NA**	**NA**	**NA**	**±1**	**NA**	**±1**	**NA**	**NA**	**±1**	**NA**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±7**	
Prior/Concomitant Medication Review	X----------X																					Sec. 5.2, 6.5, 8.1.5
Safety/Clinic Procedures																						
Full physical examination	X		X				X		X		X			X							X	Sec. 8.3.1, 8.3.7
Targeted physical examination				X	X										X		X	X	X			Sec. 8.3.1, Sec. 8.3.7
Height	X																					Sec. 8.3.1
Weight	X																				X	BMI to be taken only at Screening 1. Sec. 8.3.1
Orthostatic VS (HR, BP)	X		X			X	X		X		X											Days 1, 4, 8, 15 and 22 measurements will be predose; Sec. 8.3.2.2.
Semi-recumbent VS (HR, BP)	X	X	X			X	X		X		X		X	X		X		X			X	Days 1, 4, 8, 15 and 22 measurements will be predose; Sec. 8.3.2
RR and body temperature	X		X			X	X		X		X											Days 1, 4, 8, 15 and 22 measurements will be predose; Sec. 8.3.2.

Part 2																					
	Screening ≤28 days to Day 1		**Intervention**																		**Post-study**	**Notes**
Scheduled Timing (Week)	**Screening 1**	**Screening 2[a]**	**Week 1**				**Week 2**		**Week 3**		**Week 4**			**Post Week 4**								
Scheduled Timing (Day)			**1**	**2**	**3**	**4**	**8**	**10**	**15**	**17**	**22**	**23**	**26**	**29**	**35**	**42**	**49**	**63**	**81**	**111**	**130**	
Visit Window (Day)			**NA**	**NA**	**NA**	**NA**	**NA**	**±1**	**NA**	**±1**	**NA**	**NA**	**±1**	**NA**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±7**	
12-lead ECG	X		X			X	X		X		X			X							X	Days 1, 4, 8, 15 and 22 measurements will be predose; Sec. 8.3.3.
Domiciling			X	X	X	X	X		X		X											Sec. 8.1.11.
Standard Meals			X				X		X		X											Sec. 5.3.1.
MK-2060/Placebo Administration			X	X	X	X	X		X		X											MK-2060/Placebo will be administered SC at Time 0. Refer to Sec. 6.2, 8.1.8 and the Study Pharmacy Manual for additional information on the preparation and administration of the study drug.
Local Injection Site Reaction			X	X	X	X	X	X	X	X	X	X		X								Note: Participants who call the CRU to report an injection site reaction on non-visit days may be asked to return to the CRU as soon as possible for an additional assessment. Sec. 8.3.7.

Part 2																							
	Screening ≤28 days to Day 1		**Intervention**																			**Post-study**	**Notes**
Scheduled Timing (Week)	**Screening 1**	**Screening 2[a]**	**Week 1**				**Week 2**		**Week 3**		**Week 4**			**Post Week 4**									
Scheduled Timing (Day)			**1**	**2**	**3**	**4**	**8**	**10**	**15**	**17**	**22**	**23**	**26**	**29**	**35**	**42**	**49**	**63**	**81**	**111**	**130**		
Visit Window (Day)			**NA**	**NA**	**NA**	**NA**	**NA**	**±1**	**NA**	**±1**	**NA**	**NA**	**±1**	**NA**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±7**		
AE/SAE Review	X----------X																						All NSAEs and SAEs will be recorded up to 144-days postdose (inclusive). Sec. 8.4.
Laboratory Procedures																							
Serum hCG (WOCBP only)	X		X								X										X	Appendices 2 and 8
Serum FSH - (WONCBP only)	X																						Appendices 2, 5, and 8
HIV, Hepatitis B and C screen (per site SOP)	X																						Sec. 5.2, Appendices 2 and 8
Drug and Alcohol Screen (per site SOP)	X		X																				Screening and predose drug/alcohol screen are mandatory (predose drug screen may occur in the evening prior to Day 1 at the time of admission); any additional drug screen is conducted per site SOP. Sec. 8.3.5 and Appendix 2.

Part 2																						
	Screening ≤28 days to Day 1		**Intervention**																		**Post-study**	**Notes**
Scheduled Timing (Week)	**Screening 1**	**Screening 2[a]**	**Week 1**				**Week 2**		**Week 3**		**Week 4**			**Post Week 4**								
Scheduled Timing (Day)			**1**	**2**	**3**	**4**	**8**	**10**	**15**	**17**	**22**	**23**	**26**	**29**	**35**	**42**	**49**	**63**	**81**	**111**	**130**	
Visit Window (Day)			**NA**	**NA**	**NA**	**NA**	**NA**	**±1**	**NA**	**±1**	**NA**	**NA**	**±1**	**NA**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±7**	
24-Hour Urine Protein Collection			X																			The 24-hour urine collection will begin the evening before dosing. Sec. 8.3.4, Appendix 2.
24-Hour Urine Creatinine Collection			X																			The 24-hour urine collection will begin the evening before dosing. Sec. 8.3.4, Appendix 2.
Spot Urine Collection for Urine Protein: Urine Creatinine Ratio			X											X				X				If a participant is unable to produce a urine sample at Day 1 12-hours postdose, this spot urine can be collected the next time the participant is able to void. Sec. 8.3.4, Appendix 2.
Hematology, Chemistry, Urinalysis	X	X[d]	X			X	X		X		X		X	X		X		X	X		X	Hematology/Chemistry/Urinalysis will be obtained after an 8-hour fast. Days 1, 8, 15, and 22 samples will be predose. Sec. 8.3.5, Appendices 2 and 8.
aPTT and PT at local lab	X		X			X	X		X		X		X	X							X	Days 1, 8, 15, and 22 samples will be predose. Sec. 5.2, 8.3.5, Appendices 2 and 8

Part 2																						
	Screening ≤28 days to Day 1		**Intervention**																		**Post-study**	**Notes**
Scheduled Timing (Week)	**Screening 1**	**Screening 2[a]**	**Week 1**				**Week 2**		**Week 3**		**Week 4**			**Post Week 4**								
Scheduled Timing (Day)			**1**	**2**	**3**	**4**	**8**	**10**	**15**	**17**	**22**	**23**	**26**	**29**	**35**	**42**	**49**	**63**	**81**	**111**	**130**	
Visit Window (Day)			**NA**	**NA**	**NA**	**NA**	**NA**	**±1**	**NA**	**±1**	**NA**	**NA**	**±1**	**NA**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±7**	
Hemoccult test	X[e]			X		X	X	X	X	X	X	X		X	X	X	X	X	X	X		Sec. 8.3.6.
Biomarkers																						
Blood for Genetic Analysis[f]			X																			Collected predose from enrolled participants only. Sec. 8.8.1, Appendix 8
Pharmacokinetics																						
Blood for Plasma MK-2060			X	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	Days 1, 2, 4, 8, 15, and 22 samples will be predose. Sec. 8.6.1, Appendix 8, and Study Operations Manual
Pharmacodynamics																						
Blood for PT/aPTT/FXI activity by central lab			X	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	Days 1, 2, 4, 8, 15, and 22 samples will be predose. Sec. 8.7.1, Appendix 8, and Study Operations Manual
Blood for Plasma ADA			X						X		X						X	X	X	X	X	Days 1, 15 and 22 samples will be predose Sec. 8.7.2, Appendix 8, and Study Operations Manual

Part 2																							
	Screening ≤28 days to Day 1		**Intervention**																			**Post-study**	**Notes**
Scheduled Timing (Week)	**Screening 1**	**Screening 2[a]**	**Week 1**				**Week 2**		**Week 3**		**Week 4**			**Post Week 4**									
Scheduled Timing (Day)			**1**	**2**	**3**	**4**	**8**	**10**	**15**	**17**	**22**	**23**	**26**	**29**	**35**	**42**	**49**	**63**	**81**	**111**	**130**		
Visit Window (Day)			**NA**	**NA**	**NA**	**NA**	**NA**	**±1**	**NA**	**±1**	**NA**	**NA**	**±1**	**NA**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±7**		

ADA=antidrug antibody; aPTT=activated partial thromboplastin time; AE=adverse event; BMI=body mass index; BP=blood pressure; CRU=clinical research unit; D=Day; DNA=deoxyribonucleic acid, ECG=electrocardiogram; FBR=future biomedical research, FSH=follicle stimulating hormone; FXI=factor XI; HIV=human immunodeficiency virus; hCG=human chorionic gonadotropin; HR=heart rate; ID=identification; IEC=Independent Ethics Committee; IRB=Institutional Review Board; NSAE=nonserious adverse event; PT=prothrombin time; RR=respiratory rate; SAE=serious adverse event; SC=subcutaneous; SOP=standard operating procedure; VS=vital signs; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential

a. Screening 2 should occur within 96 hours prior to Day 1. If Screening 1 occurs within 96 hrs prior to administration of the dose of study drug, Screening 2 is not required.

b. The poststudy visit will occur approximately 130 days following administration of study drug. Procedures outlined in the poststudy visit may obtained on Day 130 (±7 days) Follow up on any clinical or laboratory AEs should occur in person if the poststudy visit occurs prior to 130 days following administration of study drug. If a participant discontinues for any reason at any time during the course of the study the participant may be asked to return to the clinic to complete the poststudy visit. The investigator may decide to perform the poststudy visit at the time of discontinuation or as soon as possible after discontinuation as outlined in Sections 7.1 and 8.1.9.

c. At the discretion of the investigator an in-person follow-up may be performed.

d. If Screening 2 occurs on Day -1, only obtain predose Hematology, Chemistry, Unrinalysis lab safety tests (these results will be used to satisfy both the Screening 2 and predose safety lab tests).

e. Hemoccult test will be provided to a participant at Screening 1 visit and returned at Screening 2 visit or prior to dosing at the time scheduled by the investigator, if Screening 2 visit does not occur.

f. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for this purpose. If the sample is collected, leftover extracted DNA will be stored for future biomedical research once the participant signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR. Blood for genetic analysis should be collected only once per participant after randomization.

1.3.3 Part 3

Part 3																						
	Scheduled Time																					
			Day 1 (hours post-dose)						**Days**													
Scheduled Timing	**Screening 1**	**Screening 2[a]**	**Predose**	**0**	**1**	**4**	**8**	**12**	**2 (D1 24 hrs)**	**3 (D1 48 hrs)**	**6 (D1 120 hrs) (±1 Day)**	**8 (D1 168 hrs)**	**11 (±1 Day)**	**14 (±1 Day)**	**21 (±2 Days)**	**28 (±3 Days)**	**42 (±4 Days)**	**60 (±5 Days)**	**90 (±5 Days)**	**120 Poststudy[b] (±5 Days)**	**134 Phone Follow-up[c] (±5 Days)**	**Notes**
Administrative Procedures																						
Informed Consent	X																					Sec. 5.1, 8.1.1.1
Informed Consent for FBR	X																					Sec. 5.1, 8.1.1.2
Inclusion/Exclusion Criteria	X	X	X																			Sec. 5.1, 5.2, 8.1.2
Participant ID Card	X																					Sec. 8.1.3
Participant ID Bracelet			X																			Sec. 8.11.2
Medical History	X	X	X																			Sec. 8.1.4
Assignment of Screening Number	X																					Sec. 8.1.6
Assignment of Randomization Number				X																		The allocation number is assigned at the time of study drug administration. Sec. 5.5, 8.1.7
Prior/Concomitant Medication Review	X----------X		Sec. 5.2, 6.5, 8.1.5																			
Safety/Clinic Procedures																						
Full physical examination	X		X						X	X										X		Sec. 8.3.1, 8.3.7

Part 3																							
	Scheduled Time																						
			Day 1 (hours post-dose)						**Days**														
Scheduled Timing	**Screening 1**	**Screening 2[a]**	**Predose**	**0**	**1**	**4**	**8**	**12**	**2 (D1 24 hrs)**	**3 (D1 48 hrs)**	**6 (D1 120 hrs) (±1 Day)**	**8 (D1 168 hrs)**	**11 (±1 Day)**	**14 (±1 Day)**	**21 (±2 Days)**	**28 (±3 Days)**	**42 (±4 Days)**	**60 (±5 Days)**	**90 (±5 Days)**	**120 Poststudy[b] (±5 Days)**	**134 Phone Follow-up[c] (±5 Days)**	**Notes**
Targeted physical examination																X		X				Sec. 8.3.1, Sec. 8.3.7
Height	X																					Sec. 8.3.1
Weight	X																			X		BMI to be taken only at Screening 1. Sec. 8.3.1
Orthostatic VS (HR, BP)	X		X								X											Sec. 8.3.2.2.
Semi-recumbent VS (HR, BP)	X		X----------X							X	X		X			X		X	X	X		Day 1 measurements will be at predose, 1- and 12-hours postdose. Sec. 8.3.2
RR and body temperature	X		X		X			X		X	X		X							X		Sec. 8.3.2.
12-lead ECG	X		X					X		X	X		X							X		Sec. 8.3.3.
Standard Meals					X----------X																	Sec. 5.3.1.
Domiciling			X----------X																			Sec. 8.1.11
MK-2060/Placebo Administration				X																		MK-2060/Placebo will be administered SC at Time 0. Refer to Sec. 6.2, 8.1.8 and the Study Pharmacy Manual for additional information on the preparation and administration of the study drug.

Part 3																						
	Scheduled Time																					
			Day 1 (hours post-dose)						**Days**													
Scheduled Timing	**Screening 1**	**Screening 2[a]**	**Predose**	**0**	**1**	**4**	**8**	**12**	**2 (D1 24 hrs)**	**3 (D1 48 hrs)**	**6 (D1 120 hrs) (±1 Day)**	**8 (D1 168 hrs)**	**11 (±1 Day)**	**14 (±1 Day)**	**21 (±2 Days)**	**28 (±3 Days)**	**42 (±4 Days)**	**60 (±5 Days)**	**90 (±5 Days)**	**120 Poststudy[b] (±5 Days)**	**134 Phone Follow-up[c] (±5 Days)**	**Notes**
Local Injection Site Reaction					X	X	X		X	X	X	X										Note: Participants who call the CRU to report an injection site reaction on Days 4, 5, and/or 7 may be asked to return to the CRU as soon as possible for an additional assessment. Sec. 8.3.7.
AE/SAE Review	X----------X																					All NSAEs and SAEs will be recorded up to 104-days postdose (inclusive). Sec. 8.4
Laboratory Procedures																						
Serum hCG (WOCBP only)	X		X																	X		Appendices 2 and 8
Serum FSH - (WONCBP only)	X																					Appendices 2, 5, and 8
HIV, hepatitis B and C screen (per site SOP)	X																					Sec. 5.2, Appendices 2 and 8

Part 3																					
	Scheduled Time																				
			Day 1 (hours post-dose)						**Days**												
Scheduled Timing	**Screening 1**	**Screening 2[a]**	**Predose**	**0**	**1**	**4**	**8**	**12**	**2 (D1 24 hrs)**	**3 (D1 48 hrs)**	**6 (D1 120 hrs) (±1 Day)**	**8 (D1 168 hrs)**	**11 (±1 Day)**	**14 (±1 Day)**	**21 (±2 Days)**	**28 (±3 Days)**	**42 (±4 Days)**	**60 (±5 Days)**	**90 (±5 Days)**	**120 Poststudy[b] (±5 Days)**	**134 Phone Follow-up[c] (±5 Days)**	**Notes**
Drug and Alcohol Screen (per site SOP)	X		X																			Screening and predose drug/alcohol screen are mandatory (predose drug screen may occur in the evening prior to Day 1 at the time of admission); any additional drug/alcohol screen is conducted per site SOP. Sec. 8.3.5 and Appendix 2
Hematology and Chemistry	X	X[d]	X							X		X				X				X		Hematology/Chemistry will be obtained after an 8-hour fast. Predose tests can be conducted up to 24 hours prior to dosing. Sec. 8.3.5, Appendices 2 and 8
aPTT and PT at local lab	X							X		X	X	X	X			X						Sec. 5.2, 8.3.5, Appendices 2 and 8
Hemoccult test	X[e]									X	X	X	X	X	X	X	X	X	X			Sec. 8.3.6

Part 3																						
	Scheduled Time																					
			Day 1 (hours post-dose)						**Days**													
Scheduled Timing	**Screening 1**	**Screening 2[a]**	**Predose**	**0**	**1**	**4**	**8**	**12**	**2 (D1 24 hrs)**	**3 (D1 48 hrs)**	**6 (D1 120 hrs) (±1 Day)**	**8 (D1 168 hrs)**	**11 (±1 Day)**	**14 (±1 Day)**	**21 (±2 Days)**	**28 (±3 Days)**	**42 (±4 Days)**	**60 (±5 Days)**	**90 (±5 Days)**	**120 Poststudy[b] (±5 Days)**	**134 Phone Follow-up[c] (±5 Days)**	**Notes**
Biomarkers																						
Blood for Genetic Analysis[f]			X																			Collected predose from enrolled participants only. Sec. 8.8.1, Appendix 8
Pharmacokinetics																						
Blood for Plasma MK-2060			X		X			X	X	X	X	X	X	X	X	X	X	X	X	X		Sec. 8.6.1, Appendix 8, and Study Operations Manual
Pharmacodynamics																						
Blood for PT/aPTT/FXI activity by central lab			X		X			X	X	X	X	X	X	X	X	X	X	X	X	X		Sec. 8.7.1, Appendix 8, and Study Operations Manual
Blood for plasma ADA			X											X	X	X	X	X	X	X		Sec. 8.7.2, Appendix 8, and Study Operations Manual

Part 3																					
	Scheduled Time																				
			Day 1 (hours post-dose)						**Days**												
Scheduled Timing	**Screening 1**	**Screening 2[a]**	**Predose**	**0**	**1**	**4**	**8**	**12**	**2 (D1 24 hrs)**	**3 (D1 48 hrs)**	**6 (D1 120 hrs) (±1 Day)**	**8 (D1 168 hrs)**	**11 (±1 Day)**	**14 (±1 Day)**	**21 (±2 Days)**	**28 (±3 Days)**	**42 (±4 Days)**	**60 (±5 Days)**	**90 (±5 Days)**	**120 Poststudy[b] (±5 Days)**	**134 Phone Follow-up[c] (±5 Days)**	**Notes**

ADA=antidrug antibody; aPTT=activated partial thromboplastin time; AE=adverse event; BMI=body mass index; BP=blood pressure; CRU=clinical research unit; D=Day; DNA=deoxyribonucleic acid, ECG=electrocardiogram; FBR=future biomedical research, FSH=follicle stimulating hormone; FXI=factor XI; HIV=human immunodeficiency virus; hCG=human chorionic gonadotropin; HR=heart rate; ID=identification; IEC=Independent Ethics Committee; IRB=Institutional Review Board; NSAE=nonserious adverse event; PT=prothrombin time; RR=respiratory rate; SAE=serious adverse event; SC=subcutaneous; SOP=standard operating procedure; VS=vital signs; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential

a. Screening 2 should occur within 96 hours prior to Day 1. If Screening 1 occurs within 96 hrs prior to administration of the dose of study drug, Screening 2 is not required.

b. The poststudy visit will occur approximately 120 days following administration of study drug. Procedures outlined in the poststudy visit may obtained on Day 120 (±5 days) Follow up on any clinical or laboratory AEs should occur in person if the poststudy visit occurs prior to 120 days following administration of study drug. If a participant discontinues for any reason at any time during the course of the study the participant may be asked to return to the clinic to complete the poststudy visit. The investigator may decide to perform the poststudy visit at the time of discontinuation or as soon as possible after discontinuation as outlined in Sections 7.1 and 8.1.9.

c. At the discretion of the investigator an in-person follow-up may be performed.

d. If Screening 2 occurs on Day -1, only obtain predose Hematology and Chemistry lab safety tests (these results will be used to satisfy both the Screening 2 and predose safety lab tests).

e. Hemoccult test will be provided to a participant at Screening 1 visit and returned at Screening 2 visit or prior to dosing at the time scheduled by the investigator, if Screening 2 visit does not occur.

f. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for this purpose. If the sample is collected, leftover extracted DNA will be stored for future biomedical research once the participant signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR. Blood for genetic analysis should be collected only once per participant after randomization.

2 INTRODUCTION

2.1 Study Rationale

Patients with CKD and ESKD have an increased prevalence of cardiovascular disease, including coronary artery disease, venous thrombosis, atrial fibrillation, and thromboembolic stroke. For patients on hemodialysis, this increased risk of thrombotic events also carries a high rate of vascular access thrombosis, particularly in those with AVGs where it can lead to access failure. Anticoagulants are therefore commonly used in this patient population. However, these patients also have an increased risk of bleeding events, which needs to be balanced with the increased risk of thrombotic events using currently marketed anticoagulants.

MK-2060 is an anti-FXI monoclonal antibody being developed for the prevention of thrombotic complications in CKD and ESKD. In contrast to most current anticoagulants, the use of agents that inhibit FXI are expected to reduce the risk of thrombotic events while having minimal effect on hemostasis. Hence, targeting FXI is an attractive option to expand the therapeutic window for anticoagulation in CKD and ESKD patients. The purpose of this study is to evaluate the safety, PK and pharmacodynamics of a single and multiple SC doses of MK-2060 in participants with Stage 4 and Stage 5 CKD (CKD4 and CKD5), and ESKD on peritoneal dialysis. Characterizing SC dosing in this study will help to broaden the Phase 3 program beyond IV dosing in ESKD patients on hemodialysis, by enabling enrollment of CKD4, CKD5, and ESKD patients with SC injection of MK-2060.

2.2 Background

Refer to the IB for detailed background information on MK-2060.

2.2.1 Pharmaceutical and Therapeutic Background

FXI is a critical component in the intrinsic pathway of the coagulation cascade. MK-2060 is an anti-FXI monoclonal antibody being developed for the prevention of thrombotic events in CKD/ESKD. Based on preclinical and human genetic data, as well as emerging clinical data using an AS approach [Buller, H. R., et al 2015] [Bethune, C., et al 2017], FXI inhibition is predicted to confer a clinically relevant antithrombotic effect with a reduced risk of bleeding complications and hence an expanded therapeutic index compared to inhibition of more downstream clotting factors such as FXa and thrombin. Therefore, FXI/FXIa inhibition is a promising therapeutic approach for the prevention of thromboembolic events.

2.2.2 Completed Clinical Studies

Study MK-2060-001:

Study MK-2060-P001 was a double-blind, randomized, placebo-controlled, single site, sequential panel study to evaluate the safety, tolerability, PK, and pharmacodynamics of single ascending dose administration of SC and IV doses of MK-2060 in healthy male participants. Forty-five healthy male participants received single doses of MK-2060 up to 120 mg administered SC (27 participants) or 40 mg IV (18 participants). MK-2060 was

generally well tolerated and there were no SAEs or discontinuations due to AEs. In healthy male participants single IV doses of 20 mg and 40 mg of MK-2060 resulted in increases in aPTT CCI baseline within 1 hour of administration (CCI FXI activity inhibition), with aPTT remaining CCI baseline for CCI hours.

MK-2060-004:

MK-2060-004 was a 2-part, double-blind, randomized, placebo-controlled, multiple-site, sequential-panel, single and multiple dose study in adult male and female ESKD participants on hemodialysis. The study evaluated the safety, PK and pharmacodynamics of IV administration of single-dose (8, 20 or 40 mg) and multiple dose (25-mg loading dose followed by QW dosing for 3 weeks) MK-2060. A total of 38 participants were enrolled. Single doses up to 40-mg and multiple 25-mg doses were generally well tolerated. Two participants discontinued the study due to a drug-related SAE of lower GI hemorrhage (placebo) and nondrug-related AE of COVID-19 infection. A total of 4 SAEs (myocardial infarction, GI hemorrhage, pneumonia, and AV graft thrombosis) were reported in 4 participants (n=1 in MK-2060 group and n=3 placebo group, respectively). The investigator deemed the myocardial infarction as not related to study intervention as the event occurred approximately 11 weeks after the last dose of MK-2060. Intervention-related AEs reported in participants who received MK-2060 included orthostatic hypotension, headache, chromaturia, hematuria, AV fistula hemorrhage, sneezing, and nausea. Anti-drug antibody assessment was positive in 2 participants of which neither participant reported AEs after showing a positive response to MK-2060.

PK data following single and multiple doses showed a t1/2 ranging from CCI days with a median observed Tmax of about CCI following infusion of MK-2060. Observed GM Cmax of single dose MK-2060 at 8, 20, and 40 mg was CCI, respectively. Observed Cmax following multiple dose MK-2060 was CCI.

Multiple-dose MK-2060 25 mg showed aPTT prolongation with a maximum mean fold-change of CCI. Overall, no effect on PT was observed.

MK-2060-008:

MK-2060-008 was a Phase 1, open-label, multi-site multiple-dose study to evaluate the safety and tolerability of coadministered IV MK-2060 and clopidogrel in adult (male and female) participants with ESKD on HD. Following a 14-day run in period, participant on clopidogrel therapy received a loading dose of 25 mg IV of MK-2060 for a total of 3 doses in Week 1 and a single dose of 25 mg IV MK-2060 in Week 2. 12 participants were enrolled in MK-2060, which was generally well tolerated when coadministered with clopidogrel. There were no bleeding related AEs in the study and there was not a significant difference in time to hemostasis following hemodialysis when clopidogrel was administered with or without concomitant administration of MK-2060. Clodipogrel was not shown to impact the PK profile of MK-2060.

2.2.3 Ongoing Clinical Studies

MK-2060-007:

MK-2060-007 is an event driven, randomized, placebo-controlled, parallel-group, multi-site, double-blind study of MK-2060 in participants with ESKD receiving hemodialysis via an AVG. This Phase 2 study is designed to evaluate the efficacy and safety of MK-2060 20 mg QW and MK-2060 6 mg QW (with 3 loading doses in Week 1). As of 10-Sep-2023, 506 participants have been randomized in MK-2060-007 and 502 have been dosed with a maximum exposure of 687 days. MK-2060-007 is ongoing and safety data are blinded and preliminary.

MK-2060-009:

This is a Phase 1 randomized, placebo-controlled, single-ascending dose clinical study to evaluate the safety, PK, and pharmacodynamics of IV MK-2060 in healthy Chinese male adult participants. As of 10-Sep-2023, 3 panels of 12 participants each (9 MK-2060: 3 placebo) were administered single 8 mg, 20 mg, and 40 mg IV doses of MK-2060 or placebo (9:3). Twenty-four (24) participants in Panel A-B have completed their last visit and all assessments. The estimated LPLV is 28-Oct-2023.

MK-2060-012:

This is a Phase 1 randomized, placebo-controlled single-dose clinical study to evaluate the safety, tolerability, PK, and pharmacodynamics of IV MK-2060 in Japanese older participants with end-stage kidney disease on dialysis. As of 10-Sep-2023, 17participants were administered a single 50 mg IV dose of MK or placebo (3:1 ratio). LPI was achieved with estimated LPLV 07-Feb-2024.

MK-2060-013

This is a randomized, placebo-controlled, single-ascending dose clinical study to evaluate safety, tolerability, PK and pharmacodynamics of MK-2060 in healthy Japanese adult participants. As of 10-Sep-2023, 4 panels of 12 participants each (3:1 ratio) were administered single 8 mg, 20 mg, and 50 mg IV doses of MK-2060, and 30 mg SC dose of MK-2060, or placebo (3:1 ratio). LPLV: is estimated 18-Dec-2023

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.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

This study is to be conducted in adult participants with chronic and/or end-stage kidney disease.

Primary Objectives	**Primary Endpoints**
Part 1: To evaluate the safety and tolerability of MK-2060 following single-dose SC administration in adult participants with Stage 4 or 5 Chronic Kidney Disease. Part 2: To evaluate the safety and tolerability of MK-2060 following multiple-dose SC administration in adult participants with Stage 4 or 5 Chronic Kidney Disease. Part 3: To evaluate the safety and tolerability of MK-2060 following single-dose SC administration in adult participants with End-Stage Kidney Disease on Peritoneal Dialysis.	Bleeding related AEs, AEs, and discontinuations due to AEs
Part 1: To evaluate plasma pharmacokinetics of MK-2060 following single-dose SC administration in adult participants with Stage 4 or 5 Chronic Kidney Disease. <u>Hypothesis:</u> The true geometric mean of AUC0-∞ after a single well tolerated dose of MK-2060 in adult participants with Stage 4 or 5 Chronic Kidney Disease is at least 11300 nM*hr. Part 2: To evaluate plasma pharmacokinetics of MK-2060 following multiple-dose SC administration in adult participants with Stage 4 or 5 Chronic Kidney Disease. <u>Estimation:</u> The effect of multiple-dose SC administration of MK-2060 in adult participants with Stage 4 or 5 Chronic Kidney Disease will be estimated.	Measurement of MK-2060 plasma AUC0-∞, AUC0-168, Cmax, C168, Tmax, terminal t1/2, CL/F and Vz/F

Part 3: To evaluate plasma pharmacokinetics of MK-2060 following single-dose SC administration in adult participants with End-Stage Kidney Disease on Peritoneal Dialysis. Estimation: The effect of single-dose SC administration of MK-2060 in adult participants with End Stage Kidney Disease on Peritoneal Dialysis will be estimated.	
Secondary Objective	**Secondary Endpoint**
Part 1: To evaluate the effect of MK-2060 on aPTT following single dose SC administration in adult participants with Stage 4 or 5 Chronic Kidney Disease. Part 2: To evaluate the effect of MK-2060 on aPTT following multiple-dose SC administration in adult participants with Stage 4 or 5 Chronic Kidney Disease. Part 3: To evaluate the effect of MK-2060 on aPTT following single dose SC administration in adult participants with End-Stage Kidney Disease on Peritoneal Dialysis.	aPTT fold change from baseline
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
Parts 1 and 3: To explore the effect of MK-2060 on Factor XI (FXI) activity levels following a single SC dose. Part 2: To explore the effect of MK-2060 on Factor XI (FXI) activity levels following multiple SC doses.	FXI activity level fold change from baseline
Parts 1 and 3: To explore the effect of MK-2060 on prothrombin time (PT) following a single SC dose. Part 2: To explore the effect of MK-2060 on prothrombin time (PT) following multiple SC doses.	PT fold change from baseline

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 explore the development and impact of ADAs measured in blood samples after single and multiple SC doses of MK-2060 is administered in adult participants with Chronic and/or End-Stage Kidney Disease.	ADAs

4 STUDY DESIGN

4.1 Overall Design

This is a 3-part, multi-site, randomized, double-blind, placebo-controlled, single-dose and multiple-dose study to assess the safety, tolerability, PK and pharmacodynamics of SC MK-2060 in participants with CKD4, CKD5, and ESKD on Peritoneal Dialysis.

In Part 1, participants with CKD4 or CKD5 (eGFR from 10 to 29) (n=12) will be randomized in a 3:1 ratio to receive a single 30-mg SC dose of MK-2060 (n=9) or placebo (n=3).

In Part 2, participants with CKD4 or CKD5 (n= 12) will be randomized in a 3:1 ratio to receive 4 loading doses of 30 mg SC MK-2060 or placebo (given daily for 4 days) followed by 30 mg SC MK-2060 (n=9) or placebo (n=3) every week for 3 additional weeks. A minimum of 4 participants with CKD5 will be enrolled in the study, of which a minimum of 3 will receive MK-2060.

Participants who successfully completed Part 1 through the post study visit may enroll in Part 2 provided screening criteria are met.

In Part 3, an open label study, participants with ESKD who are on peritoneal dialysis will receive a single 30 mg SC dose of MK-2060 (n=9).

In all 3 parts, participants will be closely monitored for safety and tolerability, including safety labs, local lab aPTT and PT results, physical exam to check incidence of bleeding, VS and 12-lead ECG, as well as local injection site reactions and for systemic reactions.

The study design is depicted in Figure 1, Figure 2, and Figure 3. Part 2 and Part 3 can be completed in parallel. For all participants, blood samples will be collected for MK-2060 plasma PK and pharmacodynamics. The precise timing of safety and tolerability measurements, PK and pharmacodynamics samples may be altered during the course of the study based on newly available data.

Because this is a Phase 1 assessment of MK-2060 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 8.11.7 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

To date, the safety and tolerability of MK-2060 have been evaluated in healthy participants dosed both via SC and IV administration (P001), and in ESKD-HD participants with IV dosing (P004 and P008). Ongoing Phase 1 studies are assessing safety and tolerability of IV

doses of MK-2060 in healthy Chinese and Japanese participants (P009 and P013), IV doses in Japanese dialysis patients (P012), and SC doses in healthy Japanese participants (P013). An ongoing Phase 2b study (P007) is evaluating the safety and efficacy of MK-2060 in ESKD-HD patients using IV dosing. The highest IV dose tested in the Phase 2b study is 20 mg IV. Because severe CKD patients not yet on dialysis (ie, CKD4, CKD5) may also derive a benefit from inhibition of FXI, enrollment of these patients in a Phase 3 study is warranted. In Phase 3, MK-2060 will be dosed IV in ESKD-HD patients due to the simplicity of IV administration during hemodialysis sessions. However, dosing in CKD4 and CKD5 patients not yet on dialysis will require SC administration, and SC PK has not yet been characterized in these patients. For patients with ESKD on peritoneal dialysis, IV administration is not practical, and enrollment of this patient population in Phase 3 requires an assessment of safety and PK of SC doses of MK-2060 in ESKD. Globally, approximately 11% of ESKD patients use peritoneal dialysis, with higher rates of utilization in some regions and therefore it is important to include this population so that they can also be candidates for MK-2060 therapy. Therefore, the purpose of this study is to characterize the SC PK of MK-2060 in CKD4, CKD5, and ESKD-Peritoneal Dialysis patients using single and multiple doses, in order to help provide information to guide dose selection for future clinical studies. Part 1 of this study will test the hypothesis that a single 30 mg SC dose of MK-2060 in CKD4 patients will achieve exposures such that if multiple doses were given and steady state exposures were achieved, our pharmacodynamics target CCI [redacted] would be projected to be achieved, within the predicted degree of interindividual PK variability. The AUC0-∞ for a single 30 mg SC dose in CKD4 patients is projected to be 11300 nM*hr with 30% GCV. These numbers are based on estimated bioavailability CCI [redacted] and other PK parameters using data from SC dosing of MK-2060 in P001 (NHV) and P004 (ESKD-HD patients). In Part 2, preliminary analysis of PK and pharmacodynamic data from Part 1 supports a 30 mg SC dose of MK-2060 to be given as a loading dose for 4 consecutive days, followed by QW doses for 3 weeks. The predicted mean Cmax after last dose of 30-mg SC dose of MK-2060 is CCI [redacted]. In Part 3, a single 30 mg SC dose of MK-2060 is proposed based on emerging data from Part 1 and to enable a direct comparison of PK for this dose between CKD4/CKD5 and dialysis patients and the single 30 mg SC dose given to Japanese NHVs in P013. PK parameters will be estimated for Parts 2 and 3 and SC dose projection will be further modified based on emerging data.

4.2.1 Rationale for Endpoints

4.2.1.1 Safety Endpoints

Based on the data from P001 (healthy participant study), P004 (ESKD on HD study), P008 (ESKD on HD coadministered with Clopidogrel), and P007 (ongoing Phase 2 study in ESKD on HD with AVG) along with preclinical safety data, it is expected that single dose SC administration of MK-2060 will be well-tolerated in participants with CKD and ESKD. Physical examinations, VS, ECGs, laboratory safety tests (serum chemistry and hematology), aPTT, PT, and AEs related to bleeding will be assessed throughout the treatment period. AEs, including local infusion site reactions and systemic reactions to MK-2060 infusion, will be assessed throughout the treatment period.

Bleeding related AEs will include any sign or symptom of bleeding, even if not requiring intervention by a medical/healthcare professional, as well as clinically relevant nonmajor bleeding or major bleeding. As with all biologic medications, MK-2060 carries a risk of acute reactions upon exposure. These reactions can be categorized as common injection reactions, hypersensitivity reactions, and high cytokine release reactions. Acute reactions are usually mild, can occur even with the first dose, and can manifest with rigors, back pain, abdominal pain, nausea, vomiting, diarrhea, dyspnea, flushing, pruritus, and changes in heart rate or blood pressure. Acute hypersensitivity reactions typically occur after repeated exposures but can occur with the first dose. In addition to signs similar to common infusion reactions, participants may develop urticaria, wheezing, coughing, facial swelling, angioedema and more significant changes in VS. Cytokine release reactions are exceedingly rare but severe. They manifest as severe headache, nausea, vomiting, back pain, fever, hypotension and multiorgan failure. The risk of any of these reactions to MK-2060 is considered low given its profile in preclinical safety studies. There were no infusion reactions, no acute hypersensitivity reactions, and no cytokine release reactions observed thus far in any MK-2060 clinical studies. See the IB for more information on the Phase 1 clinical study experience with MK-2060.

Anti-drug antibodies to MK-2060

The presence and titer of ADAs may be measured using validated assays. ADAs can develop to biologics like MK-2060. ADAs may be clinically inconsequential or may change the PK and/or drug efficacy. Moreover, ADAs may lead to safety events, such as acute or delayed hypersensitivity reactions. Thus, the titer of ADAs will be correlated with PK and safety events.

4.2.1.2 Pharmacokinetic Endpoints

Plasma PK of MK-2060

In order to characterize the PK profile of MK-2060 PK in adults with CKD and ESKD, noncompartmental PK parameters including AUC0-∞, AUC0-168, Cmax, C168, Tmax, terminal t1/2, CL/F, and Vz/F will be summarized after single- and multiple-dose SC administration.

4.2.1.3 Pharmacodynamic Endpoints

aPTT, PT and FXI activity (performed by Central Lab)

In order to assess pharmacodynamics, this study will include an assessment of aPTT prolongation levels (relative to baseline), PT and FXI activity levels, with assays performed at a Central Laboratory. For PK/pharmacodynamics modeling, aPTT and FXI activity levels will be related to plasma exposure. The time points for pharmacodynamics data collection are based on the projected PK profile of MK-2060. PK and pharmacodynamics measurements will allow comparison to PK/pharmacodynamics modeling targets at steady state.

4.2.1.4 Planned Exploratory Biomarker Research

4.2.1.4.1 Planned Genetic Analysis

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

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

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

4.2.1.5 Future Biomedical Research

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

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

4.2.2 Rationale for the Use of Placebo

A primary goal of this study is to evaluate the safety and tolerability of a single and multiple SC doses of MK-2060 in adult participants with chronic kidney disease and ESKD. A placebo-controlled study for single and multiple doses of MK-2060 will allow for an unbiased assessment of safety and tolerability of MK-2060, including local injection site reactions. In the single SC dose panel in participants with ESKD on peritoneal dialysis, an open label study design will be used based on cumulative safety and tolerability of MK-2060 in the ESKD on HD population.

4.3 Justification for Dose

As this is a Phase 1 assessment of MK-2060 in humans, and the PK, pharmacodynamic and safety profiles of the compound are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the study objectives and/or to

ensure appropriate safety monitoring of the study participants. Details of allowed modifications are provided in Section 8.11.6.

For Part 1, the 30-mg single SC dose was selected, because, from preliminary modeling and simulation analysis, this dose is anticipated to provide a maintenance level of aPTT prolongation [redacted] at steady state via QW SC dosing in at least [redacted] of CKD4 patients. The 30-mg single SC dose of MK-2060 is anticipated to result in a geometric mean Cmax of approximately [redacted] and AUC0-∞ of 11300 nM*hr. These numbers are based upon preliminary population PK modeling of observed PK of single SC doses in P001 and observed PK in ESKD-HD participants in P004. The projected exposures assume a bioavailability observed in SC dosing of MK-2060 in P001 NHV (SC/IV GMR for AUC0-∞ and AUC0-last were [redacted], respectively), and a t1/2 observed in ESKD-HD patients after IV administration (P004, [redacted]).

These exposures are significantly lower than the chronic toxicology NOAEL (Cmax approximately [redacted], AUC0-168 = [redacted] from the 4-week rhesus monkey toxicity study at 60 mg/kg/week). In P004 (Part 2), where ESKD-HD patients received multiple QW 25-mg doses of MK-2060, the observed geometric mean steady state Cmax and AUC0-168 was approximately [redacted] and [redacted], respectively, and MK-2060 was generally well tolerated.

In Part 2, preliminary analysis of PK and pharmacodynamic data from Part 1 supports a 30 mg SC dose of MK-2060 to be given as a loading dose for 4 consecutive days, followed by QW doses for 3 weeks. This dosing regimen is anticipated to achieve aPTT prolongation [redacted] from start of treatment which can be maintained at steady state via QW SC dosing in at least [redacted] of CKD4 and CKD5 patients. The predicted mean Cmax after last dose of 30-mg SC dose of MK-2060 is [redacted]. As this dose projection is based on preliminary data from Part 1 together with data from other Phase 1 studies, the dose used may be modified based on additional data.

In Part 3, a single 30 mg SC dose of MK-2060 is proposed based on emerging data from Part 1 and to enable a direct comparison of PK for this dose between CKD4/CKD5 and dialysis patients and the single 30 mg SC dose given to Japanese NHVs in P013.

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 (Section 7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

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

A study may be paused during review of newly available preclinical/clinical safety, PK, pharmacodynamic, efficacy, or biologic data or other items of interest, prior to a final

decision on continuation or termination of the study. It may be necessary to keep the study open for gathering/reviewing of additional supportive data to optimally complete the objective(s) of the study. If necessary, the appropriate amendment(s) to the protocol and/or appropriate communication(s) will be generated. If the decision has been made to end the study following this review period, the study end will be defined as the date of the Sponsor decision, and this end of study date supersedes the definitions outlined above. The Competent Authority(ies) and IRB(s)/IEC(s) will be apprised of the maximum duration of the study beyond the last participant out and the justification for keeping the study open.

4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early. A primary objective of this early Phase 1 study is to identify a safe and well-tolerated dose and/or dosing regimen that achieve PK, pharmacodynamic, and/or biologic targets in humans based on preclinical or early clinical data. Therefore, it is possible that study participants may not receive all doses specified in the protocol if this objective is achieved at lesser dose levels in this study. This would not be defined as early termination of the study, but rather an earlier than anticipated achievement of the study objective(s). If a finding (eg, PK, pharmacodynamic, efficacy, biologic targets, etc) from another preclinical or clinical study using the study intervention(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this study results in the study(ies) or program being stopped for nonsafety reasons, this also does not meet the definition of early study termination.

Early study termination is defined as a permanent discontinuation of the study due to unanticipated concerns of safety to the study participants arising from clinical or preclinical studies with the study intervention(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this study.

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

5 STUDY POPULATION

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

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

5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

Type of Participant and Disease Characteristics

1. At the time of screening, the participant has CKD 4 or 5 (Parts 1 and 2), or ESKD on Peritoneal Dialysis (Part 3). with a baseline estimated eGFR of 10 to 29 mL/min/1.73 m^2 based on the 2021 CKD-EPI Equation (Parts 1 and 2). CDK4 is defined as an eGFR from 15 to 29 mL/min/1.73 m^2. While CKD5 is defined as eGFR <15, not on dialysis, only CKD5 participants with an eGFR from 10 to 14 mL/min/1.73 m^2 will be enrolled as these patients are likely to be more stable than those with eGFR<10 and less likely to transition to dialysis during the time frame of the study.

CKD-EPI Equation:

eGFRcr = 142 x min(Scr/κ, 1)α x max(Scr/κ, 1)-1.200 x 0.9938Age x 1.012 [if female]

where:

Scr = standardized serum creatinine in mg/dL

κ = 0.7 (females) or 0.9 (males)

α = -0.241 (female) or -0.302 (male)

min(Scr/κ, 1) is the minimum of Scr/κ or 1.0

max(Scr/κ, 1) is the maximum of Scr/κ or 1.0

Age (years)

Baseline eGFR will be obtained twice (at least 72 hours apart as a part of participant screening), and the mean of the two values will be used. The 2 values used should not differ by more than 30%. The second baseline eGFR may be obtained at the time of check in.

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

2. The participant has a BMI ≥18 and ≤45 kg/m^2. See Section 8.3.1.2 for criteria on rounding to the nearest whole number. BMI=weight (kg)/height $(m)^2$.
3. Baseline health of the participant is judged to be stable based on medical history, physical examination, vital sign measurements, and ECGs performed prior to randomization/allocation.
4. The participant has liver function test (ALT and AST) results equal to or below 1.5x ULN and deemed not clinically significant by both the investigator and the Sponsor.

Demographics

5. The participant is male or female, from 18 years to 80 years of age inclusive, at the time of providing informed consent.

Female Participants

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

- Not a WOCBP

OR

- A WOCBP and:

  - Uses an acceptable contraceptive method, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 96 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
  - Has a negative highly sensitive pregnancy test (serum as required by local regulations) within 76 hours before the first dose of study intervention. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.5.
  - Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

7. The participant 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.

Consent must be documented by the participant's dated signature dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the study.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the participant must receive the IRB/ERC's approval/favorable opinion in advance of use. The participant 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 dated signature dated signature.

Specifics about a study and the study population will be added to the consent form template at the protocol level.

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

5.2 Exclusion Criteria

An individual must be excluded from the study if the individual meets any of the following criteria:

Medical Conditions

1. The participant has a history of clinically significant concomitant disease or condition (including treatment for such conditions) or diseases whose current condition is considered clinically unstable (with the exception of stable CKD) that, in the opinion of the investigator, could either interfere with the study drug, compromise interpretation of study data, or pose an unacceptable risk to the patient. Participants with a remote history of uncomplicated medical events (eg, childhood asthma) may be enrolled in the study at the discretion of the investigator.
2. The participant has rapidly fluctuating renal function as determined by historical measurements. Rapidly fluctuating renal function is defined as > 30% difference between 2 measurements of eGFR taken at least 72 hours apart as part of subject screening.

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

Exceptions: (1) Participants with adequately treated non-melanomatous skin carcinoma may participate in the study; or carcinoma in situ of the cervix or; (2) Participants with other malignancies which have been successfully treated ≥ 5 years prior to the prestudy (screening) visit where, in the judgement of both the investigator and treating physician, appropriate follow-up has revealed no evidence of recurrence from the time of treatment through the time of the prestudy (screening) visit; or (3) Participants, who, in the opinion of the study investigator, are highly unlikely to sustain a recurrence for the duration of the study

5. The participant has blood coagulation test (aPTT, PT) ≥20 % outside of normal range on prestudy (Screening), which are considered clinically significant by both the investigator and the Sponsor.
6. The participant has any other clinically significant abnormalities in laboratory test results at screening that would, in the opinion of the investigator, increase the participant's risk of participation, jeopardize complete participation in the study, or compromise interpretation of study data.
7. The participant has a history of deep vein thrombosis or pulmonary embolism. Has a history of vascular access thrombosis within 1 month prior to enrollment. Has a personal or family history of bleeding disorder (eg, hemophilia, Factor V Leiden, prothrombin gene mutation, protein C or S deficiency, ATIII deficiency, anti-phospholipid Ab syndrome).
8. The participant has a history of GI bleeding, duodenal polyps or gastric ulcer in the last 5 years or severe hemorrhoidal bleed in the last 3 months.
9. The participant has a history of or current frequent epistaxis within the last 3 months or active gingivitis.
10. The participant has ongoing anticoagulant therapy (warfarin, apixaban, dabigatran, rivaroxaban, edoxaban, betrixaban) or antiplatelet therapy (prasugrel, ticagrelor, ticlopidine). Aspirin and clopidogrel are permitted.
11. At the time of screening or pre-dose, the participant has planned significant dental procedures (including planned dental surgery), or other planned surgical procedures within duration of participation of study.
12. The participant is positive for hepatitis B surface antigen or HIV. Participants positive for hepatitis C antibodies may be enrolled with agreement of both investigator and sponsor. Positive test(s) for HBsAg, hepatitis C antibodies or HIV.
13. The participant had a major surgery and/or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the pre-study (screening) visit.
14. The participant has a history of significant multiple and/or severe allergies (e.g., food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability (i.e., systemic allergic reaction) to prescription or non-prescription drugs or food.

15. The participant has a tattoo, scar, or other physical finding at the area of the injection that would interfere with the injection or a local tolerability assessment.
16. The participant has a history (participant recall) of receiving any human immunoglobulin preparation such as IVIG or RhoGAM within the last year.
17. The participant has a history (participant recall) of receiving any biological therapy (including human blood products or monoclonal antibodies; excluding erythropoietin and insulin) within the last 3 months or 5 half-lives (whichever is longer), or vaccination within the last 1 month.

Exceptions:

- Participants who have received seasonal flu vaccine and pneumococcal vaccine within the last 1 month may be enrolled at the discretion of the investigator.
- COVID-19 vaccine may be administered. The study intervention must be given at least 72 hours following or at least 48 hours prior to any COVID-19 vaccination. Investigational COVID-19 vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.

18. Exclusion criteria for ECG:

- Heart rate <40 or >110 bpm
- QTc interval >500 msec
- Any significant arrhythmia or conduction abnormality, (including but not specific to atrioventricular block [2nd degree or higher], Wolff Parkinson White syndrome [unless curative radio ablation therapy]), which, in the opinion of the investigator and sponsor, could interfere with the safety for the individual patient.

Prior/Concomitant Therapy

19. The participant is unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs or herbal remedies beginning approximately 2 weeks (or 5 half-lives) prior to administration of the initial dose of study intervention, throughout the study (including washout intervals between treatment periods), until the poststudy visit. There may be certain medications that are permitted to treat chronic conditions and/or conditions associated with kidney disease if the participant has been on a stable regimen for approximately 2 weeks prior to study drug administration. All efforts should be made to inject other injectable medications (ie, insulin, GLP-1 analogs) for which the participant has been on a stable regimen in a location other than where the study medication/placebo is injected (see Section 6.5).

Prior/Concurrent Clinical Study Experience

20. The participant has been in another investigational study within 4 weeks (or 5 half-lives, whichever is greater) prior to the sponsor's investigational drug (MK-2060) administration. The window will be derived from the date of the last dose in the previous study.

Diagnostic Assessments

21. The participant has a BP >190 mmHg systolic or >110 mmHg diastolic.

Other Exclusions

22. The participant is under the age of legal consent.
23. The participant consumes greater than 3 servings of alcoholic beverages (1 serving is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day. Participants who consume 4 servings of alcoholic beverages per day may be enrolled at the discretion of the investigator.
24. The participant consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.
25. The participant is a regular user of any illicit drugs or has a history of drug (including alcohol) abuse within approximately 2 years. Participants must have a negative serum or saliva drug screen prior to randomization. Participants with a positive drug screen due to the use of physician prescribed medications (eg, opioids, benzodiazepines, antidepressants) may be enrolled at the discretion of the investigator. In addition, participants with a positive THC may be enrolled at the discretion of the investigator if the participants' THC use is under 4 times/month and the participants agree to not use during their study participation. Participants with positive THC on screening may have rechecks performed at the discretion of the investigator to ensure compliance with abstinence from THC use during study participation.
26. The participant is unwilling to comply with the study restrictions (see Section 5.3 for a complete summary of study restrictions).
27. The investigator has any concern regarding safe participation in the study or for any other reason the investigator considers the participant inappropriate for participation in the study.
28. 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

Fasting requirements for study procedures, such as, but not limited to, laboratory safety evaluations are specified in Section 8.

All meals on the study day of dosing will be served as to not interfere with the study procedures.

On day of dosing, participants will fast from all food and drinks, except water, for at least 8 hours prior to study drug administration. Participants will continue to fast until 2 hours after study drug/placebo administration when they will be given breakfast. Breakfast will be administered approximately 2 hours post-dose; lunch and dinner will be provided at ~ 4- and

~ 10-hours postdose respectively. Additional meals and snack(s) will be provided by the investigator as per the CRUs standard procedures. Participants will fast from all food and drinks, except water, between meals and snacks. After the 24-hour postdose procedures on the day of dosing have been completed, subsequent meals and snacks will be unrestricted in caloric content, composition, and timing.

Instructions on whether to take MK-2060 with or without food and/or drink may be modified during the study based on newly available data.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

5.3.2.1 Caffeine Restrictions

For Parts 1 and 3 participants will refrain from consumption of caffeinated beverages or xanthine-containing products from 12 hours before the pre-study and post-study visits and from 12 hours before and after study intervention administration in each treatment period. For Part 2 participants will refrain from consumption of caffeinated beverages or xanthine-containing products from 12 hours before the pre-study and post-study visits and from 12 hours before and after the first dose of 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 pre-study and poststudy visits and from 24 hours before and after study intervention administration in each treatment period.

Participants will refrain from consumption of alcohol 12 hours prior to scheduled outpatient visits.

At all other times, alcohol consumption is limited to no more than approximately 3 alcoholic beverages or equivalent servings (1 serving is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day.

5.3.2.3 Tobacco Restrictions

Smoking (and/or the use of nicotine/nicotine-containing products) is permitted during the study. Participants should follow the CRU's smoking restrictions during domiciling.

5.3.3 Activity Restrictions

Participants will avoid unaccustomed strenuous physical activity (i.e., weightlifting, running, bicycling, etc.) from the pre-study (screening) visit until administration of the initial dose of study intervention, throughout the study (including washout intervals between treatment periods) and until the poststudy visit.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized 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 within 21 days after dosing a replacement participant may be enrolled if deemed appropriate by the investigator and Sponsor. The replacement participant will generally receive the same intervention or intervention sequence (as appropriate) as the participant being replaced. The replacement participant will be assigned a unique treatment/randomization number.

The replacement participant may begin dosing at the subsequent dose level for that panel, based on investigator and Sponsor review and discussion.

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 MK-2060 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 interventions to be used in this study are outlined in Table 1.

Country-specific requirements are noted in Appendix 7.

Table 1 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
MK-2060	Experimental	MK-2060	Drug	Powder	15 mg/mL	30 mg	SC	Part 1: Day 1 Part 2: Days 1, 2, 3, 4, 8, 15, and 22 Part 3: Day 1	Test Product	IMP	Provided by Sponsor
Placebo	Placebo Comparator	Placebo	Drug	Solution	Saline	0 mg	SC	Part 1: Day 1 Part 2: Days 1, 2, 3, 4, 8, 15, and 22	Placebo	IMP	Locally

EEA=European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product; SC=subcutaneous.
The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.
In this protocol, placebo is diluent alone (normal saline); diluent is used for blinding purposes and does not contain active ingredients.

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 8.1.8 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Specific calculations or evaluations required to be performed to administer the proper dose to each participant are outlined in a separate document provided by the Sponsor. The rationale for selection of doses to be used in this study is in Section 4.3.

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Participants will be assigned randomly according to a computer-generated allocation schedule. Sample allocation schedules are shown below in Table 2, Table 3, and Table 4.

Table 2 Sample Allocation Schedule for Part 1

Treatment Group	Participants	Dose
1	n=9	MK-2060 30 mg SC
2	n=3	Placebo

n=number of participants; SC=subcutaneous

Table 3 Sample Allocation Schedule for Part 2

Treatment Group	Participants[a]	Dose
1	n=9	MK-2060 30 mg SC
2	n=3	Placebo
a. To ensure a minimum of 3 CDK4 and CKD5 participants receive MK-2060, assignment of randomization numbers for CKD4 participants will occur in ascending order (starting block). Assignment of randomization number for CKD5 participants will occur in descending order (ending block).		

n=number of participants; SC=subcutaneous

Table 4 Sample Allocation Schedule for Part 3

Treatment Group	Participants	Dose
1	n=9	MK-2060 30 mg SC

n=number of participants; SC=subcutaneous

6.3.2 Stratification

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

6.3.3 Blinding

For this study a double-blinding technique will be used. MK-2060 and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study-site personnel. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

See Section 8.1.10 for a description of the method of unblinding a participant during the study should such action be warranted.

6.4 Study Intervention Compliance

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.

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study-site staff.

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study-site staff other than the person administering the study intervention.

6.5 Concomitant Therapy

Concomitant use of the following medications will be allowed during the conduct of the study as long as the participant has been on a stable dose and treatment regimen for approximately 2 weeks prior and is able to withhold the use within four hours prior to administration of the first dose of study drug in each panel of the study. The name (generic and brand), dose and regimen for all concomitant medications should be recorded on the appropriate CRF.

All medications must be reviewed and approved by the Sponsor clinical monitor prior to enrollment of an individual patient. This list is not exhaustive, but serves as a guideline to facilitate the approval process between the investigator and the Sponsor clinical monitor

ALLOWED MEDICATIONS

Lipid Lowering Agents: Statins

Lipid Lowering Agents: Fibrates

Lipid Lowering Agents: Other

Ezetimibe

Anti-Hypertensive Medications:

Monotherapy and combination therapy with an ACE inhibitor, an angiotensin II receptor antagonist, beta blockers, calcium channel blockers, or a diuretic is allowed in the study.

Specific therapeutic categories include:

1. **ACE inhibitors**
2. **Angiotensin II Receptor Antagonists**

3. **Diuretics**
4. **Beta-blockers**
5. **Calcium channel-blockers**

Diabetes Medications

Specific therapeutic categories include:

6. **Insulin**
7. **Metformin**
8. **Sulfonylureas**
9. **Meglitinides**
10. **Thiazolidinediones**
11. **DPP-4 Inhibitors**
12. **GLP-1 Analogs**

Aspirin

Low-dose aspirin is permitted in the study.

Clopidogrel

Clopidogrel is permitted based on results from P008.

Iron

Phosphate Binders

Vitamin D

Erythropoietin

Note: All efforts should be made to inject other injectable medications (ie, insulin, GLP-1 analogs, erythropoietin) for which the participant has been on a stable regimen in a location other than where the study medication/placebo is injected. It is preferred that the MK-2060 injection site area is not used for other injections for the duration of the study, if possible.

PROHIBITED MEDICATIONS

Listed below are specific restrictions for concomitant therapy during the course of the study, from signing consent to the poststudy visit:

Oral Anticoagulants

Warfarin
Apixaban

Dabigatran
Rivaroxaban
Edoxaban
Betrixaban

Antiplatelet Medications

Prasugrel
Ticagrelor
Ticlopidine

NSAIDs (eg, ibuprofen); however, the non-NSAID paracetamol/acetaminophen may be used for minor ailments without prior consultation with the Sponsor.

6.5.1 Rescue Medications and Supportive Care

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

CRUs will be staffed with medically trained personnel with appropriate access to full service acute-care hospitals to facilitate rapid institution of medical intervention.

6.6 Dose Modification (Escalation/Titration/Other)

The dose and administration of the study intervention to any participant may be modified based on newly available safety, tolerability, pharmacokinetic and/or pharmacodynamic data observed in this and/or other MK-2060 studies. If necessary, a participant must be discontinued for the reasons described in Section 7.

6.6.1 Stopping Rules

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

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

1. An individual participant reports an SAE considered related to the study intervention by the investigator.
2. Two (2) or more participants within a Panel (at the same dose level) report Severe Nonserious AEs considered related to the study intervention by the investigator.
3. An increase in local lab aPTT >4.0-fold versus screening baseline as confirmed after repeat measurement in 2 or more participants in a panel. Local lab aPTT measured at Screening Visit should be used as baseline value.
4. An increase in local lab PT >1.5-fold versus screening baseline as confirmed after repeat measurement in 2 or more participants in a panel. Local lab PT measured at Screening Visit should be used as baseline value.

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

The emergency unblinding call center will use the intervention randomization schedule for the study to unblind participants and to unmask study intervention identity for this study. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

6.9 Standard Policies

MK-2060 will be provided by the Sponsor in sufficient quantity to complete the study.

6.9.1 Study Site Retention Samples

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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 prior to completion of the protocol-specified treatment period regimen will still continue to participate in the study as specified in Section 7.1 and Section 8.1.9, or if available, a PCL. Safety procedures include full physical examination, systemic infusion reaction assessment, semi-recumbent VS, orthostatic VS, safety lab measurements, AE reviews, and assessment of time to hemostasis if on-site dialysis. The poststudy timing and assessments should be performed as outlined in Section 1.3.2.

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 8.1.9.

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's treatment assignment has been unblinded by the investigator, MSD, or through the emergency unblinding call center.
- 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.

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 8.1.9. The procedures to be performed should a participant repeatedly fail to return

for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.
- The maximum amount of blood collected from each participant over the duration of Part 1 will not exceed ~294.8 mL, over Part 2 will not exceed ~428.3 mL, and over Part 3 will not exceed ~320.2 mL (Appendix 8 and operations/laboratory manual).
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study or FBR. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

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

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

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

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 informed consent form.

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

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

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

8.1.4 Medical History

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review before medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the study.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study. Refer to Section 6.5 for guidelines on concomitant medication use.

8.1.6 Assignment of Screening Number

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

8.1.7 Assignment of Treatment/Randomization Number

For Parts 1 and 2, all eligible participants will be randomly allocated and will receive a treatment/randomization number. For Part 3, all eligible participants will be allocated, by nonrandom assignment, and will receive a treatment/allocation number. The treatment/randomization/allocation number identifies the participant for all procedures occurring after treatment randomization/allocation. Once a treatment/randomization/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/randomization/allocation number.

8.1.8 Study Intervention Administration

Administration of study medication will be witnessed by the investigator and/or study staff according to the specifications within the Study Pharmacy Manual.

8.1.8.1 Timing of Dose Administration

MK-2060/placebo will be prepared and dosed per the instructions outlined in the Study Pharmacy Manual. All doses of MK-2060 or placebo will be given in the morning and after at least an 8-hour fast. Total dosing time should not exceed approximately 1 minute. The fast will be maintained until 2-hours postdose, at which time a standard light breakfast will be served. Participants will also remain semi-recumbent for 4 hours post-dose except to stand for the measurement of orthostatic VS (if needed) or other study procedures (for example for breakfast).

8.1.9 Discontinuation and Withdrawal

The investigator or study coordinator must notify the Sponsor when a participant has been discontinued/withdrawn from the study. If a participant discontinues for any reason at any time during the course of the study, the participant may be asked to return to the clinic (or be contacted) for a poststudy visit as per the number of days described in Section 1.3 (90 days for Part 1, 130 days for Part 2, and 120 days for Part 3) to have the applicable procedures conducted. However, the investigator may decide to perform the poststudy procedures at the time of discontinuation or as soon as possible after discontinuation. If the poststudy visit occurs prior to the safety follow-up time frame as specified in Section 8.4.1, the investigator should perform a follow-up telephone call at the end of the follow-up period (Section 8.4.1) to confirm if any AEs have occurred since the poststudy clinic visit. Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 Withdrawal From Future Biomedical Research

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

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

8.1.10 Participant Blinding/Unblinding

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Before contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is qualified physician should make reasonable attempts to enter the intensity of the AEs observed, the relation to study intervention, the reason thereof, etc, in the medical record. If it is not possible to record this assessment in the medical record before the unblinding, the unblinding should not be delayed.

If unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Once an emergency unblinding has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician must be discontinued from study intervention, but should continue to be monitored in the study.

8.1.11 Domiciling

For Parts 1 and 3 participants will report to the CRU the evening before the scheduled day of study intervention administration for each treatment period. Participants will remain in the unit until at least 48-hours postdose. For Part 2 participants will report to the CRU the evening before the scheduled day of study intervention administration on Day 1 and will remain in the unit until the completion of off all postdose procedures on Day 4 (at least 4 hours). For the remaining dosing days in Part 2, at the discretion of the investigator the participants will return to the CRU either the evening before the scheduled day of study intervention administration or the morning of the scheduled day of study intervention administration (Days 8, 15 and 22) and will remain in the unit overnight until the completion of all postdose procedures the following day (at least 4 hours). At the discretion of the investigator, participants may be requested to remain in the CRU longer.

8.1.12 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information

about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy/Immunogenicity Assessments

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

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood to be drawn over the course of the study (from pre-study to poststudy visits), including approximate blood volumes drawn by visit and by sample type per participant, can be found in 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 as per the SoA. A symptom driven physical exam will be conducted based upon any emergent symptoms at the discretion of the investigator. Height and weight will also be measured and recorded.

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

Targeted physical examination will involve a skin exam to assess for any unusual bruising or bleeding under the skin.

8.3.1.1 Body Weight and Height

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

8.3.1.2 Body Mass Index (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.

8.3.2 Vital Signs

- Body temperature, HR, RR, and BP will be assessed.
- BP and pulse measurements will be assessed semi-recumbent after at least 10 minutes rest with a completely automated device. Manual techniques will be used only if an automated device is not available.

8.3.2.1 Resting Vital Signs

Vital Sign Measurements (Heart Rate and Blood Pressure)

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

For Parts 1, 2, and 3, the Day 1 predose (baseline) HR and BP will be in triplicate measurements, obtained at least 1 to 2 minutes apart within 3 hours of dosing of study intervention. The median of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). Post-dose VS measurements will be single measurements.

Participants will continue to rest semi-recumbent from dosing until 4 hours post-dose except to stand for the measurement of orthostatic VS (if needed) or other study-related procedure.

Body Temperature

Body temperature will be a single measurement at all timepoints. The same method must be used for all measurements for each individual participant and should be the same for all participants.

Respiratory Rate

Respiratory rate (breaths per minute) will be measured and recorded as single measurements.

8.3.2.2 Orthostatic Vital Signs

Orthostatic VS (HR and systolic and diastolic BP) will also be obtained. Participants should be semi-recumbent for at least 10 minutes and then stand upright for approximately 2 minutes before measurement of orthostatic VS.

8.3.3 Electrocardiograms

- Triplicate and 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 using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals.
- At each time point when triplicate ECG are required, 3 individual ECG tracings should be obtained at least 1 to 2 minutes apart, but no more than 2 minutes apart. The full set of triplicates should be completed in no more than 6 minutes.

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

Lead placements should be rechecked in cases where unexpected ECG findings are noted.

Participants should be resting in the semi-recumbent for at least 10 minutes before each ECG measurement.

The QTc correction formula to be used at the site (for safety and inclusion/exclusion criteria assessments) is Fridericia.

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

For Parts 1, 2, and 3, the Day 1 Pre-dose ECGs will be obtained in triplicate at least 1 to 2 minutes apart (and should be completed in no more than 6 minutes) within 3 hours prior to dosing MK-2060. The median of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). Unless otherwise designated in the flow chart, post-dose ECG measurements will be single measurements.

If a participant demonstrates an increase in QTc interval ≥60 msec compared with median pre-dose 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 post-dose 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 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 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 study cardiologist should be arranged by the Principal Investigator to be available as needed to review ECG tracings with abnormalities.

8.3.4 24-Hour Urine Protein, 24-Hour Urine Creatinine and Spot Urine Collection for Urine Protein: Urine Creatinine Ratio (uPCR)

A 24-hour urine protein will be collected. The collection will begin following admission to the CRU on the evening before study intervention dosing on Day 1 and continue through to the evening of Day 1.

Spot urine for uPCR will be collected on study days as defined in the study flowchart (SoA).

8.3.5 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation In the study or within 90 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.6 Hemoccult Test

Hemoccult test will be provided to participants at Screening 1 Visit and participants will return the sample at Screening 2 Visit. Following dosing, hemoccult tests will be provided on visit days designated in the SoA and can be returned at the next scheduled visit. Further instructions and information regarding the hemoccult test will be provided in the Study Operations Manual by the Sponsor

8.3.7 Photograph of Rash

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

8.3.8 Management of Injection Reaction During and Post-Dose

As outlined in IB, the risk of injection reactions to MK-2060 is considered low since the molecule contains primarily human sequences. However, injection reactions may be observed. Since the purpose of the study is to characterize the safety profile of MK-2060, no prophylactic premedications to reduce the risk of injection reactions will be given prior to MK-2060 administration.

In rare instances, systemic injection reactions are severe and may have a fatal outcome. It is likely that most injection reactions will occur within the first 30 to 60 minutes of administration, though they may be observed up to 24 to 30 hours postdose. An anaphylactic reaction is a severe type of injection reaction that is characterized by cutaneous and mucosal symptoms, such as generalized hives, pruritus or flushing, swollen lips-tongue-uvula and angioedema, accompanied by respiratory compromise (bronchospasm, stridor or hoarseness) and/or changes in blood pressure (hypotension). Severe injection reactions, including cytokine release syndrome and hypersensitivity reactions must be promptly treated with interruption of the injection, medical management, appropriate monitoring, and life-saving measures. Appropriate resuscitation equipment and a physician should be readily available during the period of drug administration.

All participants should be evaluated for injection-type reactions. Participants should be carefully observed until complete resolution of all signs and symptoms, if a reaction occurs. Report any adverse experiences according to the guidelines in Section 8.4.

8.3.8.1 Systemic Injection Reaction Assessment

Participants will be monitored during the administration of MK-2060/placebo and for at least 4 hours and up to 24 to 48 hours postdose at the CRU after the initiation of administration. During this time, signs and symptoms of a systemic injection reaction, including but not limited to fever, VS changes (tachycardia/hypotension), pruritis, urticarial (hives), lip swelling, angioedema, bronchospasm, stridor, hoarseness, and shortness of breath will be monitored. Injection reactions must be assessed and managed promptly. Such assessment and management are discussed in Section 8.3.7.

8.3.8.2 Local Injection Reaction Assessment

A local injection site examination will be obtained as outlined in the Section 1.3 and will include an assessment of any pain, tenderness, erythema/redness and induration/swelling. These events will be evaluated based upon the system outlined in the guidance for the industry *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials* in Table 5. Injection reactions must be assessed and managed promptly per site procedure.

Participants who call the CRU to report an infusion/injection site reaction within 7 days post-dose may be asked to return to the CRU as soon as possible for an additional local injection site reaction assessment.

Table 5 Local Injection Reaction Assessment

Local Site Reaction	Mild	Moderate	Severe	Potentially Life Threatening
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hr or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness	2.5 – 5 cm	5.1 – 10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis
Adapted from the guidance for the industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.				

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

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

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

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

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity, and causality.

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

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

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

From the time of intervention randomization through ~96 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 6.

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

Table 6 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ Allocation through Protocol-specified Follow-up Period	**Reporting 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
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

Type of Event	**Reporting Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ Allocation through Protocol-specified Follow-up Period	**Reporting Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor
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 randomized 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 toward 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 SAEs) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

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

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

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

Not applicable.

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. Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
   *Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

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

8.5 Treatment of Overdose

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

Sponsor does not recommend specific treatment for an overdose. Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

The decision as to which plasma and/or urine samples collected will be measured for evaluation of PK/pharmacodynamics will be collaboratively determined by the Sponsor (eg, samples at lower doses may not be measured if samples at higher doses reveal undetectable drug concentrations). If indicated, these samples may also be measured and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers. Blood samples collected may be stored and further analysis may be performed, if required.

8.6.1 Blood Collection for Plasma MK-2060

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

8.7 Pharmacodynamics

Sample collection, storage, and shipment instructions for pharmacodynamic samples will be provided in the Study Operations Manual. Blood samples collected may be stored and further analysis may be performed, if required.

8.7.1 Blood Collection for PT, aPTT, FXI Activity

PT and aPTT at screening, predose, and postdose specified in the SoA will be performed locally for safety monitoring. All other predose and postdose PT and aPTT, as well as FXI activity will be performed at a central vendor for analysis. Sample collection, storage, and shipment instructions for the PT, aPTT, FXI activity will be provided in a separate Study Operations Manual by the Sponsor. The primary data for statistical analysis and modeling will be based on the information from the central vendor.

8.7.2 Blood for Plasma ADA

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

8.8 Biomarkers

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

- Blood for genetic analysis

8.8.1 Planned Genetic Analysis Sample Collection

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

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

8.9 Future Biomedical Research Sample Collection

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

- Leftover samples from Section 8.8.

8.10 Health Economics Medical Resource Utilization and Health Economics

Health Economics are not evaluated in this study.

8.11 Visit Requirements

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

8.11.1 Screening

Approximately 4 weeks before intervention randomization, 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 randomization if there are Day -1 procedures planned per protocol.

8.11.2 Treatment Period

Refer to the Schedule of Activities (Section 1.3) and Administrative and General Procedures (Section 8.1).

After all predose procedures have been completed and it is confirmed that the participant meets eligibility; the participant will be given a participant ID bracelet and assigned a unique randomization number associated with a specific treatment as defined by a computer-generated randomization schedule. Participants will report to the CRU prior to the scheduled day of dosing or time specified by the investigator. On the day of dosing, participants will fast from all food and drinks, except water, for at least 8 hours prior to until 2-hours poststudy drug administration when they will be given a light breakfast (see Section 5.3.1). Participants will be administered study intervention as indicated in Section 6. Participants who, on Day 1, have a significant acute illness or fever prior to the administration of study drug may be rescheduled.

8.11.3 Poststudy

Participants will be required to return to clinic approximately 90 days for Part 1, 130 days for Part 2, and 120 days for Part 3 after the last dose of study intervention for the poststudy visit. If the poststudy visit occurs fewer than 90/130/120 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at 90/130/120 days post the last dose of study intervention to determine if any AEs have occurred since the poststudy clinic visit.

8.11.4 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

At any point if a participant discontinues from treatment 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. The subset of study procedures completed will be communicated in a PCL.

CKD4 and CKD5 participants who experience disease progression and convert to ESKD on HD following administration of study intervention but prior to the post-study visit may continue to be monitored in the study per the visit requirements in the SoA.

8.11.5 Safety Phone Call Follow-Up

A safety follow-up phone call will be performed approximately 14 days after the poststudy visit (within the visit windows allowed per protocol). The safety follow-up phone call must be performed by appropriately trained study site staff. At the discretion of the investigator an in-person follow-up may be performed. If the initial call is unsuccessful, the study site should

make a total of 3 attempts. All attempts to contact the participants will be recorded in the source documents. The calls will facilitate the collection of relevant safety information. The participant will be interviewed to obtain information relating to AEs and SAEs. All safety information described by the participant must be documented in the source documents.

8.11.6 Critical Procedures Based on Study Objectives: Timing of Procedure

For this study, the blood sample for MK-2060 is the critical procedure.

At any post-dose time point, the blood sample for MK-2060 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.

- Screening 2 procedures: up to additional 4 hours of scheduled time
- PK, Pharmacodynamic and Safety Collection as outlined in Table 7, Table 8, and Table 9.

Table 7 Pharmacokinetic, Pharmacodynamic and Safety (Blood/Urine) Collection Windows for Part1

Pharmacokinetic, Pharmacodynamic, Safety Collection	**Pharmacokinetic, Pharmacodynamic, Safety Collection Window**
0 to < 4 hours	5 min
4 - < 8 hours	15 min
8 - < 24 hours	30 min
24 hours - < 48 hours	60 min
48 hours - < 120 hours	2 hours
120 hours - ≤ 168 hours	24 hours
Day 11 + Day 14	1 Day
Day 21	2 Days
Day 28	3 Days
Day 60 + Day 90	5 Days

Table 8 Pharmacokinetic, Pharmacodynamic and Safety (Blood/Urine) Collection Windows for Part 2

Pharmacokinetic, Pharmacodynamic, Safety Collection	**Pharmacokinetic, Pharmacodynamic, Safety Collection Window**
0 to < 4 hours	5 min
Days 1, 2, 3, 4, 8, 15, 22, 23, and 29	No flexible window for the scheduled day
Days 10 and 17	±1 Day
Day 26	+1 Day
Days 35, 42, 49 and 63	±2 Days
Days 81 and 111	±3 Days
Day 130	±7 Days

Table 9 Pharmacokinetic, Pharmacodynamic and Safety (Blood/Urine) Collection Windows for Part 3

Pharmacokinetic, Pharmacodynamic, Safety Collection	**Pharmacokinetic, Pharmacodynamic, Safety Collection Window**
0 to < 4 hours	5 min
4 - < 8 hours	15 min
8 - < 24 hours	30 min
24 hours - < 48 hours	60 min
48 hours - < 120 hours	2 hours
120 hours - ≤ 168 hours	24 hours
Day 11 + Day 14	1 Day
Day 21	2 Days
Day 28	3 Days
Day 60 + Day 90 + Day 120	5 Days

- Part 1, 2, and 3 Day 1 predose standard safety evaluations: VS and ECG at 3 hours; laboratory safety tests and physical exam at 24 hours
- Part 2 Days 8, 15, and 22 predose standard safety evaluations: VS, ECG, and laboratory safety tests at 3 hours.
- Post-dose standard safety evaluations: VS, ECG, laboratory safety tests, and physical exam
  - Prior to 24-hours postdose may be obtained within 15 minutes of the theoretical sampling time
  - Between 24-hours and <48-hours postdose may be obtained within 1 hour of the theoretical sampling time
  - From 48-hours to <120-hours postdose may be obtained within 2 hours of the theoretical sampling time

Note: Visit windows defined by +/- X day(s) refers to calendar days.

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

This is a Phase 1 assessment of MK-2060 in humans, and the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently outlined may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants.

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

- Repeat of or decrease in the dose of the study intervention administered in any given period/panel/part
- Addition of study pause
- 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/pharmacodynamic sampling scheme currently outlined in the protocol may be modified during the study based on newly available PK or pharmacodynamic data (e.g., to obtain data closer to the time of peak plasma concentrations). If indicated, these collected samples may also be assayed in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

Up to additional 50 mL of blood may be drawn for safety, PK, and/or pharmacodynamic analyses. The total blood volume withdrawn from any single participant will not exceed the maximum allowable volume during his/her participation in the entire study (Appendix 8).

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

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

9 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this study. Full details can be found in the subsequent sections.

Safety

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

9.2 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be conducted by, or under the direct auspices of, the Early Clinical Development Statistics Department in collaboration with the Quantitative Pharmacology and Pharmacometrics Department and Translational Pharmacology Department of the Sponsor.

If, after the study has begun, changes are made to the statistical analysis plan stated below, then these deviations to the plan will be listed, along with an explanation as to why they occurred, in the Clinical Study Report.

9.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3.

9.4 Analysis Endpoints

<u>Primary Endpoints</u>

1. Primary endpoints are bleeding related AEs, AEs, and discontinuations due to AEs.

- Pharmacokinetics: The pharmacokinetic variables of primary interest for MK-2060 are measurement of MK-2060 plasma AUC0-∞, AUC0-168, Cmax, C168, Tmax, terminal t1/2, CL/F and Vz/F

Part 1 Hypothesis:

The true geometric mean AUC0-∞ is at least 11300 nM*hr. This value is based on the preliminary modeling and simulation analyses using data form MK-2060 P001 and MK-2060 P004.

Secondary Endpoints

2. Pharmacodynamics: The pharmacodynamics variable of secondary interest is fold-change in baseline in aPTT values. Baseline is defined as the predose value.

Exploratory Endpoints:

Pharmacodynamics: The pharmacodynamics variables of exploratory interest are Factor XI activity levels and prothrombin time.

9.5 Analysis Populations

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

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

Per-Protocol (PP): The Per-Protocol Population consists of the set of data generated by the subset of participants who comply with the protocol sufficiently to ensure that these 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 from at least one treatment will be included in the Per-Protocol dataset.

9.6 Statistical Methods

Summary statistics and plots will be generated for raw laboratory safety tests, ECGs, and/or VS as well as for change from baseline, as deemed clinically appropriate. For all endpoints descriptive summary will be provided. For categorical measurements, counts and percentage numbers will be provided. Similarly, for continuous measurements, mean, standard deviation, median, min, max will be provided. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline) as appropriate. Values will be listed for each PK parameter (including Tmax and apparent terminal t1/2), and appropriate 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*sqrt(exp(s2)-1), where s2 is the observed variance on the natural log-scale.)

Descriptive statistics as well as appropriate plots will be displayed for aPTT fold change from baseline. Similar statistics will be provided for the fold changes in the exploratory endpoints such as PT and FXI activity levels.

To test the part 1 primary hypothesis, the posterior probability that the true geometric mean of AUC0-∞ after a single well-tolerated dose of MK-2060 in adult participants with CKD4 is at least 11345 nM*hr, will be calculated using a noninformative prior. The CV for AUC0-∞ is expected to be approximately 30% (assuming similar variability as in MK-2060 P004). If this posterior probability exceeds 60%, then the primary research hypothesis will be supported.

Since Part 2 and Part 3 involves estimation, descriptive statistics (mean, median, standard deviation, min, max values) will be provided for primary and secondary endpoints.

9.7 Interim Analyses

No interim analysis is planned for this study.

9.8 Multiplicity

Since there is a single prespecified primary hypotheses, no adjustments for multiplicity are needed.

9.9 Sample Size and Power Calculations

For Part 1, approximately 12 participants will be enrolled for this study. Participants will be randomized in a 3:1 ratio to receive a single 30-mg SC dose of MK-2060 (n=9) or placebo (n=3).

Thus, with all 9 participants in MK-2060 group completing the study and a posterior probability threshold of 60%, there is approximately 82% probability of supporting the primary hypothesis if the true geometric mean of AUC0-∞ is 12800 assuming CV=30% and natural log-normal distribution for AUC0-∞. We assume that at 30-mg dose SC dose, the true GM is 12800. A table with PP calculations with assumptions about various values of the true GM and with CV=30% is as follows:

True Geometric Mean	Probability of Go (%)
12500	75.6%
12600	77.9%
12700	80.3%
12800	82.4%
12900	84.4%
13000	86.2%

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Interventional Clinical Trials

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

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, planning, 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 MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 and ICH General Considerations for Clinical Studies E8, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Input may be considered from a broad range of stakeholders, including patient advocacy groups/patients representing the trial population, caregivers, and healthcare providers to ensure operational feasibility. Trial design also includes

proactive identification of critical to quality factors utilizing a risk-based approach. Plans are then developed to assess and mitigate risks to those factors as appropriate during the trial. 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. Individuals involved in trial conduct receive training commensurate with their role prior to their becoming involved in 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 and ICH Guidelines. 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. Trial designs include procedures and systems for the identification, monitoring, and reporting of safety concerns. 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.

During trial planning, the need for an independent Data Monitoring Committee (DMC) is assessed. DMC review of data accumulated during the conduct of the trial is integral to the well-being of trial participants.

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.

E. Trial Results

At the time of providing informed consent and in accordance with local laws and regulations, participants should be informed about the plans for availability of trial results.

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 medical record review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

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

10.1.3 Data Protection

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

Not applicable.

10.1.5 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.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, 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, https://euclinicaltrials.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 Regulation 536/2014 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 Regulation 536/2014, 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.

10.1.7 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.

For investigators located in countries with serious breach reporting requirements, investigator will promptly report to the Sponsor any serious breach or suspected serious breach that occurs in compliance with those requirements. Unless more specifically defined in the applicable requirements, a serious breach is any breach of the applicable clinical trial regulation or of the clinical trial protocol which is likely to affect to a significant degree: (i) the safety or rights of a trial participant, or (ii) the reliability and robustness of the data generated in the clinical trial.

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 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.

10.1.10 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 10 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 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 10 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	BUN	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin if total bilirubin is above the upper limit of normal)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose	Calcium	Alkaline phosphatase	
Coagulation	aPTT, PT			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Urine Tests	• 24-hour urine collection for urine protein • 24-hour urine collection for urine creatinine • Spot urine protein: urine creatinine ratio			

Laboratory Assessments	Parameters
Other Screening Tests	• FSH, as needed in WONCBP only • Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines) • Serology (HIV antibody, HBsAg, and hepatitis C virus antibody) • Serum β human chorionic gonadotropin (β hCG) pregnancy test (as needed for female participant)

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; HBsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; [HIV=human immunodeficiency virus]; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WBC=white blood cell; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential

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

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- Note: For purposes of AE definition, study intervention 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."
- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

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

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

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

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

d. Results in persistent or significant disability/incapacity
   - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
   - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect
   - In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events
   - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
   - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4 Additional Events Reported

Additional events that require reporting

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

- Is a cancer.
- Is associated with an overdose.

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/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 Study intervention cause the AE?

- The determination of the likelihood that the Study intervention 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 Study intervention 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 Study intervention 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 Study intervention? 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 Study intervention 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 Study intervention; (3) the study is a single-dose drug study; or (4) Study intervention(s) is/are only used 1 time.)

  - **Rechallenge:** Was the participant re-exposed to the Study intervention 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) Study intervention(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 STUDY INTERVENTION, OR IF RE-EXPOSURE TO THE STUDY INTERVENTION 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 Study intervention or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Study intervention relationship).
  - Yes, there is a reasonable possibility of Study intervention relationship:
    - There is evidence of exposure to the Study intervention. The temporal sequence of the AE onset relative to the administration of the Study intervention is reasonable. The AE is more likely explained by the Study intervention than by another cause.
  - No, there is not a reasonable possibility of Study intervention relationship:
    - Participant did not receive the Study intervention OR temporal sequence of the AE onset relative to administration of the Study intervention is not reasonable OR the AE is more likely explained by another cause than the Study intervention. (Also entered for a participant with overdose without an associated AE.)
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

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

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

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
  - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure email of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

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

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

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

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

Women of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

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

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

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

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

10.5.2 Contraceptive Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen- only contraceptive implant[d] • IUS[e] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen- containing) hormonal contraception[d] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[d] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Methods That Are Not Considered Highly Effective *Failure rate of >1% per year when used consistently and correctly.*
• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods).
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [d] If locally required, in accordance with CTFG guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation. [e] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male and female condom should not be used together (due to risk of failure with friction).

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

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

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

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

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

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

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

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

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

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

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

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

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

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history, and intervention outcomes is 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 that 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 used in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility, which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3, 4]

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

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

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

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

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

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

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

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

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

12. Questions

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

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618
2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html
3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: Blood Volume Tables

Part 1						
	Prestudy	**Treatment Periods**	**Poststudy**	**Total Collections**	**mL Per Collection**	**Total mL/ Test**
Laboratory Safety Tests	2	4	1	7	12.5	87.5
HIV/Hepatitis Screen (at the discretion of the investigator)	1	0	0	1	5	5
Blood for Planned Genetic Analysis	0	1	0	1	8.5	8.5
FSH (Females only)	1	0	0	1	3.5	3.5
Serum β-hCG pregnancy test (Females only)	1	1	1	3	3.5	10.5
Blood for plasma ADA and MK-2060	0	5	1	6	2.7	16.2
Blood for PT and aPTT at local lab	1	6	0	7	3	21
Blood for PT, aPTT, and Factor XI activity at central lab	0	12	1	13	10	130
Blood for MK-2060 only	0	7	0	7	1.8	12.6
					Total Blood Volume per Male Participant[a]	**280.8 mL**
					Total Blood Volume per Female Participant[a]	**294.8 mL**

ADA=anti-drug antibody; aPTT=activated partial thromboplastin time; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; PT=prothrombin time

[a] If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (no more than 50 mL in total) may be obtained.

Part 2						
	Prestudy	**Treatment Periods**	**Poststudy**	**Total Collections**	**mL Per Collection**	**Total mL/ Test**
Laboratory Safety Tests	2	10	1	13	12.5	162.5
HIV/Hepatitis Screen (at the discretion of the investigator)	1	0	0	1	5	5
Blood for Planned Genetic Analysis	0	1	0	1	8.5	8.5
FSH (Females only)	1	0	0	1	3.5	3.5
Serum β-hCG pregnancy test (Females only)	1	2	1	4	3.5	14
Blood for plasma ADA and MK-2060	0	7	1	8	2.7	21.6
Blood for PT and aPTT at local lab	1	7	1	9	3	27
Blood for PT, aPTT, and Factor XI activity at central lab	0	16	1	17	10	170
Blood for MK-2060 only	0	9	0	9	1.8	16.2
					Total Blood Volume per Male Participant[a]	**410.8 mL**
					Total Blood Volume per Female Participant[a]	**428.3 mL**

ADA=anti-drug antibody; aPTT=activated partial thromboplastin time; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; PT=prothrombin time

[a] If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (no more than 50 mL in total) may be obtained.

Part 3						
	Prestudy	**Treatment Periods**	**Poststudy**	**Total Collections**	**mL Per Collection**	**Total mL/ Test**
Laboratory Safety Tests	2	4	1	7	12.5	87.5
HIV/Hepatitis Screen (at the discretion of the investigator)	1	0	0	1	5	5
Blood for Planned Genetic Analysis	0	1	0	1	8.5	8.5
FSH (Females only)	1	0	0	1	3.5	3.5
Serum β-hCG pregnancy test (Females only)	1	1	1	3	3.5	10.5
Blood for plasma ADA and MK-2060	0	7	1	8	2.7	21.6
Blood for PT and aPTT at local lab	1	6	0	7	3	21
Blood for PT, aPTT, and Factor XI activity at central lab	0	14	1	15	10	150
Blood for MK-2060 only	0	7	0	7	1.8	12.6
Total Blood Volume per Male Participant[a]						**306.2 mL**
Total Blood Volume per Female Participant[a]						**320.2 mL**

ADA=anti-drug antibody; aPTT=activated partial thromboplastin time; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; PT=prothrombin time

[a] If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (no more than 50 mL in total) may be obtained.

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

For all laboratory values obtained at pre-study (screening) visit and/or pre-dose 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 (e.g., 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
Ab	antibody
ACE	angiotensin converting enzyme
ADA	anti-drug antibodies
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AS	anti-sense oligo
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC0-∞	area under the concentration-time curve extrapolated to infinity
AUC0-168	area under the concentration-time curve from 0 to 168 hours postdose
AUC0-last	area under the concentration-time curve to the last measurable concentration
AV	arteriovenous
AVG	arteriovenous graft
BMI	body mass index
BP	blood pressure
C	plasma concentration
C168	concentration at 168 hours
CCU	Critical Care Unit
CI	confidence interval
Cmax	maximum plasma concentration
CKD	Chronic Kidney Disease
CKD4	Stage 4 Chronic Kidney Disease
CKD5	Stage 5 Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
CL/F	apparent total clearance
COVID-19	coronavirus of 2019
CrCl	creatinine clearance
CR	complete response
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	coefficient of variation
DBP	diastolic blood pressure
DDI	drug-drug interaction
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DPP-4	dipeptidyl peptidase-4
ECG	electrocardiogram

Abbreviation	Expanded Term
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ER	Emergency Room
ESKD	End Stage Kidney Disease
ESKD-HD	End Stage Kidney Disease on Hemodialysis
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FGA	Fibrin Generation Assay
FSH	follicle-stimulating hormone
FXa	Factor Xa
FXI	Factor XI
FXIa	Factor XIa
GCP	Good Clinical Practice
GCV	geometric coefficient of variation
GI	gastrointestinal
GLP-1	glucagon-like peptide 1
GM	geometric mean
GMR	geometric mean ratio
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HD	hemodialysis
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG4	immunoglobulin G4
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
IVIG	intravenous immune globulin

Abbreviation	Expanded Term
LPI	last patient in
LPLV	last patient last visit
mAb	monoclonal antibody
MDRD	Modification of Diet in Renal Disease
NHV	normal healthy volunteer
NOAEL	no observed adverse effect level
NSAID	nonsteroidal anti-inflammatory drug(s)
OTC	over-the-counter
P	protocol (number)
PCL	Protocol Clarification Letter
PK	pharmacokinetic
PI	principal investigator
PP	per-protocol
PR	PR interval
PT	prothrombin time
QTc	Q-T corrected (corrected Q-T interval)
QW	once weekly
RhoGAM	A brand of Rh immunoglobulin
RNA	ribonucleic acid
RR	respiratory rate
SAE	serious adverse event
SBP	systolic blood pressure
SC	subcutaneous (ly)
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SoA	schedule of activities
SOC	standard of care
SOP	Standard Operating Procedures
SUSAR	suspected unexpected serious adverse reaction
t1/2	half life
Tmax	time to maximum plasma concentration
TGA	thrombin generation assay
THC	tetrahydrocannabinol
TMDD	target-mediated drug disposition
ULN	upper limit of normal
uPCR	urine protein to creatinine ratio
USP	United States Pharmacopeia
Vd	volume of distribution
VS	vital signs
Vz/F	apparent volume of distribution
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential

11 REFERENCES

[Bethune, C., et al 2017]	Bethune C, Walsh M, Jung B, Yu R, Geary RS, Bhanot S. Pharmacokinetics and pharmacodynamics of Ionis-FXI(RX), an antisense inhibitor of factor XI, in patients with end-stage renal disease on hemodialysis. Blood. 2017;130:1116.	[0559X2]
[Buller, H. R., et al 2015]	Buller HR, Bethune C, Bhanot S, Gailani D, Monia BP, Raskob GE, et al. Factor XI antisense oligonucleotide for prevention of venous thrombosis. N Engl J Med. 2015 Jan 15;372(3):232-40.	[04T0MV]