Official Protocol Title:	A Single-Dose Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of MK-2060 in Japanese Older Participants with End-Stage Renal Disease on Dialysis
NCT number:	NCT05769595
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Title Page

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Protocol Title: A single-dose clinical study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of MK-2060 in Japanese older participants with end-stage renal disease on dialysis.

Protocol Number: 012-00

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):

Approval Date: 09 December 2022

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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
Original Protocol	09-DEC-2022	Not applicable

Table of Contents

LIST OF TABLES

Confidential

LIST OF FIGURES

Confidential

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A single-dose clinical study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of MK-2060 in Japanese older participants with end-stage renal disease on dialysis.

Short Title: Single Dose Study of MK-2060 in Japanese Older Participants on Dialysis

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

In Japanese older participants with end-stage renal disease on dialysis,

[Will be populated by selections made in Section 3 Objectives and Endpoints]

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability following a single dose intravenous administration of MK-2060.	• Adverse events
Secondary	
• To evaluate plasma pharmacokinetics of MK-2060 following a single dose intravenous administration of MK-2060.	• AUC0-inf, AUC0-last, AUC0-168, Cmax, C168, Tmax, Tlast, t1/2, CL and Vz
• To evaluate the effect of MK-2060 on activated partial thromboplastin time following a single dose intravenous administration of MK-2060.	• Activated partial thromboplastin time

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Risk reduction of major thrombotic cardiovascular
Population	Japanese older participants with end-stage renal disease on dialysis
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Placebo
Study Blinding	Double-blind
Blinding Roles	Investigator, Participants or Subjects, Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 8 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately up to 16 participants will be randomized as described in Section 9.9.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Intervention Group Name</th><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Adminis-tration</th><th>Regimen</th><th>Use</th></tr>
<tr><td>MK-2060</td><td>MK-2060</td><td>50 mg</td><td>Once</td><td>Intravenous</td><td>Single 60-minutes infusion</td><td>Test product</td></tr>
<tr><td>Placebo</td><td>Placebo</td><td>0 mg</td><td>Once</td><td>Intravenous</td><td>Single 60-minutes infusion</td><td>Placebo</td></tr>
</table>
</td></tr>
<tr><td>Total Number of Intervention Groups/ Arms</td><td>2</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate in the study for approximately up to 192 days (6.5 months) from the time the participant provides documented informed consent through the final contact. After a screening phase of up to 28 days, each participant will receive a single dose of assigned intervention and will be followed for approximately 164 days (5.5 months).</td></tr>
</table>

Study Governance Committees:

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

Study Accepts Healthy Volunteers: No

A list of abbreviations is in Appendix 9.

1.2 Schema

The study design is depicted in Figure 1 and Table 1.

Figure 1 Study Schema

* Screening 1 should occur within 28 days prior to intervention randomization.
Screening 2 should occur within 5 to 8 days prior to intervention randomization.
Screening 2 should occur after review of all data from Screening 1.
Dialysis should be done at Screenings 1 and 2.

Table 1 Study Schema

N [a]	Dose [b, c]
CCI	MK-2060 50 mg
	Placebo

a Japanese older participants with ESRD on HD or HDF. Approximately up to 16 participants will be randomized and a minimum of approximately CCI HDF participants should be included.

b Dosing in this study will be initiated after CCI of safety data from the highest IV dose in MK-2060-013 has been reviewed. Available safety, PK and/or PD data in other MK-2060 clinical studies might also be reviewed prior to initiate dosing in this study.

c The suggested doses may be adjusted downward based on newly available safety, PK and/or PD data observed in MK-2060-013 and/or in other MK-2060 clinical studies.

Placebo: 0.9% sodium chloride infusion
MK-2060-013: Single Dose Study of MK-2060 in Healthy Japanese Participants

1.3 Schedule of Activities

	Screening		Intervention																		Post-study	Phone Call	Note
Visit Number	1	2	[redacted]																				
Scheduled Day	Scr1	Scr2	1～2							3		5	8	12	15	22	29	60	90	120	150	164	
Scheduled Hour (0= Initiation of Administration)			Pre dose	0	1	3.5	8	12	24	48	52	96	168										
Window (Day)												[redacted]											Window of Screening: See Section 8.11.1
Administrative Procedures																							
Informed Consent	X																						
Informed Consent FBR	X																						
Inclusion/ Exclusion Criteria	X	X	X																				
Participant ID Card	X																						
Medical History	X																						
Prior/ Concomitant Medication Review	X ---------- X																						
Assignment of Screening Number	X																						
Participant Registration	X		X	X																			At informed consent, randomization and administration
Assignment of Randomization Number			X																				

	Screening		Intervention																	Post-study	Phone Call	Note
Visit Number	1	2	3									4	5	6	7	8	9	10	11	12	13	
Scheduled Day	Scr1	Scr2	1～2							3		5	8	12	15	22	29	60	90	120	150	164	
Scheduled Hour (0= Initiation of Administration)			Pre dose	0	1	3.5	8	12	24	48	52	96	168										
Window (Day)												+1		±1	±2	±2	±3	±5	±5	±7	±7	±7	Window of Screening: See Section 8.11.1
MK-2060/Placebo Administration				X -- X																			See Section 8.1.8.1
Meal						X ---------- X																	A meal will be provided at approximately 4 hours postdose. At the discretion of the investigator, additional meals and/or snack(s) will be provided (e.g. snack at approximately 2 hours postdose)
Domiciling			[redacted]																				See Section 8.1.11.
Safety Procedures																							
Physical examination	X		X						X	X			X		X		X	X	X	X	X		A local infusion site (i.e., dialysis vascular access site) examination will be included in all postdose physical examination.
Systemic Infusion Reaction Assessment					X	X	X		X	X													

	Screening		Intervention																	Post-study	Phone Call	Note
Visit Number	1	2	3									4	5	6	7	8	9	10	11	12	13	
Scheduled Day	Scr1	Scr2	1～2							3		5	8	12	15	22	29	60	90	120	150	164	
Scheduled Hour (0= Initiation of Administration)			Pre dose	0	1	3.5	8	12	24	48	52	96	168										
Window (Day)												+1		±1	±2	±2	±3	±5	±5	±7	±7	±7	Window of Screening: See Section 8.11.1
Assessment of Time to Hemostasis	X	X				X					X		X				X			X			See Section 8.3.3.
Height	X																						
Weight	X																				X		
Resting Vital Signs (BP, PR and RR)	X	X	X ---------- X					X	X	X		X	X	X						X	X		On Day 1~2, BP, PR and RR will be measured at predose, 15 min, 30 min, and 1, 2, 3.5, 12 and 24 hours postdose. Predose PR and BP will be triplicate measurements obtained at least 1 to 2 minutes apart within 3 hours of starting dialysis session.
Resting Vital Signs (body temperature)	X	X	X		X	X			X	X		X	X	X						X	X		
12-lead ECG	X		X			X			X	X			X								X		
Hematology and Chemistry	X	X	X						X	X			X	X	X	X	X		X		X		
aPTT and PT	X				X			X		X		X	X	X	X	X			X				
CCI			X																				

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	Screening		Intervention																		Post-study	Phone Call	Note
Visit Number	1	2	3									4	5	6	7	8	9	10	11	12	13		
Scheduled Day	Scr1	Scr2	1～2							3		5	8	12	15	22	29	60	90	120	150	164	
Scheduled Hour (0= Initiation of Administration)			Pre dose	0	1	3.5	8	12	24	48	52	96	168										
Window (Day)												+1		±1	±2	±2	±3	±5	±5	±7	±7	±7	Window of Screening: See Section 8.11.1
Hemoccult Test	X									X		X	X	X	X	X	X	X					
HIV, hepatitis B and C screen	X																						
Saliva Drug Screen	X																						
FSH	X	X																					As needed.
AE/SAE review	X ---------- X																						
Pharmacokinetics																							
Blood for Plasma MK-2060 Assay			X		X			X	X	X	X	X	X X	X	X	X	X X	X	X	X X	X		Days 8, 29 and 120: two draws for a pre- dialysis and a post-dialysis sample.
Blood for plasma ADA			X												X	X	X	X	X	X	X		
Pharmacodynamics																							
Blood for aPTT/PT/FXI activity			X		X			X	X	X	X	X	X X	X	X	X	X X	X	X	X X	X		Days 8, 29 and 120: two draws for a pre- dialysis and a post-dialysis sample.
Biomarkers																							
Blood for Genetic Analysis			X																				See Section 8.8.1.

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2 INTRODUCTION

MK-2060 is an anti-FXI mAb being developed for the prevention of thrombotic vascular events in ESRD. FXI is an integral component of the intrinsic pathway of the coagulation cascade. Based on preclinical and human genetic data, as well as emerging clinical data using an ASO approach (Ionis) and mAb (Bayer), 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 complications.

2.1 Study Rationale

The purpose of this study is to assess the safety, tolerability, PK and PD of MK-2060 after a single dose IV administration in Japanese older participants with ESRD on dialysis. Data from this study etc. will be used to aid dose selection of MK-2060 in Japanese participants in future studies.

2.2 Background

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

2.2.1 Pharmaceutical and Therapeutic Background

FXI inhibition is predicted to confer a clinically relevant anti-thrombotic effect with a limited risk of bleeding complications and hence an expanded therapeutic index compared to inhibition of more downstream clotting factors such as FXa and thrombin. Currently, several Factor XI inhibitors (ASO, mAb, SMi) are being investigated in either Phase 1 or 2 studies, across a range of populations, but limited data has been made available to confirm the proof of concept in ESRD patients as a suitable indication.

2.2.2 Clinical Studies

As of CCI [redacted], MK-2060 has been evaluated in 2 completed Phase 1 studies (MK-2060-001 and MK-2060-004), 1 ongoing Phase 1 study (MK-2060-008) and 1 ongoing Phase 2 study (MK-2060-007).

MK-2060-001:

MK-2060-001 was a double-blind, randomized, placebo-controlled, sequential panel, SAD study in non-Japanese healthy male participants to evaluate the safety, tolerability, PK and PD profiles of MK-2060 administered SC or IV. A total of 45 non-Japanese healthy participants received single MK-2060 doses of up to 120 mg administered SC (27 participants) and up to 40 mg administered IV (18 participants). Refer to the latest IB for detailed results.

MK-2060-004:

MK-2060-004 was a double blind, randomized, placebo-controlled, sequential panel single (Part 1) and multiple (Part 2) dose study to evaluate the safety, tolerability, PK and PD characteristics of MK-2060 single (up to 40 mg) and multiple (25 mg dose on Days 1, 3, and 5, followed by 3 once-weekly maintenance doses of 25 mg) IV doses in non-Japanese older participants with ESRD on HD. Overall, 38 participants were enrolled in the study: 24 participants in Part 1 and 21 participants in Part 2 (7 participants in Part 1 also participated in Part 2). Refer to the latest IB for detailed results.

2.2.3 Ongoing Clinical Studies

MK-2060-008:

MK-2060-008 is an open label, multi-site, multiple dose trial of MK-2060 in non-Japanese participants with ESRD on HD to evaluate the safety and tolerability of MK-2060 and clopidogrel administered in combination in participants with ESRD on HD. This study will enroll up to 12 ESRD participants receiving clopidogrel as background therapy. After an approximately 14-day run-in period to enable measurement of baseline time to hemostasis and AE monitoring, each participant will receive a loading dose of 25 mg IV MK-2060 for a total of 3 doses in week 1 and a single dose of 25 mg IV MK-2060 in week 2.

MK-2060-007:

MK-2060-007 is an event driven, randomized, placebo-controlled, parallel-group, multi-site, double-blind study of MK-2060 in non-Japanese participants with ESRD on HD via an AVG. This phase 2 study is designed to evaluate the efficacy and safety of MK-2060 [redacted] QW and MK 2060 [redacted] QW (with three loading doses in Week 1). As of [redacted] participants enrolled in MK-2060-007 with a maximum exposure of [redacted]. MK-2060-007 is ongoing and safety data are blinded and preliminary.

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

In Japanese older participants with end-stage renal disease on dialysis,

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability following a single dose intravenous administration of MK-2060.	• Adverse events
Secondary	
• To evaluate plasma pharmacokinetics of MK-2060 following a single dose intravenous administration of MK-2060.	• AUC0-inf, AUC0-last, AUC0-168, Cmax, C168, Tmax, Tlast, t1/2, CL and Vz
• To evaluate the effect of MK-2060 on activated partial thromboplastin time following a single dose intravenous administration of MK-2060.	• Activated partial thromboplastin time
Tertiary/Exploratory	
• To explore the effect of MK-2060 given as a single dose intravenous administration on Factor XI activity levels.	• Factor XI activity
• To explore the effect of MK-2060 given as a single dose intravenous administration on prothrombin time.	• Prothrombin time
• To explore the effect of MK-2060 given as a single dose intravenous administration on time to hemostasis after decannulation of the dialysis vascular access site.	• Time to hemostasis after decannulation of vascular access
• To explore the presence and titer of anti-drug antibodies in plasma samples following a single dose intravenous administration of MK-2060.	• Presence and titer of anti-drug antibodies

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Objectives	Endpoints
• 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

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, placebo-controlled, parallel-group, multi-site, double-blind study of MK-2060 in Japanese older participants with ESRD on dialysis. The study will evaluate the safety, tolerability, PK and PD of a single dose IV administration of MK-2060 in Japanese older participants with ESRD on dialysis (participants assigned male sex at birth or WONCBP between the age of 50 to 80 years).

The study design is depicted in Figure 1 and Table 1.

Approximately up to 16 participants will be randomized in a ratio of CCI and receive a single dose of MK-2060 or placebo (0.9% sodium chloride infusion). All participants will be domiciled until approximately CCI hours postdose (completion of dialysis on Day CCI Blood samples for PK, PD and ADA assay will be obtained predose and at selected time points up to 150 days postdose. All participants will be closely monitored for safety and tolerability for approximately 164 days.

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 8.11.6 for examples of modifications permitted within the protocol parameters.

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

4.2 Scientific Rationale for Study Design

MK-2060 is being developed for the prevention of thrombotic vascular events in ESRD patients, thus the objectives of this study are to evaluate safety, tolerability, PK, and PD of MK-2060 after a single dose IV administration in Japanese patient population [older participants with ESRD on dialysis (participants assigned male sex at birth or WONCBP

between the age of 50 to 80 years)]. Approximately up to 16 participants with ESRD on dialysis who meet study eligibility criteria may be enrolled in this study.

Dialysis modality in this study includes HD and HDF. The Japanese patients treated by HDF have been increasing in number rapidly since 2012. HD and HDF accounted for 49.3% and 47.1% of all dialysis patients, respectively in 2020 [JSDT Renal Data Registry 2020]. Therefore, this study will enroll both HD and HDF participants. Since only HD participants were enrolled in MK-2060-004 (Phase 1 study in non-Japanese participants), this study will mainly enroll HD participants and a minimum of approximately [redacted] HDF participants will be enrolled. [redacted] is not removed by both HD and HDF, it is anticipated that there is no PK difference between HD and HDF patients.

The mean age of prevalent dialysis patients in Japan was 69.40 years, indicating a gradual annual increase. The age group of 70 to 74 had the highest percentage both in males and females [JSDT Renal Data Registry 2020]. The mean age of HD and HDF patients was 70.00 years and 67.21 years, respectively. The mean dialysis vintage of HD patient was 6.99 years and 50.7% was less than 5 years of dialysis vintage. On the other hand, the mean dialysis vintage of HDF patient was 8.44 years and 40.9% was less than 5 years of dialysis vintage. HDF is applied to relatively young patients with a longer dialysis vintage than HD in 2018 [JSDT Renal Data Registry 2018]. Therefore, this study is being conducted in older participants ages from 50 years to 80 years.

In the Part 1 of MK-2060-004, the exposure (AUC0-inf and Cmax) after single IV dose at 8 mg MK-2060 in non-Japanese ESRD participants on HD is comparable to non-Japanese healthy participants (MK-2060-001) while the exposure after single IV dose at 20 mg and 40 mg in non-Japanese ESRD participants on HD are slightly lower than that in non-Japanese healthy participants due to higher clearance. The terminal t1/2 ranged from ~14 days for MK-2060 8 mg to ~21 days for MK-2060 40 mg in non-Japanese ESRD participants on HD [redacted]. PK samples were also collected pre- and post-dialysis, with the post-dialysis PK concentration approximately [redacted] higher than pre-dialysis indicting that MK-2060 is not cleared via dialysis and the reduction in volume due to dialysis slightly increases the MK-2060 concentration. Based on single dose PK and aPTT or FXIa activity data, [redacted] The PK and aPTT or FXI activity (relative of baseline) data from MK-2060-001 and following single IV doses from MK-2060-004 suggests a comparable but [redacted] for participants with ESRD and healthy participants.

It is also not anticipated that race significantly alter the PK and PD of MK 2060. As mAbs are primarily eliminated via catabolism, there is expected to be no ethnic differences of the clearance between Japanese and non-Japanese participants. Since the PK and PD values were corelated [redacted] in non-Japanese, PD responses in Japanese participants are also expected to be similar to that in non-Japanese participants The impact of race on MK-2060 PK and PD will be further assessed by conducting single dose study in Japanese healthy participants (MK-2060-013).

In MK-2060-001, in general, a single SC dose of MK-2060 up to 120 mg or a single IV dose of MK-2060 up to 40 mg in non-Japanese healthy participants assigned male sex at birth was well tolerated. There were no SAEs, ECIs, or deaths reported, no participants discontinued from the study due to an AE. There were no AEs suggestive of hypersensitivity. In Part 1 of MK-2060-004, a single IV dose up to 40 mg has been generally well-tolerated in non-Japanese participants with ESRD on HD. There were no ECIs or deaths reported, no participants discontinued from the study due to an AE. There were no AEs suggestive of hypersensitivity. In Part 2 of MK-2060-004, multiple IV doses of 25 mg have been generally well tolerated in non-Japanese participants with ESRD on HD. There were no deaths reported. There were no AEs suggestive of hypersensitivity. Two participants receiving placebo were discontinued from study intervention due to AEs including lower gastrointestinal hemorrhage (SAE, related) and COVID-19 infection (nonserious, not related). Four (4) participants experienced SAEs: 1 (6.3%) in MK-2060 (severe myocardial infarction on Day 103, not related) and 3 (60.0%) in placebo. All SAEs resolved by the end of the study. In addition, IONIS has demonstrated using a FXI ASO that inhibition of the FXI pathway in ESRD participants on HD (mean age of 61 years) is generally safe and well-tolerated [Bethune, C., et al 2017].

Therefore, the study of MK-2060 in Japanese older participants with ESRD on dialysis is supported.

4.2.1 Rationale for Endpoints

4.2.1.1 Safety Endpoints

This will be the first introduction of MK-2060 to Japanese older participants with ESRD on dialysis. Based on the data from MK-2060-004, it is expected that IV administration of MK-2060 will be well-tolerated in participants with ESRD on dialysis. However, the safety and tolerability of MK-2060 are primary endpoints and will be carefully monitored. PEs, VSs, 12-lead ECGs, laboratory safety tests (hematology, chemistry, aPTT and PT) and bleeding related AEs will be assessed. AEs, including local infusion site reactions and systemic reactions to infusion, will be collected through Day 164.

As with all biologic medications, MK-2060 carries a risk of acute reactions upon exposure, particularly with IV administration. The risk of any of infusion reactions to MK-2060 is considered low given its profile in preclinical safety studies and available safety data in MK-2060-001 and MK-2060-004. However, given potential safety risks, participants will be monitored closely for systemic reactions to infusion with scheduled VSs and PEs. In addition to monitoring for acute reactions to MK-2060, the infusion site reactions will be assessed for signs of reactogenicity.

Time to hemostasis after decannulation of vascular access:

An exploratory objective of this study is to explore the effect of MK-2060 given as a single dose IV administration on time to hemostasis after decannulation of the dialysis vascular access site in Japanese ESRD patients. In the dialysis unit after the completion of dialysis the dialysis catheters are removed from the dialysis access site (i.e., AV fistula or AV graft).

Upon decannulation, pressure is held until adequate hemostasis has been obtained. In this study, the process, which was used in MK-2060-004 and MK-2060-008, is standardized such that change in time to hemostasis from baseline (i.e., Screening 1 and 2) can be assessed. This exploratory analysis may allow for a very preliminary read on bleeding risk with administration of MK-2060 in the Japanese ESRD patient population.

In general, both single dose and multiple doses of MK-2060 in non-Japanese participants with ESRD on HD (MK-2060-004) had no effect on time to hemostasis at the end of HD after dosing. In Parts 1 and 2, the maximum observed fold-change for time to hemostasis was mostly around 1 across all doses of MK-2060 and placebo throughout the study.

Anti-drug antibodies to MK-2060:

The amino acid sequence of MK-2060 is highly similar to standard human CCI The mechanism of action of MK-2060 is not immunomodulatory and the ESRD population is less likely to have a robust immune response.

The presence and titer of ADAs will be measured using validated assays. ADAs can develop to biologics like MK-2060. If needed, positive ADAs will be further evaluated to determine whether they are able to neutralize MK-2060 activity against FXI.

From MK-2060-001, a total of 45 participants were evaluable for immunogenicity assessment. One participant had a single positive sample at the Day 90 timepoint. The remaining 44 participants did not have positive samples.

From MK-2060-004, overall, CCI participants were evaluable for immunogenicity assessment: CCI participants in Part 1 and CCI participants in Part 2. Of the CCI participants, CCI were treatment emergent positive. All other participants were negative for ADA. In Part 1, CCI treatment emergent positive with CCI CCI reported no AEs CCI CCI treatment emergent positive with CCI no reported AEs. The magnitude of response (ie, maximum postdose titer value) in both participants with a positive response to MK-2060 was near the limit of detection of the ADA assay (titer value of CCI In both ADA positive participants, the presence of ADA did not affect the MK-2060 safety and PK profile.

Based on the PK profiles observed to date and available ADA analysis data from both MK-2060-001 and MK-2060-004, it is unlikely that ADA have affected the current PK profiles. Therefore, the overall risk of immunogenicity is expected to be low for MK-2060.

4.2.1.2 Pharmacokinetic Endpoints

In order to characterize the PK profile of MK-2060 in Japanese older participants with ESRD on dialysis, non-compartmental PK parameters AUC0-inf, AUC0-last, AUC0-168, Cmax, C168, Tmax, Tlast, t1/2, CL and Vz will be summarized following a single dose IV administration. Evaluation of plasma PK data of MK-2060 following a single dose IV administration in Japanese older participants with ESRD on dialysis is a secondary objective of this study.

4.2.1.3 Pharmacodynamic Endpoints

In order to assess PD, this study will include an assessment of aPTT/PT prolongation levels, and FXI activity levels, with assays being performed at a central laboratory for PD. For PK/PD modeling, aPTT and FXI activity levels will be related to plasma exposure. The time points for PD data collection are based on the projected PK profile of MK-2060. Evaluation of the effects of MK-2060 on aPTT following a single dose IV administration in Japanese older participants with ESRD on dialysis is a secondary objective of this study.

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

The primary goal of the study is to evaluate the safety and tolerability of MK-2060 in Japanese older participants with ESRD on dialysis. A placebo-controlled study will allow for an unbiased assessment of safety and tolerability of MK-2060. Secondary and exploratory outcomes are also supported by the use of placebo, including evaluation of the effect of MK-

2060 on aPTT following single IV dose, which should only be observed in participants with active treatment.

4.3 Justification for Dose

The dose to be administered in this study will not exceed 50 mg.

The single IV dose of 50 mg in this study would cover the exposures at the steady state obtained from the possible maximum dose of Phase 3 study (i.e. CC mg IV or lower QW). This is also the planned highest dose in a single IV dose study in Japanese healthy participants (MK-2060-013) and dose in this study may be adjusted downward based on available safety, PK and/or PD data in MK-2060-013 and/or other MK-2060 clinical studies.

In MK-2060-004, a single IV dose up to 40 mg and multiple IV doses of 25 mg QW have been generally well-tolerated in non-Japanese participants with ESRD on HD. Apart from mechanism-based aPTT increases, there were no clinically significant changes from baseline for ECGs, safety labs. Similarly, an exploratory assessment of time to vascular access site hemostasis after removal of the hemodialysis catheters remained unchanged from baseline.

Given dose proportionality in exposures generally observed in previous clinical studies, a single IV dose of 50 mg in Japanese older participants with ESRD on dialysis in this study is projected to result in a Cmax of CCI

These predicted Cmax CCI) in this study are slightly lower compared to the observed values at the steady state at 25 mg QW in MK-2060-004 (Cmax of 90.9 nM and AUC0-168 of 9880 nM•hr). In addition, these predicted AUC0-168 CCI in this study provided an AUC margin of approximately CCI , to the AUC at the NOAEL (AUC0-168 at 60mg/kg of 7920 day•µg/mL = 1.28 x 10^6 hr•nM) in 4 week SC and IV toxicity study in rhesus monkeys.

The maximum aPTT change from baseline was CCI (around Tmax) at the steady state after multiple IV doses of 25 mg QW in MK-2060-004. As mentioned above, the predicted Cmax CCI in this study is slightly lower than the observed Cmax CCI at the steady state in MK-2060-004. Given this together with CCI between PK and PD responses, maximum aPTT change from baseline in this study is expected to be lower than that observed in MK-2060-004.

Please refer to Section 4.2 above for further rationale as to why significant PK and PK-PD differences with MK-2060 in Japanese older participants with ESRD on dialysis are not anticipated.

As this is a Phase 1 assessment of MK-2060 in humans, and the PK, PD 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.

4.3.1 Rationale for Dose Interval and Study Design

This is a single dose study, in which participants will only receive one IV administration. MK-2060 or placebo will be given 30 minutes after the initiation of dialysis and administered via the post-dialyzer line (V side) over approximately 60 minutes. Participants will be enrolled and dosed on a rolling basis.

Dosing in this study will be initiated after at least CCI days of safety data from the highest IV dose in MK-2060-013 (Single ascending dose study in Japanese healthy participants) has been reviewed.

MK-2060 is a fully human mAb and does not exhibit highly species-specific action, nor is it directed towards immune system targets. Safety assessment studies and clinical studies (MK-2060-001 and MK-2060-004) with MK-2060 provide no contraindications to the initiation of this study via IV routes. No dose-limiting toxicities were observed in the 4-week nonhuman primate toxicity trial. These considerations suggest that the risk of unanticipated severe reactions is low. However, due to uncertainties inherent in early phase clinical testing, this study will include a period of observation on a CRU after dosing. CRUs will have appropriate access to a full service acute-care hospital to facilitate rapid institution of medical intervention as indicated.

There will be frequent, careful assessments of AEs throughout the postdose period. The participants will be dosed and observed until discharge CCI hours postdose; completion of dialysis on Day CCI for safety monitoring, and then they will continue to be monitored throughout the study period as indicated in Section 1.3. Following discharge, the additional measures are being taken in this protocol to ensure the safety of study participants as indicated in Section 8.1.11.

Due to the physio-chemical properties of mAb therapeutics, transfer to the seminal compartment and subsequent vaginal uptake of a mAb is essentially zero, as demonstrated in rabbits, monkeys, and humans [Breslin, W. J., et al 2014], [Moffat, G. J., et al 2014], and [Sohn, W., et al 2015]. In addition, in an embryofetal developmental toxicity study in pregnant rabbits administered MK-2060, there was no evidence of embryofetal lethality or teratogenicity up to 120 mg/kg/day (the highest dose evaluated; 1 dose QW for 2 weeks) providing an estimated systemic exposure margin of 234-fold the observed AUC0-168hr of 63 day•µg/mL after multiple 60-minute IV infusion doses of 25 mg IV at steady state in ESRD patients. Therefore, there is no risk to pregnant partners of male participants receiving MK-2060, and male contraception during clinical studies with MK-2060 is not warranted.

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 the 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.

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. Japanese descent with all 2 biological parents of Japanese descent.

2. On HD or HDF with spKt/V ≥ 1.2, using AV fistula or AV graft ≥ 3 months prior to Screening 1 at a healthcare center, and is on the same dialysis regimen [type of dialyzer, blood flow rate, dialysate flow rate, dialysis time and dialysis frequency (3 times per week)] ≥ 2 weeks prior to Screening 1.

3. Be judged to plan to continue or anticipate the use of the current AV fistula or AV graft until the poststudy visit.

4. BMI ≤ 40 kg/m^2, inclusive. See Section 8.3.4 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height $(m)^2$.

Demographics

5. Is male or female, from 50 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 a WONCBP, as defined in Appendix 5.

Informed Consent

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

Additional Categories

8. Willing to comply with the study restrictions (see Section 5.3 for a complete summary of study restrictions).

5.2 Exclusion Criteria

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

Medical Conditions

1. On peritoneal dialysis (including the combination of HD or HDF) or other dialysis modalities except for HD and HDF.

2. History of any clinically significant concomitant disease or condition (including treatment for such conditions) or diseases whose current condition is considered clinically unstable in the opinion of the investigator. Participants with a remote history of uncomplicated medical events (eg, uncomplicated kidney stones, as defined as spontaneous passage and no recurrence in the last 5 years, or childhood asthma) may be enrolled in the study at the discretion of the investigator.

3. Mentally incapacitated, has significant emotional problems at the time of Screening 1 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. History of cancer (malignancy).

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

5. History of deep vein thrombosis or pulmonary embolism. History of vascular access thrombosis within 1 month prior to Screening 1. Personal or family history of bleeding disorder (e.g., hemophilia, Factor V Leiden, prothrombin gene mutation, protein C or S deficiency, ATIII deficiency, anti-phospholipid Ab syndrome).

6. History of GI bleeding, duodenal polyps or active gastroduodenal ulcer within 5 years prior to Screening 1, or history of severe hemorrhoidal bleed within 3 months prior to Screening 1. Patients who had colonic polyps at low risk for bleeding through an endoscope performed prior to Screening 1, but who are judged not to require or anticipate requiring re-examination until the poststudy visit, may be enrolled at the discretion of the investigator.

7. History of frequent epistaxis within 3 months prior to Screening 1 or active gingivitis.

8. At the time of screening or predose, planned significant dental procedures (including planned dental surgery), or other planned surgical procedures within duration of participation in the trial.

9. History of significant multiple and/or severe allergies (eg, food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability (ie, systemic allergic reaction) to prescription or nonprescription drugs or food.

10. Positive test(s) for hepatitis B surface antigen or HIV antigen and antibody. Participants positive for hepatitis C antibodies may be enrolled with agreement of both the investigator and Sponsor. Serology tests will be performed at Screening 1 by the central laboratory for safety.

11. The participant had a major surgery and/or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to Screening 1.

12. A tattoo, scar, or other physical finding at the area of vascular access site and blood collection sites that would interfere with a local tolerability assessment.

Prior/Concomitant Therapy

13. History (participant recall) of receiving any human immunoglobulin preparation such as IVIG or RhoGAM within 1 year prior to Screening 1.

14. History (participant recall) of receiving any biological therapy (including human blood products or monoclonal antibodies; excluding erythropoietin and insulin) within 3 months (or 5 half-lives, whichever is greater) prior to Screening 1, or vaccination within 1 month prior to the dose of study intervention.

Exceptions:

- Participants who have received seasonal flu vaccine and pneumococcal vaccine within 1 month prior to the dose of study intervention may be enrolled at the discretion of the investigator.

- COVID-19 vaccine may be administered. Study intervention must be given at least 72 hours following or at least 48 hours prior to any COVID-19 vaccination. Investigational COVID-19 vaccines (i.e., those not licensed or approved for Emergency Use) are not allowed.

15. Requires or anticipates requiring the use of following prohibited medications until the poststudy visit.

- Anticoagulants (Intradialytic heparin is permitted)

- Antiplatelet medications (low dose aspirin is permitted)

- NSAIDs (e.g., ibuprofen) (acetaminophen used for minor ailments and topical NSAIDs is permitted)

Prior/Concurrent Clinical Study Experience

16. Participated in another investigational study within 1 month (or 5 half-lives, whichever is greater) prior to Screening 1. The window will be derived from the date of the last visit in the previous study.

Diagnostic Assessments

17. Has a BP > 190 mmHg systolic or > 110 mmHg diastolic obtained at Screening 2 or predose.

18. Has blood coagulation test (aPTT or PT) above 1.2X ULN at Screening 1 (confirmed by recheck) from the central laboratory for safety.

19. Has ALT or AST above 1.5X ULN at Screening 1 or 2 which are considered clinically significant by the investigator from the central laboratory for safety.

20. Exclusion criteria for ECG performed at Screening 1 or predose:

- HR < 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.
- Non-sustained or sustained ventricular tachycardia (greater than 2 consecutive ventricular ectopic beats at a rate of greater than 1.7/second).

Other Exclusions

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

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

23. A regular user of cannabis, any illicit drugs or has a history of drug (including alcohol) abuse within approximately 2 years. Participants must have a negative saliva drug screen at Screening 1. Participants with a positive drug screen due to the use of physician prescribed medications may be enrolled at the discretion of the investigator.

24. 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.

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

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

5.3.1.1 Diet Restrictions

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

On dosing day, participants will fast from all food and drinks, except water and non-caffeinated tea (e.g. barley tea), for at least 8 hours before initiation of study intervention administration. Participants will fast from all food and drinks, except water and non-caffeinated tea, between initiation of study intervention administration and the first scheduled meal. Meals and/or snacks will be provided by the investigator at time points indicated in the SoA. Participants will fast from all food and drinks, except water and non-caffeinated tea, between provided meals and snacks. The meal content should be consistent within a given clinical site (if possible). After the 24-hour postdose procedures have been completed, subsequent meals and snacks will be unrestricted in caloric content, composition, and timing.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

5.3.2.1 Caffeine Restrictions

Participants will refrain from consumption of caffeinated beverages or xanthine-containing products from 12 hours before Screening 1 and 2 and poststudy visits and from 12 hours before and after initiation of study intervention administration. Participants will follow the caffeine restrictions defined by the CRU from 12 hours after initiation of study intervention administration during domiciling. 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 Screening 1 and 2 and poststudy visits and from 24 hours before and after initiation of study intervention administration. Participants will follow the alcohol restrictions defined by the CRU from 24 hours after initiation of study intervention administration during domiciling. 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], wine [118 mL], or distilled spirits [29.5 mL]) per day.

5.3.2.3 Tobacco Restrictions

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

5.3.3 Activity Restrictions

Participants will avoid unaccustomed strenuous physical activity (ie, weightlifting, running, bicycling, etc) and contact sports including ones have bleeding risk (ie, boxing, football, etc.) from Screening 1 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 withdraws from the study, a replacement participant may be enrolled if deemed appropriate by the investigator and Sponsor. The replacement participant will generally receive the same intervention or intervention sequence (as appropriate) as the participant being replaced. The replacement participant will be assigned a unique treatment/randomization number.

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 study intervention(s) provided by the Sponsor will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted before dosing the replacement participant. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 2.

Country-specific requirements are noted in Appendix 7.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Inter-vention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen	Use	IMP or NIMP/ AxMP	Sourcing
MK-2060	Experimental	MK-2060	Drug	Lyophilized Powder	CCI	50 mg	IV Infusion	Single 60-minutes infusion	Test Product	IMP	Provided centrally by the Sponsor
Placebo	Placebo Comparator	Placebo	Drug	Sterile Solution	Saline	0 mg	IV Infusion	Single 60-minutes infusion	Placebo	IMP	Provided centrally by the Sponsor

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.

The normal saline provided by the Sponsor as placebo should be used to reconstitute MK-2060.

Normal saline = 0.9% Sodium Chloride Injection

All supplies indicated in Table 2 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.

A sample allocation schedule is shown in Table 3.

Table 3 Sample Allocation Schedule

N [a]	Dose
[redacted]	MK-2060 50 mg
[redacted]	Placebo

[a] Japanese older participants with ESRD on HD or HDF. Approximately up to 16 participants will be randomized and a minimum of approximately [redacted] HDF participants should be included.

Placebo: 0.9% sodium chloride infusion

6.3.2 Stratification

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

6.3.3 Blinding

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.

The date and (start and end) 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

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during time periods specified by this protocol. The investigator should discuss any questions regarding concomitant medication or vaccine with the Sponsor.

PROHIBITED MEDICATIONS

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

- Oral anticoagulants [Intradialytic heparin or other anticoagulants for injection (postdose only) are permitted]
- Antiplatelet medications (low dose aspirin is permitted)
- NSAIDs (e.g., ibuprofen) (acetaminophen used for minor ailments and topical NSAIDs is permitted)
- Other study interventions

RESTRICTED MEDICATIONS

Concomitant use of the following medications including FDCs will be allowed during the conduct of the study as long as the subject has been on a stable dose and treatment regimen for at least approximately 2 weeks prior and is able to withhold the use within four hours prior to administration of the dose of study intervention. This list is not exhaustive but serves as a guideline.

- Lipid Lowering Agents: Statins, Fibrates, Ezetimibe
- Anti-Hypertensive Medications: angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, beta blockers, calcium channel blockers, diuretic
- Diabetes Medications: Insulin, GLP-1 Analogs, Glinides, DPP-4 Inhibitors, α-GI
- Iron
- Phosphate Binders
- Vitamin D
- Erythropoietin
- HIF-PH inhibitors

6.5.1 Rescue Medications and Supportive Care

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

6.6 Dose Modification (Escalation/Titration/Other)

The dose of the study intervention to any participant may be adjusted downward based on newly available safety, PK and/or PD data observed in this study and/or other MK-2060 studies.

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. The study can be restarted based on joint agreement with the Sponsor and investigator. If needed, a substantial amendment may 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 (at the same dose level) report Severe Nonserious AEs considered related to the study intervention by the investigator.
3. If one or more infusion AEs of severe intensity considered related to the study intervention by the investigator occurs in 2 or more participants.

4. An increase aPTT > 4.0-fold versus baseline as confirmed after repeat measurement in 2 or more participants. aPTT values from the central laboratory for safety will be used for this rule and aPTT measured at the Screening Visit should be used as baseline value.

5. An increase PT > 1.5-fold versus baseline as confirmed after repeat measurement in 2 or more participants. PT values from the central laboratory for safety will be used for this rule and PT measured at the Screening Visit should be used as baseline value.

Participants who receive intradialytic heparin will likely have an increased aPTT at the 1-hour timepoint post dosing due to the pharmacologic effects of heparin. In order to allow for the evaluation of the pharmacologic effects of MK-2060 alone, the 12-hour post-dose aPTT will be the first timepoint used to assess aPTT stopping criteria for participants who receive intradialytic heparin. Heparin dosed at the time of dialysis should not interfere with aPTT at this 12-hour post-dose timepoint (heparin t1/2 is ~1hr). All other aPTT at safety labs throughout the course of the study will be drawn pre-dialysis and in the absence of heparin.

These criterion for aPTT (> 4.0-fold in 2 or more participants) was based upon that aPTT prolongations greater than 3-fold have been observed in severe FXI-deficient populations [Asakai, R., et al 1991]. Using the same aPTT assay which was used by the central laboratory for PD in this study, samples of pooled normal human plasma were compared to those from FXI-deficient patients, which were tested individually [Ellsworth K 2018]. In normal human plasma, the clot time ranged between 31.8 and 36.4 seconds. In plasma from FXI deficient patients, the clot time ranged between 99.5 and 128.1 seconds, which corresponded to a range of 2.9 to 3.9-fold prolongation in aPTT compared to that of the normal human plasma. From data collected in MK-2060-001, it appears that higher doses of

MK-2060 provide similar inhibition as the severe FXI-deficient phenotype, evidenced by MK-2060-associated increases in aPTT (local lab) up to 3.9-fold at the highest dose in MK-2060-001 (120 mg administered subcutaneously). These aPTT prolongations occurred in the absence of prolongation of PT and were associated with >95% inhibition of FXI activity, with no evidence of MK-2060-related AE. Therefore, the stopping criterion based upon an aPTT is >4-fold after repeat measurement in 2 or more participants.

The safety of participants will be assessed on an ongoing basis, and while conditions that could warrant stopping dosing are not limited to those noted above, these criteria are meant to pre-specify circumstances under which the study may be stopped to review the available safety data. Importantly, if any criterion listed above occurs, further dosing will be stopped and review of available safety data by the investigator and Sponsor will be required prior to continuing the study, which might include modification of safety monitoring procedures.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

This study is blinded but supplies are provided as open label; therefore, an unblinded pharmacist or qualified study-site personnel will be used to blind supplies. Study intervention identity (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

The emergency unblinding call center will use the intervention randomization schedule for the study to unblind participants and to unmask study intervention identity. 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.

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

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

7.2 Participant Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in Section 8.1.9. 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.

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 the study will not exceed 340.8 mL (Appendix 8).

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

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

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

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

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention 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 prior medication use and record prior medication taken by the participant basically within 2 weeks before Screening 1 (the details are defined in the data entry guidelines).

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

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

Any individual who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.11.1. Pre-trial screening logs may be collected for review by the Sponsor. If applicable, any information that would make the participant identifiable will be removed.

8.1.7 Assignment of Randomization Number

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

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

8.1.8 Study Intervention Administration

Study intervention will be administered by the investigator and/or appropriately qualified designee according to the specifications within the pharmacy manual.

8.1.8.1 Timing of Dose Administration

After the Day 1 predose procedures have been completed and it is confirmed that the participant meets eligibility, the participant will be assigned a unique randomization number by the participant registration center.

The participant will be administered MK-2060 or placebo as an IV infusion. The time of initiating IV infusion will be designated as time “0” and the exact time (start and end) of administration will be recorded. MK-2060 or placebo will be given 30 minutes after the initiation of dialysis and administered via the post-dialyzer line (V side) over approximately 60 minutes. Infusion time may increase or pause, and restart based upon on tolerability.

Blood samples at Day 1 postdose to Day 2 will be collected in the opposite arm or back of the hand from the dialysis vascular access site.

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 8.11.3 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.

At the end of the study, random code/disclosure envelopes or lists and unblinding logs are to be returned to the Sponsor or designee.

8.1.11 Domiciling

Participants will report to the CRU the day before the scheduled day of administration of the study intervention or the scheduled day of administration of the study intervention at the discretion of the investigator. Participants will remain in the CRU until the [redacted]-hour, postdose procedures (completion of dialysis on Day [redacted] have been performed (Day [redacted]. At the discretion of the investigator, participants may be requested to remain in the CRU longer.

Following discharge, the following measures are being taken in this protocol to ensure the safety of study participants:

- Participants will be informed that they could be taking an anticoagulant as a participant in this study, and that this might increase the risk of bleeding as might occur in surgery, dental procedures, or strenuous exercise/contact sport activities.

- Participants will be required to avoid scheduling any non-urgent/elective surgical or dental procedures, and to avoid strenuous physical activity and contact sport activities for the duration of the trial.

- Participants will be provided with an identification card, which identify them as participants in an anti-coagulant research study and, in the event of an emergency, will serve to notify healthcare providers that they might be at risk for provoked bleeding.

- If aPTT values are > 3-fold above baseline, or PT values are > 1.5-fold above baseline (at any time point), participants will be asked to remain in the clinic for at least [redacted] hours, and until aPTT and/or PT values are no longer increasing (upon retest), at the discretion of the investigator. aPTT and PT values from the central laboratory for safety will be used and aPTT and PT measured at the Screening Visit should be used as baseline value.

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 Assessments

There are no efficacy assessments in this study.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood to be drawn over the course of the study (from prestudy to poststudy visits), including approximate blood volumes drawn by visit and by sample type per participant, can be found in Appendix 2.

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

8.3.1 Physical Examinations

A physical examination will be conducted by an investigator per institutional standard. Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Management of Infusion Reaction During and Post-dose

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

In rare instances, systemic infusion reactions are severe and may have a fatal outcome. It is likely that most infusion 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 infusion reaction that is characterized by cutaneous and mucosal symptoms, such as generalized hives, pruritis or flushing, swollen lip-tongue-uvula and angioedema, accompanied by respiratory compromise (bronchospasm, stridor or hoarseness) and/or changes in blood pressure (hypotension). Severe infusion reactions, including cytokine release syndrome and hypersensitivity reactions must be promptly treated with interruption of the infusion, medical management, appropriate monitoring, and life-saving measures. Appropriate resuscitation equipment and a physician should be readily available during the period of drug administration. Less severe infusion reactions may respond to a reduction in the infusion rate and medical management.

8.3.2.1 Local Infusion Reaction Assessment

A local infusion site examination will be obtained as outlined in 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 [Food and Drug Administration. Sep-2007.] in Table 4. A local infusion reaction must be assessed and managed promptly per site procedure.

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

Table 4 Local Infusion 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

8.3.2.2 Systemic Infusion Reaction Assessment

Participants will be monitored during the administration of MK-2060/placebo for 48 hours postdose at CRU after the initiation of administration. During this time, signs and symptoms of a systemic infusion 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. Infusion reactions must be assessed and managed promptly.

8.3.3 Assessment of Time to Hemostasis

Assessment of time to adequate hemostasis will be conducted at the conclusion of each onsite dialysis session. Procedure for assessment of time to hemostasis will be provided in the Operations Manual. Baseline time to hemostasis will be established by the assessments performed during the screening period (mean of two assessments at Screening 1 and 2).

8.3.4 Height and Weight

Height and weight will be measured and recorded. Hight and body weight will be obtained with the participant's shoes off and jacket or coat removed.

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.

Dry weight (body weight after HD or HDF) should be used for BMI calculations.

8.3.5 Resting Vital Signs

Blood Pressure and Pulse Rate

BP and PR measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. The correct size of the BP cuff and the correct positioning on the participant is essential to increase the accuracy of BP measurements.

Participants should be resting in a semi-recumbent or supine position for at least 10 minutes prior to having BP and PR measurements obtained. The same position must be used for all measurements for each individual participant.

The predose (baseline) BP and PR will be triplicate measurements, obtained at least 1 to 2 minutes apart within 3 hours of dosing MK-2060/placebo. The median of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). Screening and postdose BP and PR measurements will be single measurements.

Respiratory Rate and Body Temperature

RR and body temperature will be single measurement per timepoint at all timepoints. The same method must be used for all measurements for each individual participant.

8.3.6 Electrocardiograms

Twelve (12)-lead ECG will be obtained and reviewed by an investigator or medically qualified designee as outlined in the SoA. The HR will be calculated and PR, QRS, QT, and QTc intervals will be measured, and then these will be recorded. The correction formula to be used for QTc is Fridericia.

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. Participants assigned female sex at birth may need to remove interfering garments.

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.

Participants should be resting in the semi-recumbent or supine position for at least 10 minutes before each ECG measurement. The same position must be used for all measurements for each individual participant.

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

8.3.7 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 150 days after the dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.8 Photograph of Rash

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

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

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an 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 164 days after cessation of intervention, all AEs, SAEs and other reportable safety events must be reported by the investigator.

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

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 5.

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

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

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

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Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period	Reporting Time Period: After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
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 towards the safety of participants and the safety of a study intervention under clinical investigation are met.

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

Information in this section is not applicable since participants are participants capable of producing ejaculate whose partner's pregnancy/lactation information is not required.

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

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

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

8.5 Treatment of Overdose

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

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 samples collected will be measured for evaluation of PK or PK-Pharmacodynamics will be collaboratively determined by the Sponsor. If indicated, these samples may also be measured and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers. Blood samples collected may be stored and further analysis may be performed, if required.

8.6.1 Blood Collection for Plasma MK-2060 and ADA

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

8.7 Pharmacodynamics

Sample collection, storage, and shipment instructions for PD samples (aPTT/PT/FXI activity) will be provided in the Study Operations Manual. They will be performed at a central vendor for PD. The PD data for statistical analysis and potential modeling work will be based on the information from the central vendor for PD. Blood samples collected may be stored and further analysis may be performed, if required.

aPTT and PT at screening, predose, and postdose specified in the SoA will be performed by the central laboratory for safety to monitor safety as defined in Section 8.3.7.

8.8 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research 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.

The planned genetic analysis sample should be obtained predose on Day 1 but may be collected at the next scheduled blood draw, if needed. Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the Operations/Laboratory Manual.

8.9 Future Biomedical Research Sample Collection

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

- Leftover DNA for future research

8.10 Medical Resource Utilization and Health Economics

Medical Resource Utilization and 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

Before intervention randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

Screening 1 should occur within 28 days prior to intervention randomization. Screening 2 should occur within 5 to 8 days prior to intervention randomization. Screening 2 should occur after review of all data from Screening 1. Dialysis should be done at Screenings 1 and 2.

Participants may be rescreened after consultation with the Sponsor. Rescreening should include all screening procedures (except for blood collection for FSH if a postmenopausal state was confirmed by FSH test) listed in the SoA, including consent review. Rescreen procedures cannot be conducted the day prior to intervention randomization.

8.11.2 Treatment Period

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

8.11.3 Poststudy

Participants will be required to return to clinic 150 (±7) days after the dose of study intervention for the poststudy visit.

8.11.4 Phone Call Follow-up

A phone call follow-up or on-site follow-up (dialysis day) will be performed 164 (±7) days after the dose of study intervention. The follow-up will facilitate the collection of relevant safety information. The participants will be interviewed to obtained information relating to AEs and SAEs since the poststudy clinic visit. All safety information described by the participants must be documented in the source documents and be reviewed by the investigator.

If the follow-up occurs less than 164 days after the dose of study intervention, a subsequent follow-up should be made at 164 (+7) days post the dose of study intervention to determine if any AEs have occurred since 1st follow-up.

If the initial call is unsuccessful, the study site staff should make a total of 3 attempts. All attempts to contact the subjects will be recorded in the source documents.

8.11.5 Critical Procedures Based on Study Objectives: Timing of Procedure

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

At any postdose 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.

- Blood collection for PK, PD, ADA, laboratory safety tests, including aPTT/PT, and genetic analysis as outlined in Table 6.

Table 6 Blood Collection Windows

Collection Time	Collection Window
Predose	Within 3 hrs prior to the initiation of dialysis
1 hr	Immediately prior to the end of IV infusion (i.e. no more than 5 min before anticipated time of the end of IV infusion)
12 hrs	±15 min
24 hrs	±1 hr
48 hrs	± 1 hr and prior to the initiation of dialysis
52 hrs	Post dialysis
96 hrs	± 2 hrs and prior to the initiation of dialysis. If this prescribed time is not dialysis day, +1 day and prior to the initiation of dialysis.
168 hrs	± 2 hrs and prior to the initiation of dialysis. Blood samples for PK and PD will be also collected at post dialysis.
Day 12	±1 day and within 12 hrs prior to the initiation of dialysis
Days 15 and 22	±2 days and within 12 hrs prior to the initiation of dialysis
Day 29	±3 days and within 12 hrs prior to the initiation of dialysis. Blood samples for PK and PD will be also collected at post dialysis.
Days 60 and 90	±5 days and within 12 hrs prior to the initiation of dialysis
Day 120	±7 days and within 12 hrs prior to the initiation of dialysis. Blood samples for PK and PD will be also collected at post dialysis.
Day 150	±7 days and within 12 hrs prior to the initiation of dialysis

- Safety evaluations for PE, systemic infusion reaction assessment, VS and 12-lead ECG as outlined in Table 7.

Table 7 Safety Evaluations Windows

Evaluation Time	Evaluation Window
Predose	Within 3 hrs prior to the initiation of dialysis
15 and 30 min 1 and 2 hrs	±15 min
3.5 hrs	±15 min
8 hrs	±15 min
12 hrs	±30 min
24 hrs	±1 hr
48 hrs	± 2 hrs and prior to the initiation of dialysis
96 hrs	± 2 hrs and prior to the initiation of dialysis. If this prescribed time is not dialysis day, +1 day and prior to the initiation of dialysis.
168 hrs	± 2 hrs and prior to the initiation of dialysis
Day 12	±1 day and within 12 hrs prior to the initiation of dialysis
Days 15 and 22	±2 days and within 12 hrs prior to the initiation of dialysis
Day 29	±3 days and within 12 hrs prior to the initiation of dialysis
Days 60 and 90	±5 days and within 12 hrs prior to the initiation of dialysis
Days 120 and 150	±7 days and within 12 hrs prior to the initiation of dialysis

- Assessment of time to adequate hemostasis: After dialysis catheters are removed from the dialysis access site.

- Hemoccult Test: within 2 days of specified timepoint.

8.11.6 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.

- Addition of PK pause

- Instructions to take study intervention with or without food or drink may 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 (eg, to obtain data closer to the time of peak plasma concentrations). If indicated, these collected samples may also be assayed in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

Up to additional 50 mL of blood may be drawn for safety, 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, vital signs, ECG, safety laboratory tests, etc) may be modified during the study based on newly available data. Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information. These changes will not increase the number of study procedures for a given participant during his/her participation in the entire study.

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

9 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

This section contains a summary of the statistical analyses for this trial. Full detail can be found in the subsequent sections.

Safety

AEs will be tabulated by treatment group. Summary statistics and plots will be generated for raw laboratory safety tests, ECGs, and vital sign 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).

Pharmacokinetics

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

Pharmacodynamics

Individual aPTT fold-change from baseline values will be natural log-transformed and evaluated with a linear mixed effect model containing fixed effects for treatment, time and treatment by time interaction and random effect for participant. Least squares means and 95% confidence intervals for each treatment, and for the between-treatment difference (MK-2060-placebo) and 90% CI at each dose level, will be obtained by time. These estimates will be back-transformed to obtain GM aPTT fold-change from baseline by treatment time and the GMR (MK-2060 fold-change from baseline/placebo fold-change from baseline) by dose and time.

The proportion of participants with a fold-increase in aPTT 168 hours after a single dose of at least 1.5 will be tabulated.

Sample Size and Power Calculations

The total participants of approximately 16 (MK-2060=approximately CCI placebo=approximately CC is considered to be adequate to address the primary objective of the study.

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 Clinical Biostatistics 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 the Section 3.

9.4 Analysis Endpoints

Primary Endpoints

1. AEs

Secondary Endpoints

1. Pharmacokinetics: Plasma AUC0-inf, AUC0-last, AUC0-168, Cmax, C168, Tmax, Tlast, t1/2, CL and Vz

2. Pharmacodynamics: aPTT (fold change from baseline)

Exploratory Endpoints

1. Factor XI activity (fold change from baseline)
2. Prothrombin time (fold change from baseline)
3. Time to hemostasis
4. ADA

For change from baseline, the baseline is defined as the panel-specific pre-dose value.

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 (APaT): 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.

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 major protocol deviations. Major protocol deviations will be identified to the extent possible prior to unblinding by individuals responsible for data collection, 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. This population will be used for the PK and PD analyses.

9.6 Statistical Methods

Safety

AEs will be tabulated by treatment. Summary statistics and plots will be generated for raw laboratory safety tests, ECGs, and vital sign 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).

Pharmacokinetics

Values will be listed for each PK parameter 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 x standard

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

Pharmacodynamics

Individual aPTT fold-change from baseline values will be natural log-transformed and evaluated with a linear mixed effect model containing fixed effects for treatment, time and treatment by time interaction and random effect for participant. Least squares means and 95% confidence intervals for each treatment, and for the between-treatment difference (MK-2060-placebo) and 90% CI at each dose level, will be obtained by time. These estimates will be back-transformed to obtain GM aPTT fold-change from baseline by treatment time and the GMR (MK-2060 fold-change from baseline/placebo fold-change from baseline) by dose and time.

The proportion of participants with a fold-increase in aPTT 168 hours after a single dose of at least CCI will be tabulated.

Summary statistics will be provided for PD endpoints by time.

The relationship between plasma concentrations and aPTT, FXI activity, and PT may be explored graphically.

ADA

The number of participants with positive / negative antibody drug response to antibodies to MK-2060 will be summarized. Frequency counts for the maximum antibody titer for participants classified as positive will also be reported.

9.7 Interim Analyses

No formal interim analysis is planned.

9.8 Multiplicity

Since there are no pre-specified hypotheses, no adjustments for multiplicity are needed.

9.9 Sample Size and Power Calculations

The total participants of approximately 16 (MK-2060=approximately CCI, placebo=approximately CCI is considered to be adequate to address the primary objective of the study.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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 Publication Policy

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

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

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

10.1.5 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.6 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

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.

10.1.7 Data Quality Assurance

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

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

Confidential

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

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

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

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

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

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

10.1.8 Source Documents

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

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

10.1.9 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 8 will be performed by the central laboratory for safety tests.
- Local laboratory results are only required in the event that the central laboratory for safety results is not available in time for study intervention administration. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make a study intervention decision, the results must be entered into the CRF.
- 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 8 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 and direct bilirubin
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose (fasting)	Calcium	Alkaline phosphatase	
Other	• aPTT and PT • CCI [redacted] • Hemoccult Test			
Other Screening Tests	• FSH (as needed) • Saliva drug screen • Serology (HIV antigen and antibody, hepatitis B surface antigen, and hepatitis C virus antibody) • All study-required laboratory assessments will be performed by a central laboratory for safety, with the exception of saliva drug screen.			
Note: Before blood drawing for glucose, participants will fast from all food and drinks, except water and non-caffeinated tea, for at least 8 hours.				

The investigator must document their review of each laboratory safety report.

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

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

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

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

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

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

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

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

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

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

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

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

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

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

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

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

a. Participants for Enrollment

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

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

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

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

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

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

5. Biorepository Specimen Usage[3, 4]

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

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

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

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

7. Retention of Specimens[3, 4]

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

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

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

8. Data Security[3, 4]

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

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

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

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

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

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

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

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

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

12. Questions

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

13. References

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

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

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

10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: Blood Volume Table

	Prestudy	Treatment Periods	Poststudy	Total Collections	mL Per Collection	Total mL/ Test
Safety:						
Hematology and Chemistry	2	9	1	12	9.0	108.0
aPTT and PT	1	9		10	1.8	18.0
CCI		1		1	2.0	2.0
HIV, hepatitis B and C screen	1			1	5.0	5.0
FSH	2			2	2.0	4.0
PK/PD/Biomarker						
Blood for Plasma MK-2060 PK and ADA assay		7	1	8	2.7	21.6
Blood for Plasma MK-2060 PK assay only		11		11	1.8	19.8
Blood for aPTT/PT/FXI activity		18	1	19	8.1	153.9
Blood for Planned Genetic Analysis		1		1	8.5	8.5
Total Blood Volume per Participant [a]						336.8
Total Blood Volume per Participant (including FSH) [a]						340.8

[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: Abbreviations

Abbreviation	Expanded Term
ADA	anti-drug antibodies
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
α-GI	α-Glucosidase Inhibitor
ALT	alanine aminotransferase
APaT	All Participants as Treated
aPTT	activated partial thromboplastin time
ASO	anti-sense oligo
AST	aspartate aminotransferase
ATIII	antithrombin III
AUC	area under the plasma concentration-time curve
AUC0-168	area under the plasma concentration-time curve from time 0 to 168 hours post-dose
AUC0-inf	area under the plasma concentration-time curve from time 0 to infinity
AUC0-last	area under the plasma concentration-time curve from time 0 to the time of the last measurable concentration
AV	arteriovenous
AxMP	auxiliary medicinal product
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
C168	plasma concentration at 168 hours post-dose
CFR	Code of Federal Regulations
Cmax	maximum plasma concentration
CL	clearance
COVID-19	Coronavirus disease caused by sever acute respiratory syndrome coronavirus 2
CRF	Case Report Form
CCI [redacted]	[redacted]
CRU	clinical research unit
CSR	clinical study report
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DPP-4	Dipeptidyl Peptidase-4
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
EEA	European Economic Area
EMA	European Medicines Agency
ER	emergency room
ESRD	End-stage renal disease

Abbreviation	Expanded Term
FBR	future biomedical research
FDAAA	Food and Drug Administration Amendments Act
FDC	Fixed Dose Combination
FSH	follicle-stimulating hormone
FSR	First Site Ready
FXa	Factor Xa
FXI	Factor XI
FXIa	Factor XIa
GCP	Good Clinical Practice
GCV	geometric coefficient of variance
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
HD	hemodialysis
HDF	hemodiafiltration
HIF-PH	hypoxia-inducible factor prolyl-hydroxylase
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ID	identification
IEC	Independent Ethics Committee
IgG	immunoglobulin G
CCI	[redacted]
IMP	investigational medicinal product
IRB	Institutional Review Board
IV	intravenous
IVIG	intravenous immunoglobulin
mAb	monoclonal antibody
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
NCS	not clinically significant
NIMP	noninvestigational medicinal product
NSAID(s)	non-steroidal anti-inflammatory drug(s)
NOAEL	no observed adverse effect level
PD	pharmacodynamic(s)
PE	physical examination
PK	pharmacokinetic(s)
PP	per protocol
PR	pulse rate
PT	prothrombin time

Abbreviation	Expanded Term
QW	every week
QTc	QT corrected (corrected QT interval)
RBC	red blood cell
RhoGAM	a brand of Rh immunoglobulin
RNA	ribonucleic acid
RR	respiratory rate
SAD	single ascending dose
SAE	serious adverse event
SC	subcutaneous (ly)
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SLAB	supplemental laboratory test(s)
SMi	small molecular inhibitor
SoA	schedule of activities
spKt/V	single-pool Kt/V
SUSAR	suspected unexpected serious adverse reaction
Tinf	time at the end of infusion
Tlast	time of last measurable concentration
Tmax	time to maximum observed plasma concentration
t1/2	half life
ULN	upper limit of normal
VS	vital signs
V side	Vein side
Vz	volume of distribution
WBC	white blood cell
PONCBP	participant/participants of nonchildbearing potential

Confidential

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