Official Protocol Title:	A Randomized Parallel-group, Placebo-controlled, Double-blind, Event-driven, Multi-center Phase 2 Clinical Outcome Trial of Prevention of Arteriovenous Graft Thrombosis and Safety of MK-2060 in Patients With End Stage Renal Disease Receiving Hemodialysis
NCT number:	NCT05027074
Document Date:	14-Dec-2022

Title Page

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Protocol Title: A Randomized Parallel-group, Placebo-controlled, Double-blind, Event-driven, Multi-center Phase 2 Clinical Outcome Trial of Prevention of Arteriovenous Graft Thrombosis and Safety of MK-2060 in Patients With End Stage Renal Disease Receiving Hemodialysis

Protocol Number: 007-04

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):

EudraCT	2020-002397-27
IND	142237

Approval Date: 14 December 2022

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 04	14-DEC-2022	To add a test of the efficacy hypothesis at the interim analysis and to reduce the study power.
Amendment 03	23-JUN-2022	Canada-specific amendment created to fulfill health authority request.
Amendment 02	06-APR-2022	Germany-specific amendment created to fulfill health authority request.
Amendment 01	08-MAR-2022	To update an inclusion criterion and provide sites with additional screening time to identify suitable participants for this study.
Original Protocol	12-JAN-2021	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 4

Overall Rationale for the Amendments:

To add a test of the efficacy hypothesis at the interim analysis and to reduce the study power.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.2 Schema 1.3 Schedule of Activities 4.1 Overall Design 4.4.1 Clinical Criteria for Early Study Termination 9.1 Statistical Analysis Plan Summary 9.6 Statistical Methods 9.7 Interim Analyses 9.8 Multiplicity 9.9.1 Efficacy 10.1.4.2 External DMC 10.8 Appendix 8: PK Substudy	Added a test of the efficacy hypothesis at the interim analysis.	To permit the study to stop early for efficacy.
9.9 Sample Size and Power Calculations	Reduced the study power to 80%.	To allow study completion within reasonable timelines due to slower than expected efficacy event accrual.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 3 Hypotheses, Objectives, and Endpoints 4.2.1.1 Efficacy Endpoints 9.4.1 Efficacy Endpoints 9.6.1.2 Secondary Efficacy Endpoints	Updated the secondary objective from 'reducing the number of AVG thrombosis events' to 'increasing the time to each AVG thrombosis event (first and recurrent)' and the statistical analysis.	The Andersen-Gill model will be used to analyze the time to each AVG thrombosis event (first and recurrent).
1.3 Schedule of Activities	Added reference to Section 6.4 Study Intervention Compliance.	Consultation between the investigator and Sponsor is required for study interruptions >4 consecutive doses.
	Added note for vital status assessment.	A participant's vital status should be assessed whenever in question.
	Added note for FSH assessment.	FSH is assessed to confirm postmenopausal status.
2.1 Study Rationale	Updated background on clinical trials for FXI inhibitors.	New clinical study data became available.
2.2.2 Preclinical and Clinical Studies	Updated description of Study P004.	Study P004 was completed.
2.3 Benefit/Risk Assessment	Updated section with data from the current Investigator's Brochure.	Study P004 was completed and new clinical study data became available.
3 Hypotheses, Objectives, and Endpoints	Updated the endpoints for evaluation of exposure-response or dose-response of MK-2060 QW for AVG thrombosis events.	To clarify that pharmacokinetic endpoints will be collected (steady state C_{max} and C_{trough})

Section # and Name	Description of Change	Brief Rationale
4.1 Overall Design 4.2.1.1 Efficacy Endpoints 9.6.2 Analysis Methods for Safety Analyses 10.1.4.3 Clinical Adjudication Committee	Death was added to the list of events needing adjudication.	To adjudicate all deaths, including deaths that are not captured within the secondary safety endpoint (ie, major bleed) or the exploratory efficacy endpoint (major thrombotic cardiovascular event).
4.1 Overall Design 9.6.1.1 Primary Efficacy Endpoint 9.6.2 Analysis Methods for Safety Analyses	Added statement regarding censoring kidney transplant events in the primary efficacy analysis and safety analyses.	To avoid including in the analysis events (both efficacy and safety) occurring in participants who underwent kidney transplant, which could confound the results.
4.3.1 Starting Dose for This Study	Removed paragraph related to ongoing Study P004	Study P004 was completed.
5.2 Exclusion Criteria	Exclusion criterion #7 was revised.	To clarify that regular use of aspirin in doses >150 mg per day is prohibited and to allow the use of periprocedural heparin, low-dose heparin for DVT prophylaxis while hospitalized, and topical NSAIDs.
6.5 Concomitant Therapy	Added aspirin in doses >150 mg per day to the list of prohibited medications.	
6.1 Study Intervention(s) Administered	Updated the NIMP definition to NIMP/AxMP	To align with EU CTR.
6.3.2 Stratification	Added note to clarify the 'aspirin use' stratification criterion.	'As needed' aspirin use is not included in the stratification criterion.

Section # and Name	Description of Change	Brief Rationale
6.4 Study Intervention Compliance	Revised the statement regarding the management of participants with study intervention interruptions.	To clarify which study intervention interruptions require consultation between the investigator and Sponsor.
7.1 Discontinuation of Study Intervention	Added discontinuation criterion for participants with prolonged study intervention interruptions and clarification for participant reloading.	To provide the option to maintain participants in the study after a prolonged study intervention interruption (>4 consecutive doses).
8.2 Efficacy Assessments	Revised statement regarding PRO questionnaire administration.	To clarify that the PRO questionnaires are administered by the interviewer (investigator or qualified designee).
8.11.6 Premature Discontinuation Visit	Added time frame for the Safety Follow-up Visit for discontinued participants who continue to be monitored in the trial.	To clarify the timing of the Safety Follow-up Visit.
Title Page Section 10.1.1 Code of Conduct for Clinical Trials Throughout Document	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Section 10.7 Appendix 7: Country-specific Requirements	Country-specific amendments for Germany and Canada were added to this global amendment. Changes are outlined in Section 10.7 and referenced in Sections 1.3 Schedule of Activities, 5.2 Exclusion Criteria, and 8.3.5.1 Serum Pregnancy Test.	To consolidate country-specific amendments 2 and 3.

Section # and Name	Description of Change	Brief Rationale
10.9 Appendix 9: Hemostasis	Added information related to an in vivo study of reversal of MK-2060-induced aPTT prolongation by transfusion of FFP in rhesus monkeys. Change is referenced in Section 6.5.2 Surgery Guidance.	To include additional data that may assist study investigators with the management of bleeding events.
Throughout Document	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Randomized Parallel-group, Placebo-controlled, Double-blind, Event-driven, Multi-center Phase 2 Clinical Outcome Trial of Prevention of Arteriovenous Graft Thrombosis and Safety of MK-2060 in Patients With End Stage Renal Disease Receiving Hemodialysis

Short Title: MK-2060 Global Study in Patients with End Stage Renal Disease Receiving Hemodialysis

Acronym: FXI Hemodialysis Study

Hypotheses, Objectives, and Endpoints:

In adult patients with ESRD receiving hemodialysis via an AVG:

Primary Objectives	Primary Endpoints
- Objective: To evaluate the efficacy of MK-2060 compared to placebo in increasing the time to first arteriovenous graft thrombosis event. Hypothesis: At least 1 of the MK-2060 doses is superior to placebo in increasing the time to first occurrence of arteriovenous graft thrombosis event	- Arteriovenous graft thrombosis events
Secondary Objectives	Secondary Endpoints
- Objective: To evaluate the efficacy of MK-2060 compared to placebo in increasing the time to each arteriovenous graft thrombosis event (first and recurrent).	- Arteriovenous graft thrombosis events
- Objective: To assess the safety and tolerability of MK-2060.	- Adverse events - Major bleeding events or clinically relevant non-major bleeding events (per International Society on Thrombosis and Haemostasis criteria) - Discontinuation of study intervention due to adverse event(s)

Overall Design:

Study Phase	Phase 2
Primary Purpose	Prevention
Indication	Prevention of arteriovenous graft thrombosis
Population	Patients with ESRD receiving hemodialysis via an arteriovenous graft
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Placebo
Study Blinding	Double-blind
Blinding Roles	Sponsor Investigator Care Provider Outcomes Assessor Participants or Subjects
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 20 months from the time the first participant is enrolled until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 489 participants will be randomized.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Intervention Group Name</th><th>Drug</th><th>Loading Dose Strength</th><th>Maintenance Dose Strength</th><th>Dose Frequency</th><th>Route of Adminis-tration</th><th>Regimen/ Treatment Period</th></tr>
<tr><td>MK-2060 High Dose</td><td>MK-2060</td><td>20 mg</td><td>20 mg</td><td>Loading dose – 1 dose, 3 times during Week 1 QOD.
Maintenance dose – 1 dose QW after Week 1</td><td>IV</td><td>Double-blind treatment period</td></tr>
<tr><td>MK-2060 Low Dose</td><td>MK-2060</td><td>6 mg</td><td>6 mg</td><td>Loading dose – 1 dose, 3 times during Week 1 QOD.
Maintenance dose – 1 dose QW after Week 1</td><td>IV</td><td>Double-blind treatment period</td></tr>
<tr><td>Placebo</td><td>Placebo</td><td>0 mg</td><td>0 mg</td><td>Loading dose – 1 dose, 3 times during Week 1 QOD.
Maintenance dose – 1 dose QW after Week 1</td><td>IV</td><td>Double-blind treatment period</td></tr>
<tr><td colspan="7">IV= intravenous; QOD= every other day; QW= once a week.
Note: Study intervention to be administered during routine hemodialysis sessions.</td></tr>
</table>
</td></tr>
<tr><td>Total Number of Intervention Groups/ Arms</td><td>3</td></tr>
<tr><td>Duration of Participation</td><td>This is an event-driven study expected to run for approximately 20 months from FPE until LPLV. After a screening period of up to 30 days, eligible participants will be treated with study intervention until full accrual of events, with an expected median treatment duration of 10 months. Participants will be monitored for safety events from the time of providing documented informed consent through the final contact, 3 months after the last treatment dose.</td></tr>
</table>

Study Governance Committees:

Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	Yes
Study governance considerations are outlined in Appendix 1.	

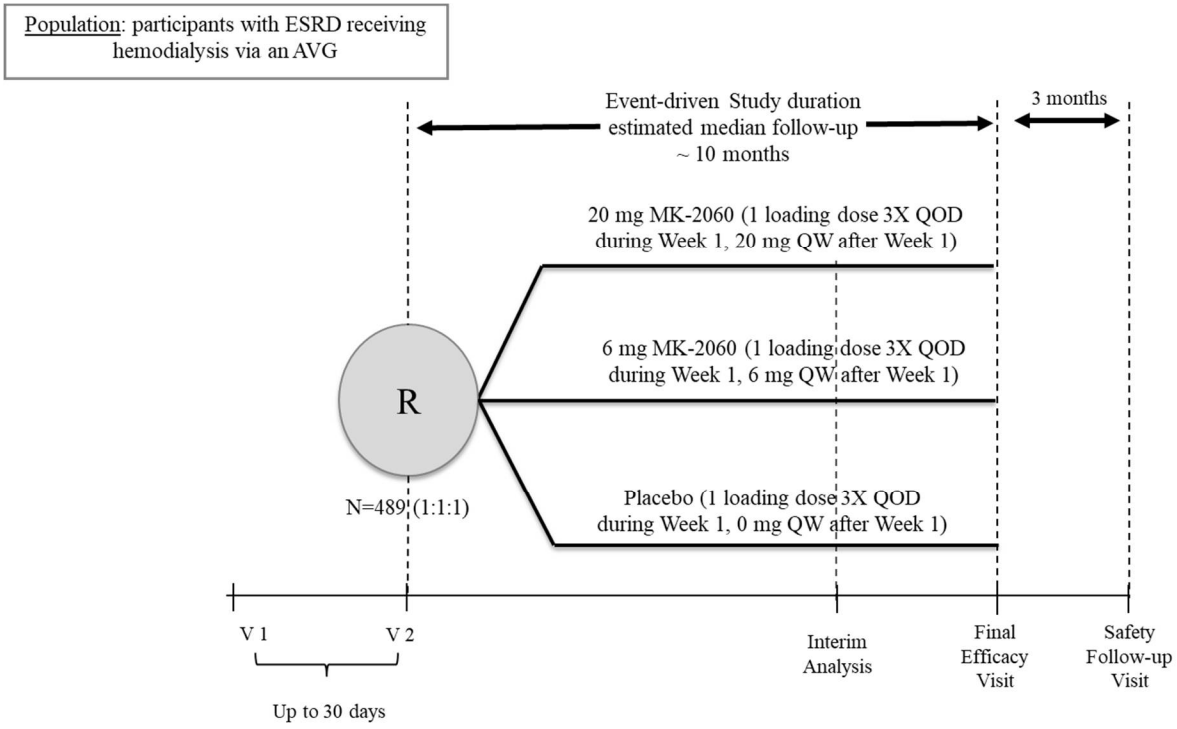
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 10.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



AVG= arteriovenous graft; ESRD= end-stage renal disease; FP= first patient; LPLV= last patient last visit; QOD= every other day; QW= once a week; R= randomization; V= visit.

Note: FP randomized to LPLV will be approximately 20 months.

1.3 Schedule of Activities

Study Period	Screening		Treatment Period										Premature Intervention Discontinuation				Notes
Visit Number/Title	1 Screen	2 Rand	3	4	5	6	7	8	9	Visit n	Final Efficacy Visit	Safety Follow-up Visit	Premature Discon. Visit	Safety Follow-up Visit	Visit n	Final Efficacy Visit	
Scheduled Days/Month	Day -30 to Day 1	Day 1	Day 3	Day 5	Day 8	Day 15	Day 29	Day 57	Day 85	Every 3 months	Based on Efficacy Cutoff date[a]	3 months after Final Efficacy Visit	Study Intervention Discon.	3 months after Discon.	Every 3 months	Based on Efficacy Cutoff date[a]	
Visit Window			±1 day	±1 day	±1 day	±3 days	±3 days	±5 days	±7 days	±7 days		±7 days	±7 days	±7 days	±7 days		Refer to Section 6.4.
Administrative Procedures																	
Informed Consent	X																
Informed Consent for Future Biomedical Research	X																
Informed Consent for PK Substudy	X																
Informed Consent for QoL Questionnaires	X																At preselected sites
Inclusion/ Exclusion Criteria	X	X															
Participant Identification Card	X	X															Add randomization number to card on Day 1
Medical History	X																
Identification of External Contact Person	X																For vital status assessment
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Treatment/ Randomization Number		X															
Study intervention Administration		X	X	X	X	Following first 3 loading doses, study intervention to be administered weekly during regularly scheduled hemodialysis sessions											See Section 8.1.8 for details.

Study Period	Screening		Treatment Period										Premature Intervention Discontinuation				Notes
Visit Number/Title	1 Screen	2 Rand	3	4	5	6	7	8	9	Visit n	Final Efficacy Visit	Safety Follow-up Visit	Premature Discon. Visit	Safety Follow-up Visit	Visit n	Final Efficacy Visit	
Scheduled Days/Month	Day -30 to Day 1	Day 1	Day 3	Day 5	Day 8	Day 15	Day 29	Day 57	Day 85	Every 3 months	Based on Efficacy Cutoff date[a]	3 months after Final Efficacy Visit	Study Intervention Discon.	3 months after Discon.	Every 3 months	Based on Efficacy Cutoff date[a]	
Visit Window			±1 day	±1 day	±1 day	±3 days	±3 days	±5 days	±7 days	±7 days		±7 days	±7 days	±7 days	±7 days		Refer to Section 6.4.
Clinical Procedures/Assessments																	
Full Physical Examination	X										X		X			X	
Systemic Infusion Reaction Assessment		X	X	X													Any infusion reaction must be reported as an AE
Height	X																
Weight	X	X			X	X	X	X	X	X	X	X	X	X	X	X	Post-dialysis
Directed Physical Examination		X				X	X		X	X							
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Pre-dialysis. BP and HR to be measured in triplicate.
12-lead ECG	X										X		X			X	
Clinical Events Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Collection of events for selected endpoints
Vital Status Assessment			X	X	X	X	X	X	X	X	X	X	X	X	X	X	Assessed whenever participant's vital status is in question.
AE/SAE Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Participants should be trained to contact the site to report AEs as soon as they occur
KDQOL-SF & EQ-5D-5L Questionnaires		X								X	X		X				At preselected sites every 6 months
Central Laboratory Assessments																	
Serum FSH – (WOCBP only)	X	X[b]															To confirm postmenopausal status.
Pregnancy test (Serum) in WOCBP	X[c]						X	X	X	X			X				Germany-specific requirements are in Appendix 7

Study Period	Screening		Treatment Period										Premature Intervention Discontinuation				Notes
Visit Number/Title	1 Screen	2 Rand	3	4	5	6	7	8	9	Visit n	Final Efficacy Visit	Safety Follow-up Visit	Premature Discon. Visit	Safety Follow-up Visit	Visit n	Final Efficacy Visit	
Scheduled Days/Month	Day -30 to Day 1	Day 1	Day 3	Day 5	Day 8	Day 15	Day 29	Day 57	Day 85	Every 3 months	Based on Efficacy Cutoff date[a]	3 months after Final Efficacy Visit	Study Intervention Discon.	3 months after Discon.	Every 3 months	Based on Efficacy Cutoff date[a]	
Visit Window			±1 day	±1 day	±1 day	±3 days	±3 days	±5 days	±7 days	±7 days		±7 days	±7 days	±7 days	±7 days		Refer to Section 6.4.
Coagulation (INR, PT, aPTT)	X																To be collected separate from hematology laboratory tests
Hematology	X	X	X	X	X	X	X	X	X	X	X		X			X	
Liver Function Tests		X			X	X	X	X	X	X	X		X			X	
Chemistry		X			X	X	X	X	X	X	X		X			X	
Pharmacokinetics/Immunogenicity/Pharmacodynamics/ Biomarkers																	
Blood for PK evaluation		X[d]			X[e]	X[e]	X[e]		X[d]	X[e]	X[e]		X[e]				Record date and time of collection. To be collected for all participants in main study.
Blood for ADA		X					X		X	X	X		X				Collect pre-dialysis
Blood for PT/aPTT/FXI Activity		X			X	X	X	X	X	X	X		X				Collect predose (Sections 8.8 and 8.10)
Blood for Genetic Analysis		X															Collect predose from enrolled participants only

ADA= anti-drug antibodies; AE= adverse event; aPTT= activated partial thromboplastin time; BP= blood pressure; Discon= discontinuation; ECG= electrocardiogram; EQ-5D-5L= Euro quality of life 5-dimensional, 5-level questionnaire; FSH= follicle stimulating hormone; FXI= factor XI; KDQOL-SF= kidney disease quality of life questionnaire-short form; PK= pharmacokinetics; QoL= quality of life; SAE= serious adverse event; WOCBP= women of childbearing potential.
Visit n= Starting from Visit 9 (Day 85) all subsequent visits will be scheduled every 3 months until study completion is reached.
a. Efficacy Cutoff will be declared when the required number of events has accrued for the primary efficacy endpoint (see Section 9.7). If the study stops at IA, the Final Efficacy Visits will be scheduled to occur within 14 days of Sponsor's notification to stop the study. If the study continues, the Final Efficacy Visits will be scheduled to occur in the 14 days following the Final Analysis efficacy cutoff date.
b. All WOCBP will have an FSH test at Visit 1. Serum FSH at Visit 2 is only required for participants who have less than 1 year of amenorrhea.
c. A pregnancy test must be performed at Visit 1. In addition, 1 pregnancy test must be performed within 6 days before the first dose of study intervention (see Section 5.1).
d. Trough and peak sample collection. Trough sample to be collected pre-dialysis **before any IV heparin is administered to the participant**. Peak sample to be collected approximately 30 minutes **after** infusion ends. If dosing and drawing is from the same access point, flush the access point with saline before sample collection. Record the time samples were drawn, time infusion was started, and time the infusion ended.
e. Trough sample collection only. To be collected pre-dialysis (**before any IV heparin is administered to the participant**). Record the time the sample was drawn and the time infusion was started.

Note: For sites participating in the PK substudy, see Table 10 – PK Substudy Schedule of Activities.

2 INTRODUCTION

2.1 Study Rationale

The purpose of this study is to evaluate the efficacy and safety of MK-2060 in ESRD participants receiving hemodialysis via an AVG. Data from this study will be used to aid dose selection of MK-2060 in future studies with the ultimate goal of proving MK-2060 effective in preventing major thrombotic cardiovascular events in individuals with ESRD.

ESRD patients, specifically those on hemodialysis, carry an elevated risk for thrombotic events with associated morbidity and mortality. The relative risk in dialysis patients compared to the general population is >5 fold for MI, ~6 fold for ischemic stroke, and ~2.2-fold for VTE [Tveit, D. P., et al 2002] [Casserly, L. F. 2003] [Winkelmayer, W. C., et al 2011] [Reinecke, H., et al 2009]. This tendency to thrombosis is particularly problematic for ESRD patients receiving hemodialysis via an AVG. Successful hemodialysis relies on brisk blood flow through the AVG. AVGs are prone to developing thrombi, which often lead to AVG failure, with annual rates of AVG failure from thrombosis of >50% [Miller, P. E., et al 2000]. While ESRD patients have a substantial need to reduce the risk of thrombotic events, doing so with anticoagulants is met with the challenges that these patients have an increased risk of clinically important bleeding due to uremia-related platelet dysfunction, concurrent use of antiplatelet agents, and the uncertainty in dose adjustment of anticoagulants in ESRD patients. These factors make the therapeutic window for many of these patients unfeasibly small with conventional anticoagulants [Lau, Y. C., et al 2016]. As a result, warfarin is generally avoided in ESRD due to its complex management and risk of bleeding in this setting. DOACs such as FXa inhibitors are not included in guideline recommendations for ESRD due to their reliance on renal clearance and a lack of clinical data. There exists significant unmet need in preventing thrombotic vascular events in ESRD patients and a demand for novel therapies.

Targeting activity of FXI is a novel approach in anticoagulation. FXI is a key component in the intrinsic pathway, activated by circulating thrombin, which in turn leads to greater thrombin production and amplification of clot formation. Congenital loss of activity of FXI (hemophilia C) leads to reduction in lifetime risk of thrombosis and cardiovascular events but is associated with only minimal disruption of hemostasis [Preis, M., et al 2017]. Pharmacologic efforts to suppress FXI production or activity, for example using antisense oligonucleotides, mAb, or small molecule inhibitors, have demonstrated successful reduction of clot formation with minimal bleeding effects and suggest FXI is a highly desirable pharmacological target [Buller, H. R., et al 2015] [Weitz, J. I., et al 2020] [Verhamme, P., et al 2021] [Weitz, J. I., et al 2021] [Nopp, S., et al 2022]. MK-2060 is a human anti-FXI mAb that inhibits FXI activation of FXIa. Targeting FXI inhibition with MK-2060 may achieve effective anticoagulation for ESRD patients without a prohibitive increase in bleeding events.

The Phase 2 study aims to demonstrate MK-2060 is an effective anticoagulant in ESRD patients receiving hemodialysis via an AVG. Selecting only ESRD patients with AVGs and focusing on AVG thrombosis events allows rapid assessment of the anticoagulant properties of MK-2060 relative to placebo due to the high frequency of these events while at the same

time providing an estimate of the bleeding risk associated with FXIa inhibition from MK-2060.

2.2 Background

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

2.2.1 Pharmaceutical and Therapeutic Background

Factor XI is a critical component in the intrinsic pathway of the coagulation cascade. MK-2060 is an anti-FXI mAb being developed for the prevention of thrombotic complications in ESRD. MK-2060 acts by preventing activation of FXI and blocking FXIa. Based on preclinical and human genetic data, as well as emerging clinical data from other groups using either an antisense oligonucleotide or a mAb approach, inhibiting FXI activity leads to a clinically relevant antithrombotic effect with minimal risk of bleeding complications and hence is expected to have an expanded therapeutic index compared to inhibition of more downstream clotting factors such as FXa and thrombin [Buller, H. R., et al 2015] [Bethune, C., et al 2017]. Therefore, FXIa inhibition is a promising therapeutic approach for the prevention of thromboembolic complications.

2.2.2 Preclinical and Clinical Studies

Preclinical studies

The antithrombotic efficacy of MK-2060 was assessed in cynomolgus monkeys using an AV shunt model of thrombosis developed and validated at MSD [Wickham, L. A., et al 2016] with reduction in thrombus weight upon treatments with CCI [redacted] MK-2060. In cardiac telemetry studies, MK-2060 was administered SC at a single dose of 60 mg/kg to conscious, adult, male, telemetered rhesus monkeys. There were no effects on ECG intervals (PR, QRS, QT, and QTci), arterial BP parameters (SBP, DBP, and mean BP), and HR at 60-mg/kg SC dose. Based on the absence of findings from this cardiac telemetry study, the NOEL for cardiovascular effects after a single SC dose in rhesus monkeys was ≥60 mg/kg MK-2060.

MK-2060 was assessed in rhesus monkeys in a repeat-dose 2-week (3 doses per week) toxicity study, a repeat-dose 4-week (1 dose every week in SWs 1 to 3 SC and 1 dose in SW 4 IV) toxicity study with an 8-week treatment-free period, and a repeat-dose 6-month (QW SC) toxicity study with a 3-month treatment-free period. An exploratory toxicity and toxicokinetic study in nonpregnant rabbits was also conducted. MK-2060 effects on embryo-fetal development were evaluated in a rabbit pEFD study. All animals survived to scheduled termination. There were no test article-related organ weight changes, gross observations, or histomorphologic findings at the final (end of dosing) necropsy or recovery (end of treatment-free period) necropsy.

Clinical Studies

Study MK-2060-P001

Study MK-2060-P001 was a double-blind, randomized, placebo-controlled, single site, sequential panel study to evaluate the safety, tolerability, PK, and PD of single ascending dose administration of SC and IV doses of MK-2060 in healthy male participants. Forty-five healthy male participants received single doses of MK-2060 up to 120 mg administered SC (27 participants) or 40 mg IV (18 participants). MK-2060 was generally well tolerated and there were no SAEs or discontinuations due to AEs. In healthy male participants single IV doses of 20 mg and 40 mg of MK-2060 resulted in increases in [redacted] for 120 hours. Refer to the IB for a detailed overview of the study, and available PK, PD, and safety results.

Study MK-2060-P004

Study MK-2060-004 was a double-blind, randomized, placebo-controlled, multiple-site, sequential panel study to evaluate the safety, tolerability, PK, and PD of single (Part 1) and multiple (Part 2) doses of IV administration of MK-2060 in older adult participants (age ≥40 and ≤80; men and WONCBP) with ESRD on hemodialysis. The study had 2 parts: Part 1 assessed single ascending IV doses (8 mg, 20 mg, and 40 mg). In each of the 3 panels in Part 1, Panels A-C, 8 participants were randomized to receive a single dose of MK-2060 or placebo in a treatment ratio of 3:1 (6 active and 2 placebo). Part 2 followed Part 1 and assessed multiple doses in older participants with ESRD on hemodialysis (n=21; 16 active and 5 placebo). MK-2060 was generally well tolerated. No deaths or SAEs considered related to MK-2060 by the investigator were reported, and no participant discontinued due to an AE considered related to MK-2060 by the investigator. There were no AEs suggestive of hypersensitivity.

Across Part 1 and Part 2 of the study, apart from mechanism-based aPTT increases, there were no clinically significant changes from baseline for ECGs, safety laboratory tests, and no changes in hematology laboratory tests suggestive of bleeding. Similarly, an exploratory assessment of time to vascular access site hemostasis after removal of the hemodialysis needles remained unchanged from baseline.

Based on mean concentration-time profiles, MK-2060 showed a biphasic terminal phase in participants with ESRD, with an apparent median observed T_{max} of approximately 1 hour at end of infusion, which was consistent across dose levels in Parts 1 and 2. After single-dose administration in participants with ESRD, $t_{1/2}$ ranged from approximately 14 days (8 mg MK-2060 IV) to approximately 21 days (40 mg MK-2060 IV), compared to ≥30 days in healthy participants. Exposure ($AUC_{0\text{-}inf}$ and C_{max}) after single IV administration of 8 mg MK-2060 in participants with ESRD was comparable to that in healthy participants while exposure after single IV administration of 20 mg or 40 mg MK-2060 in participants with ESRD was slightly lower than that in healthy participants due to higher clearance. After multiple dose administrations in participants with ESRD, observed CL (0.0171 L/h) was consistent with that observed after single doses of 20 mg and 40 mg MK-2060 and slightly

higher than that after single doses of 8 mg MK-2060; $t_{1/2}$ was approximately 19 days, which was consistent with that after single doses. In participants with ESRD, observed PK concentration profiles after multiple IV MK-2060 doses were consistent with projected PK concentrations after single IV MK-2060 doses, suggesting that the PK of IV MK-2060 is not time-dependent in patients with ESRD.

After single-dose administration in participants with ESRD, the mean observed aPTT fold-change (relative to baseline) at 168 hours increased with higher doses and the mean observed FXI activity fold-change (relative to baseline) at 168 hours showed dose-dependent decreases. aPTT values returned to near-baseline at Day 22 and FXI activity values returned to near-baseline at Day 29. After multiple dose administrations of 25 mg MK-2060 in participants with ESRD, the mean observed CCI CCI mean observed CCI CCI CCI

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

In clinical studies to date, FXI inhibitors have generally been demonstrated to be well tolerated, with a low bleeding risk [Piccini, J. P., et al 2022] [Shoamanesh, A., et al 2022] [European Society of Cardiology 2022] (see Section 2.1).

In 2 completed Phase 1 studies, 80 participants received MK-2060. No deaths or SAEs considered related to MK-2060 by the investigator have been reported, and no participant has discontinued from the studies due to an AE considered related to MK-2060 by the investigator. No dose-dependent patterns of drug-related AEs, or clinically meaningful trends in laboratory values (chemistry, hematology, urinalysis) apart from mechanism-based aPTT increases, physical examination, VS, or ECG safety parameter values have been observed as a function of treatment. There were no AEs suggestive of hypersensitivity. Safety-related study stopping rules have not been triggered.

The high dose of MK-2060 (20 mg) selected for Phase 2 is predicted to provide effective anticoagulation in ESRD participants. In general, anticoagulants have been associated with increased rates of bleeding events though the degree of anticoagulation provided by a specific class of anticoagulant is not related to its bleeding risk. Completed preclinical and clinical studies have not identified an increase in bleeding events with MK-2060, though preclinical and Phase 1 studies have demonstrated a dose-dependent prolongation of aPTT with MK-2060 treatment. With a prolonged aPTT there is a theoretical increase in risk of bleeding events, however there is little empirical evidence for a direct correlation between pharmacological prolongation of aPTT and bleeding risk [Thachil, J. 2014]. Hemophilia C patients (FXI deficiency) also have a prolonged aPTT with minimal disruption in hemostasis outside major surgeries.

Medical monitoring by the Sponsor including blinded assessment for safety signals will occur throughout the study to ensure appropriate safety reporting and identification of early safety signals. Unblinded safety monitoring during the study will be performed by an external DMC at routine intervals, in addition to an efficacy and futility assessment at the IA. This will allow for ongoing benefit/risk assessment throughout the study (Section 9.7, and Section 10.1.4).

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

In adult patients with ESRD receiving hemodialysis via an AVG:

Objectives	Endpoints
Primary	
• Objective: To evaluate the efficacy of MK-2060 compared to placebo in increasing the time to first arteriovenous graft thrombosis event. Hypothesis: At least 1 of the MK-2060 doses is superior to placebo in increasing the time to first occurrence of arteriovenous graft thrombosis event	• Arteriovenous graft thrombosis events
Secondary	
• Objective: To evaluate the efficacy of MK-2060 compared to placebo in increasing the time to each arteriovenous graft thrombosis event (first and recurrent).	• Arteriovenous graft thrombosis events
• Objective: To assess the safety and tolerability of MK-2060.	• Adverse events • Major bleeding events or clinically relevant non-major bleeding events (per International Society on Thrombosis and Haemostasis criteria) • Discontinuation of study intervention due to adverse event(s)

Objectives	Endpoints
Tertiary/Exploratory	
CCI [redacted]	
• Objective: To evaluate the pharmacokinetics and pharmacokinetic-pharmacodynamic relationship of MK-2060.	• Pharmacokinetics ○ Steady state C_{max} and C_{trough} • Pharmacodynamics ○ aPTT
• Objective: To evaluate anti-drug antibodies to MK-2060 during treatment with study intervention	• Anti-drug antibodies to MK-2060
• Objective: To evaluate exposure-response or dose-response of MK-2060 QW for arteriovenous graft thrombosis events.	• Pharmacokinetics ○ Steady state C_{max} and C_{trough} • Arteriovenous graft thrombosis events
• Objective: To evaluate the effect of MK-2060 versus placebo on patient-reported health-related quality of life using the Kidney Disease Quality of Life Questionnaire-Short Form	• Scale scores as measured by the Kidney Disease Quality of Life Questionnaire-Short Form
• Objective: To evaluate changes in the Visual Analog Scale and characterize health utilities using the EuroQoL 5-Dimensional, 5-level questionnaire	• Visual Analog Scale scores as measured by the EuroQoL 5-Dimensional, 5-level questionnaire • Health utilities as measured by the EuroQoL 5-Dimensional, 5-level questionnaire
• Objective: To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in the study.	• Germline genetic variation and association to clinical data collected in this study

4 STUDY DESIGN

4.1 Overall Design

This is an event-driven, randomized, placebo-controlled, parallel-group, multi-site, double-blind study of MK-2060 in participants with ESRD receiving hemodialysis via an AVG. This study is designed to evaluate the efficacy and safety of MK-2060 20 mg QW and MK-2060 6 mg QW.

During the screening period, participants will be assessed against the inclusion and exclusion criteria to select a suitable population of individuals receiving hemodialysis via a functioning AVG. Individuals using daily aspirin or heparin during dialysis are eligible; however, those using $P2Y_{12}$ inhibitors or systemic anticoagulants are not eligible (Section 6.5). Individuals with recent major bleeding events or at risk for future major bleeding events are excluded from participation (Section 5.2).

After a screening period of up to 30 days, approximately 489 eligible participants will be randomized in a 1:1:1 ratio and treated with MK-2060 20 mg, MK-2060 6 mg, or placebo (Section 6.1). During the loading phase on Week 1, participants will receive 1 loading dose of study intervention during 3 consecutive dialysis sessions. Starting on Week 2, participants will receive study intervention as a weekly dose of MK-2060 20 mg, MK-2060 6 mg, or placebo during their regularly scheduled dialysis session, maintaining this schedule until the required number of AVG thrombosis events is observed in the study (see Section 9.9.1). A clinical adjudication committee, whose members are blinded to the study-group assignments, will adjudicate clinical events of AVG thrombosis, bleeding, major thrombotic cardiovascular events, and death (see Section 10.1.4.3, Appendix 1). After the last treatment dose, each participant will be followed for 3 months to monitor for AEs. PROs will be completed in a subset of study sites to assess the impact of treatment intervention from the participant's perspective. Participants who undergo kidney transplant will be censored from the analysis on the date of the kidney transplant for all efficacy analyses (Section 9.6.1.1) or 3 months after the date of the kidney transplant for all safety analyses (Section 9.6.2), to avoid post-transplant events that could confound the results.

Safety monitoring will occur throughout the study. Acute infusion reactions will be assessed during the initial 3 infusions of study intervention in each participant. Participants will be assessed frequently for AEs and laboratory abnormalities at study visits throughout the study (Section 1.3). The Sponsor will provide continuous blinded medical monitoring of AEs, laboratory results, and adherence to the study protocol during the study. An external DMC will provide unblinded assessment of the safety events at regular intervals during the study (Section 10.1.4).

An IA will be conducted when approximately 60% of the primary endpoint events are available to assess efficacy and futility (non-binding) (Section 9.7). At the IA, the eDMC will assess safety and efficacy endpoint events as described in Section 9.7 and Section 10.1.4. The study may stop at the IA if the criterion for efficacy is met. If the efficacy criterion is met at IA, the eDMC may nonetheless recommend study continuation after considering safety factors, including the type and quality of bleeding events (Section 4.2.1.3). If the study is not

stopped at the IA, the study will continue until all 171 primary endpoint events have occurred.

PK and PD sampling will occur in all participants during the study. A PK substudy will conduct sparse sampling in a subset of participants (approximately 100) to provide additional PK values to allow more comprehensive PK-PD modeling of MK-2060 (Appendix 8).

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

4.2 Scientific Rationale for Study Design

The overall clinical strategy for the FXI inhibitor MK-2060 is focused on developing an efficacious and well tolerated anticoagulant to prevent major thrombotic cardiovascular events in patients with ESRD. Within this strategy, the Phase 2 and Phase 3 studies will build the evidence of MK-2060's efficacy, first as a well-tolerated anticoagulant in ESRD patients and second as an anticoagulant that prevents major thrombotic cardiovascular events in ESRD patients. The primary efficacy endpoints selected for Phase 2 and Phase 3 are therefore different reflecting the separate though related objectives.

The purpose of this Phase 2 event-driven study is to evaluate the efficacy and safety of dose-ranging MK-2060 in ESRD participants receiving hemodialysis via an AVG. Up to approximately 489 adult participants with ESRD on hemodialysis who meet study eligibility criteria may be enrolled in this study.

Primary endpoint

Thrombosis of an AVG represents a clinically significant thrombotic event occurring in a large arterialized vessel in patients with ESRD and is predictive of CV events [Girerd, S., et al 2020]. The study design will assess the efficacy of MK-2060 at a low dose (6 mg) and a high dose (20 mg) in reducing AVG thrombosis. The results will provide evidence to support selection of a single dose of MK-2060 for larger studies investigating the efficacy of MK-2060 in the prevention of major thrombotic cardiovascular events in patients with ESRD.

Participant population

The population studied in Phase 2 is restricted to ESRD patients receiving hemodialysis via an AVG. Patients receiving both traditional hemodialysis and hemodiafiltration are allowed to participate in the study. This population was selected based on data from the USRDS registry data (MSD CORE Chronic Disease Research Group ESRD Epidemiology Study 2020, unpublished data on file) indicating that patients with AVGs have a higher rate of vascular access failure due to thrombosis (69.4 events per 100 patient years) compared to those with AVF (13.1 events per 100 patient years). Therefore, selecting AVG thrombosis as the primary endpoint in this population will result in rapid accrual of endpoints and assessment of MK-2060's anticoagulant properties. Successful use of the AVG for 4 weeks

prior to study enrollment is used to establish a degree of stability in AVG function at the time of recruitment. This will help avoid recruitment of individuals with immature AVGs, which have not proven to be reliably cannulated for dialysis or with AVGs in the process of failing or on the verge of requiring an intervention.

Dose selection

The planned doses for this study are a high dose (20 mg loading dose on alternating days during the first week for a total of 3 doses followed by 20 mg weekly doses) and a low dose (6 mg loading dose on alternating days during the first week for a total of 3 doses followed by 6 mg weekly doses). These doses have been chosen based on the Phase 1 PK-PD data from MK-2060-P004 studying single and multiple ascending doses in ESRD participants. The high dose arm (20 mg) is expected to result in ~90% of participants having CCI [redacted] at MK-2060 trough, while the low dose arm (6 mg) is expected to result in ~40% of participants having an CCI [redacted] at MK-2060 trough.

Internal preclinical studies have demonstrated that an increase in CCI [redacted] baseline with MK-2060 is required to achieve equivalent anticoagulation effect as apixaban in a preclinical AV shunt thrombosis model. In addition, clinical data from other factor XI compounds suggest that CCI [redacted] from baseline is needed for clinical efficacy [Buller, H. R., et al 2015] [Weitz, J. I., et al 2020]. Finally, genetic data from hemophilia C (FXI deficiency) supports ~30% to 50% FXI deficiency as being sufficient to decrease the risk of MACE and thromboembolic events, CCI [redacted] [Preis, M., et al 2017].

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The overarching purpose of the Phase 2 study is to identify a dose of MK-2060 that provides safe and effective anticoagulation to prevent thrombotic events in medium to large arterialized vessels in ESRD patients. The Phase 2 endpoint of AVG thrombosis event in ESRD patients receiving hemodialysis via an AVG will assess the anti-thrombotic properties of MK-2060 in ESRD participants. Vascular access thrombosis has been associated with future CV events in multiple studies with evidence suggesting therapies effective in preventing CV events may also reduce vascular access thrombosis [Girerd, S., et al 2020] [Kuo, T. H., et al 2015] [Kim, H. J., et al 2016] [Tanner, N. C. 2015]. AVG thrombosis will act as a surrogate for major thrombotic cardiovascular events, which include fatal and non-fatal MI, ischemic stroke, PE and acute limb ischemia, and VTE and will be the focus of the Phase 3 study.

The primary endpoint is defined as the time to first occurrence of an AVG thrombosis event. An AVG thrombosis event is defined as the sudden occlusion of the participant's AVG requiring thrombectomy/thrombolysis, or clinical evidence of thrombosis with surgical, radiological or pathological conformation of an AVG thrombosis. This endpoint will be adjudicated by an independent CAC (Section 10.1.4.3, Appendix 1). The detailed definition of AVG thrombosis event will be provided in the CAC Charter. The CAC's determination

will be based on review of the clinical history of the event along with associated radiological, surgical or pathological reports from the event to establish the occurrence of a thrombotic occlusion of the AVG.

Selection of this endpoint will allow assessment of MK-2060's efficacy as an anticoagulant in preventing thrombotic events in medium to large arterialized vessels in ESRD patients. The secondary efficacy endpoint is the time to each AVG thrombosis event (first and recurrent) from randomization until the efficacy cutoff date.

A CAC, whose members are blinded to the study-group assignments, will adjudicate all reported clinical events of AVG thrombosis (primary and secondary endpoint), major thrombotic CV events (tertiary/exploratory endpoint), and death (see Section 10.1.4.3, Appendix 1).

4.2.1.2 Patient-reported Outcomes Endpoints

Patient-reported outcomes can provide unique information on the impact of treatment intervention from the participant's perspective as some domains are difficult to observe or are subjective and are best when collected directly from the participant. This study will include 2 PRO interviewer-administered questionnaires, the KDQOL-SF and the EQ-5D-5L, administered in a subset of study sites.

The KDQOL-SF questionnaire was developed for patients with kidney disease and those on dialysis to measure the effect of the disease on activities of daily living, work status, sexual function, sleep, and social interaction. It also captures symptoms and patient satisfaction with treatment and incorporates the SF-36 generic health-related QoL measure [Maruish, M. E. 2011], which was developed by the RAND Corporation in 1997, includes 80 items, and can be completed in approximately 16 minutes [Hays, R. D., et al 1997]. It has demonstrated good internal consistency and reliability [Barotfi, S., et al 2006]. In a review article of PRO measures in chronic kidney disease, Aiyegbusi et al. evaluated 25 measures from 66 published studies. They found strong evidence of internal and structural validity, moderate evidence of test-retest validity, and limited evidence for content validity for the KDQOL-SF, recommending this instrument for research use in patients on dialysis [Aiyegbusi, O. L., et al 2017].

The EQ-5D-5L is a generic questionnaire used to assess current health status as reported by patients and will provide data to develop health utilities for use in health economic analyses [Rabin, R. and de Charro, F. 2001]. It consists of 5 domain questions and 1 VAS response. The domain questions assess mobility, self-care, usual activities, pain/discomfort, anxiety/depression, with 5-level response options (no problems, slight problems, moderate problems, severe problems, and extreme problems). Summary scores will be calculated from the 5 domain scores according to scoring instructions from the EuroQol group and the EQ-5D-5L value sets for the US and for Europe. Scores range from 1.00 for perfect health to 0.00 for death. The EQ-5D VAS included in the EQ-5D-5L records patient self-rated health on a 20 cm vertical VAS with endpoints labeled 'the best health you can imagine' and 'the worst health you can imagine' and is scored on a 0 to 100 scale. The EQ-5D-5L is available in over 60 translations with established validity, reliability, and responsiveness

[Pickard, A. S., et al 2007] and is appropriate for a wide range of health conditions and treatments [EuroQol Research Foundation 2019]. It has been used in patients with ESRD and is a valid and sensitive health utility measure in this population [Lee, A. J., et al 2005] [Manns, B. J., et al 2002] [Gerard, K., et al 2004]. Minimally important difference estimates for the EQ-5D utility score range between 0.03 and 0.05 [McClure, N. S., et al 2018]. In cases when a validated translation is needed and not available for a specific language, participants who speak that language will be exempt from the requirement to complete the questionnaire.

The KDQOL-SF and EQ-5D-5L PROs are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

4.2.1.3 Safety Endpoints

General safety and tolerability will be evaluated by clinical review of all relevant parameters, including AEs, vital signs, laboratory safety tests (ie, blood chemistry, hematology, pregnancy testing), and systemic infusion reaction assessment. 12-lead ECGs will be performed, and vital status assessment will be collected.

A CAC, whose members are blinded to the study-group assignments, will adjudicate all site reported bleeding AEs (See Section 10.1.4.3, Appendix 1). The secondary endpoint of time to first occurrence of ISTH major bleeds plus clinically relevant non-major bleeding events will also be evaluated.

Bleeding Endpoints

Events meeting the ISTH criteria [Schulman, S. 2005] for major bleeding or clinically relevant non-major bleeding will be reported as bleeding endpoints.

Major bleeding events have a symptomatic presentation and include the following criteria:

1. Fatal bleeding, and/or

2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, intramuscular with compartment syndrome, and/or

3. Bleeding causing a decrease in hemoglobin level of 20 g/L or more or leading to transfusion of 2 or more units of whole blood or red cells.

Clinically relevant non-major bleeding events have signs or symptoms of hemorrhage that do not meet the criteria for major bleeding events, but do meet at least 1 of the following criteria:

1. Requiring medical intervention by a healthcare professional
2. Leading to hospitalization or increased level of care
3. Prompt a face-to-face evaluation by a healthcare professional

4.2.1.4 Pharmacokinetic Endpoints

The PK data from this study may be combined with data from other Phase 1 and Phase 2 studies for population PK analysis using nonlinear mixed effects modeling. The key exploratory endpoints for MK-2060 are C_{max} and C_{trough}. If data permit, estimates of population PK parameters such as CL, Vc, as well as estimates of inter-individual and residual variability will be determined. In addition, effects of demographic or laboratory factors (eg, age, race, weight, gender, renal function) on PK parameters will be assessed if possible. The results of this population PK analysis will be summarized in a separate report.

4.2.1.5 Immunogenicity Endpoints

Immunogenicity to MK-2060 will be described as the results of the ADA assay from samples taken during the double-blind treatment period.

ADA samples will be collected before the administration of study intervention at selected visits and from all participants. The incidence and magnitude (titer) of ADA positive participants and potential effects of ADA on PK, PD, and safety will be reported, as appropriate.

4.2.1.6 Pharmacodynamic Endpoints

PD endpoints that will be assessed include changes from baseline through the end of the study in FXI activity and aPTT with assays being performed at a central laboratory.

FXI activity is the most direct measure of MK-2060's efficacy in binding to FXI and FXIa and inhibiting FXIa activity.

aPTT prolongation level (relative to baseline) is an immediate measure of the antithrombotic effect of FXIa inhibition from MK-2060 and an important measure to allow comparison of MK-2060 with other FXIa inhibitors. Baseline is defined as the individual's predose aPTT value.

4.2.1.7 Planned Exploratory Biomarker Research

4.2.1.7.1 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 absorption, distribution, metabolism, and excretion; 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 multi-study assessment of genetic factors involved in the response to understand study disease or related conditions.

Variation across the human genome may be analyzed for association with clinical data collected in the study.

4.2.1.8 Future Biomedical Research

The Sponsor will conduct FBR on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for FBR.

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 that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR research are presented in Appendix 6.

4.2.2 Rationale for the Use of Placebo

The purpose of this study is to evaluate the efficacy and safety of dose-ranging MK-2060 in adult participants with ESRD on hemodialysis via an AVG. A placebo-controlled study will allow for a blinded and unbiased assessment of efficacy (AVG thrombosis), safety, and tolerability. Secondary outcomes are also supported using placebo, including evaluation of

the effect of MK-2060 on bleeding risk and on time to first major thrombotic cardiovascular event.

The efficacy and safety profile of any drug is best characterized versus placebo, especially when it is being studied in a population with subjective event reporting (eg, ESRD patients receiving hemodialysis via an AVG).

4.3 Justification for Dose

4.3.1 Starting Dose for This Study

Intravenous administration of MK-2060 in participants on hemodialysis allows a simple infusion of the study intervention during hemodialysis by the treating provider with minimal disturbance to the participant. Participants will be randomized into 1 of 3 parallel treatment groups and will be treated with a fixed dose throughout the study.

The 2 IV doses of MK-2060 will be administered in parallel treatment arms, a low dose (6 mg), and a high dose (20 mg) arm, with an additional control arm (placebo). See Section 4.3.2 and Section 4.3.3 for the criteria used to select the high dose and low dose to be studied.

4.3.2 Maximum Dose/Exposure for This Study

The maximum dose used for the study is equivalent to the dose administered in the high dose arm (20 mg). Participants randomized to the high dose arm will receive this fixed dose throughout the study duration which starts with a loading phase (1 dose at dialysis on alternating days during the first week for a total of 3 doses) and is followed by a maintenance phase (1 dose each week). This high dose is projected to result in ~90% of participants with an CCI [redacted] at C_{min} during steady state. This projection is based on a PK-PD model developed from the results of single ascending dose and multiple studies completed in ESRD patients receiving hemodialysis (MK-2060-P004).

The high dose (20 mg) selected for the study is below the maximum IV dose (40 mg IV x 1) tested in single-dose Phase 1 studies in normal healthy volunteers and participants with ESRD on hemodialysis. The 40 mg IV dose was well tolerated in those participants. Steady-state exposures in the high dose arm with 20 mg dosed on Day 1, Day 3, and Day 5 followed by weekly dosing are projected to have a median $AUC_{0\text{-}168h}$ 9065 nM*hr in ESRD patients at steady state. This predicted $AUC_{0\text{-}168h}$ is significantly below (<1%) the chronic toxicology NOAEL ($AUC_{0\text{-}168h}$ = 1.28 x 10^6 nM*hr from the 4-week rhesus monkey toxicity study at 60 mg/kg/week).

Since this is an event-driven study, the overall duration will depend upon the rate of recruitment and endpoint accrual. Based on the estimated recruitment and endpoint rate in the placebo arm, the median treatment duration is expected to be approximately 10 months.

4.3.3 Rationale for Dose Interval and Study Design

During Phase 1 single and multiple ascending dose testing, MK-2060 demonstrated good safety and tolerability, a steady state PK profile compatible with weekly IV dosing, and biomarker confirmation (FXI activity and aPTT) of on-target pharmacology. In this study, the dosing interval will vary between the loading phase and the maintenance phase. Employing a loading phase, with dosing on Day 1, Day 3, and Day 5 during Week 1, will achieve steady state in PK and PD within the first week as opposed to over 6 weeks with no loading phase. During the maintenance phase, study intervention will be administered once weekly on the same day each week.

The MK-2060 doses for the low (6 mg) and high dose (20 mg) arms in Phase 2 were chosen to provide a range that covers the dynamic range of PD seen with MK-2060 in the Phase 1 dose-ranging studies. The reason for choosing the MK-2060 high dose arm (20 mg) is described in Section 4.3.2. The MK-2060 low dose (6 mg) was chosen to allow for separation in the predicted PD and PK response to 6 mg dose MK-2060 relative to the responses predicted for the 20 mg MK-2060 dose. The 6 mg dose MK-2060 is projected to result in ~40% of participants with an CCI [redacted] at C_{min} during steady state.

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 required number of AVG thrombosis are observed (unless the study stops for futility) and the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

4.4.1 Clinical Criteria for Early Study Termination

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

Early study termination may also be considered after assessing efficacy and futility at the IA (Section 9.7).

5 STUDY POPULATION

Male/female participants of at least 18 years of age with ESRD receiving hemodialysis via an AVG will be enrolled in this study.

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. Has a current diagnosis of ESRD.

2. Has been receiving hemodialysis (including hemodiafiltration) prescribed ≥3 times per week for a minimum of 3 hours per session via mature normally functioning ($_{sp}$Kt/V ≥1.2), uninfected AVG. Criterion must be met for at least 75% of the sessions over the 4 weeks prior to randomization.

Demographics

3. Is male or female, ≥18 years of age inclusive, at the time of providing documented informed consent.

Female Participants

4. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies: (Section 10.5.1)

   - Is not a WOCBP

     OR

   - Is a WOCBP and using an acceptable contraceptive method, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Appendix 5 during the intervention period and for at least 90 days, corresponding to the time needed to eliminate any study intervention (eg, 5 terminal half-lives) after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

   - A WOCBP must have a negative highly sensitive pregnancy test (serum) within 6 days before the first dose of study intervention.

   - The participant must be excluded from participation if the serum pregnancy result is positive.

   - Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.5.

- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

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

Informed Consent

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

5.2 Exclusion Criteria

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

Medical Conditions

1. Has a recent history of cancer (<1 year). Non-melanoma skin cancers are allowed.

2. Has a mechanical/prosthetic heart valve.

3. Had a recent hemorrhagic stroke or lacunar stroke (<1 month).

4. Had recent evidence of bleeding requiring hospitalization or unplanned medical attention (<1 month), a history (≤2 years) of recurrent bleeding episodes including epistaxis, GI bleeds or GU bleeds requiring medical treatment or events requiring treatment with blood products.

5. Has a recent history of drug or alcohol abuse or dependence (<1 year).

6. Life expectancy <12 months.

Prior/Concomitant Therapy

7. Is currently receiving or planning to receive anticoagulants or antiplatelet medications *(Individuals who plan to be on low-dose aspirin (up to 150 mg per day) during the study or require intradialytic heparin are permitted in the study).*

   Prohibited Medications (Section 6.5)
   Oral Anticoagulants:

   - Warfarin
   - Apixaban
   - Dabigatran
   - Rivaroxaban
   - Edoxaban
   - Betrixaban

   IV/SC Anticoagulants:

   - IV/SC Heparin and LMWH
   - IV Warfarin
   - IV Argatroban
   - IV Bivalirudin
   - IV Lepirudin
   - SC fondaparinux
   - IV antithrombin III

   Note: Participants on medically indicated anticoagulants (other than intradialytic heparin, periprocedural heparin, or low-dose heparin for DVT prophylaxis while hospitalized) are excluded from the study (ie, participants may not discontinue prescribed anticoagulant therapy to meet study eligibility criteria in order to enroll in the study). If a participant has prior anticoagulant use, they must have discontinued the anticoagulant for 7 days prior to randomization.

Antiplatelet Medications ($P2Y_{12}$ inhibitor use is excluded)

- Aspirin in doses >150 mg per day (regular use)
- Clopidogrel
- Prasugrel
- Ticagrelor
- Ticlopidine

Note: Participants taking any antiplatelet agent (except for aspirin in doses ≤150 mg per day) will undergo a 7-day washout period prior to randomization. Individuals may not discontinue prescribed antiplatelet therapy to meet study eligibility criteria.

NSAIDs (eg, ibuprofen)

Note: topical NSAIDs are permitted.

Prior/Concurrent Clinical Study Experience

8. Has participated in another investigational study within 4 weeks (or 5 half-lives of the investigational drug), whichever is greater, prior to the Screening Visit. The window will be derived from the date of the last use of study treatment in the previous study.

Diagnostic Assessments

9. Has abnormal coagulation laboratory results including INR >2.0 and/or PT or aPTT >20% above the normal range.

10. Has thrombocytopenia (platelet count <50,000/μL).

11. Has documented severe hypertension (SBP >200 mmHg or DBP >110 mmHg, pre-dialysis) at screening or randomization.

Other Exclusions

12. Is planning on receiving a living donor renal transplant within 12 months (participants are permitted to be candidates for deceased donor renal transplants)

13. Is planning on receiving an AVF placement within 12 months.

14. Is planning non-urgent invasive dental surgeries that are liable for significant blood loss within 12 months.

15. Has had a hypersensitivity reaction to any component of MK-2060 drug product.

16. 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.

17. Canada-specific criterion, see Appendix 7.

5.3 Lifestyle Considerations

There are no lifestyle restrictions (see Section 5.2 for drug or alcohol abuse exclusion).

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 is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

Rescreening is allowed once per participant (Section 8.1.6).

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention OR withdraws consent will not be replaced.

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 of blinded study interventions provided by the Sponsor will be packaged to support enrollment in the study. 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 1.

Table 1 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength	Dosage Level(s)	Route of Admin	Treatment Period	Use	IMP or NIMP/AxMP	Sourcing
MK-2060 Low Dose	Experimental	MK-2060 Low Dose	Drug	Lyophilized Powder	6 mg	6 mg	IV Infusion	V2 to Vn	Test Product	IMP	Sponsor
MK-2060 High Dose	Experimental	MK-2060 High Dose	Drug	Lyophilized Powder	20 mg	20 mg	IV Infusion	V2 to Vn	Test Product	IMP	Sponsor
Placebo	Placebo Comparator	Placebo	Drug	Sterile Solution	0 mg	0 mg	IV Infusion	V2 to Vn	Placebo	IMP	Local

EEA =European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product

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

In this protocol, placebo for (placebo comparator arm) is diluent alone (normal saline); diluent is used for blinding purposes and does not contain active ingredients.

Vn= Patients final dose of study medication (the timing of Vn will be determined by the rate of primary endpoint accrual)

All supplies indicated in Table 1 will be provided per the "Sourcing" column depending upon 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 the Pharmacy Manual provided by the Sponsor.

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

Intervention randomization will occur centrally using an IRT system. There are 3 study intervention arms. Participants will be assigned randomly in a 1:1:1 ratio among 3 arms.

6.3.2 Stratification

Intervention randomization will be stratified according to the following strata:

1. Region (US, non-US)
2. Previous thrombosis of active AVG (yes/no)
3. Regular aspirin use up to 150 mg daily at baseline (yes/no)

   Note: 'As needed' aspirin use should not be considered for stratification.

These strata have been selected for their importance as prognostic factors for AVG thrombosis to ensure balance in these characteristics between treatment groups. Hemodialysis outcomes vary across regions based on difference in baseline characteristics of dialysis populations in each region and regional variations in dialysis prescriptions. An AVG that has had a thrombotic event is at a higher risk of developing a subsequent thrombotic event than one without prior thrombosis. Since a significant proportion of the study participants are expected to have a prior AVG thrombosis at enrollment it is important to balance this risk factor between treatment arms with stratification of randomization. Aspirin use is expected to be associated with an increased bleeding risk and potentially decreased AVG thrombosis risk in ESRD patients therefore it is important to have aspirin use balanced between treatment arms.

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. MK-2060 and placebo will be prepared by an unblinded pharmacist or designee so that study intervention has an identical presentation regardless of treatment assignment. This will maintain blinding to treatment assignment of the participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration, clinical evaluation of the participants and recording of study data. If local dialysis center guidance requires medications to be prepared and administered by the same individual, the unblinded pharmacist or designee may administer blinded study medication to participants but will otherwise have no role in the study, including interaction with study participants. The infusion bags and IV line (through which study intervention is administered) do not require opaque coverings as the differences between the clinical materials are not visually distinguishable within the infusion bags, tubing, or syringe.

The allocation schedule will be blinded in the study database. 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 for more than 4 consecutive doses require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the appropriate eCRF. The dose of study intervention will be confirmed by the unblinded pharmacist or designee. The study participant identification will be confirmed at the time of dosing by the blinded study staff. Refer to the Study Operations Manual.

6.5 Concomitant Therapy

Medications specifically prohibited in the exclusion criteria are not allowed during the ongoing study unless there is a clinical indication to initiate a prohibited medication. In those cases, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Any medication (including over the counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency (route will be captured for concomitant medication taken at the time of an SAE)

Participants previously receiving intradialytic heparin to prevent clotting in the blood circuit are permitted to continue with intradialytic heparin use during the study.

The Sponsor should be contacted if there are any questions regarding concomitant or prior therapy.

PROHIBITED MEDICATIONS

Listed below are specific restrictions for concomitant therapy during the study, from providing documented informed consent to the Final Efficacy Visit (or Premature Discontinuation Visit):

Oral Anticoagulants (intradialytic heparin is permitted in the study)

- Warfarin
- Apixaban
- Dabigatran
- Rivaroxaban
- Edoxaban
- Betrixaban

IV/SC Anticoagulants:

- IV/SC Heparin and LMWH
- IV Warfarin
- IV Argatroban
- IV Bivalirudin
- IV Lepirudin
- SC fondaparinux
- IV antithrombin III

Note: Participants on medically indicated anticoagulants (other than intradialytic heparin, periprocedural heparin, or low dose heparin for DVT prophylaxis while hospitalized) are excluded from the study (ie, participants may not discontinue prescribed anticoagulant therapy to meet study eligibility criteria in order to enroll in the study). If a participant has prior anticoagulant use, they must have discontinued the anticoagulant for 7 days prior to randomization.

Antiplatelet Medications (Aspirin use up to 150 mg per day is allowed, $P2Y_{12}$ inhibitor use is excluded)

- Aspirin in doses >150 mg per day (regular use)
- Clopidogrel
- Prasugrel
- Ticagrelor
- Ticlopidine

Note: Participants taking any antiplatelet agent (except for aspirin in doses ≤150 mg per day) will undergo a 7-day washout period prior to reinitiation of study medication. Participants may not discontinue prescribed antiplatelet therapy to meet study eligibility criteria.

NSAIDs (eg, ibuprofen)

Note: topical NSAIDs are permitted.

6.5.1 Rescue Medications and Supportive Care

The mechanism of MK-2060 is expected to provide substantial anticoagulant benefits with very minimal additional bleeding risk. Management of all bleeding events in the study is under the discretion of the treating physician and may be directed by the local guidelines and consultation with a hematologist.

Management of bleeding events in participants receiving MK-2060 may be guided by the experience of treatments proven effective in patients with inherited FXI deficiency or endogenous FXI inhibitors (see Section 6.5.2). In these conditions, treatment with tranexamic acid alone or in combination with either FFP or recombinant FVIIa has proven efficacious in managing bleeding risk.

Major and clinically relevant non-major bleeding events will prompt interruption of study intervention and a hematology consult. Usual means to achieve hemostasis should be applied and, if required, treatment with IV tranexamic acid with use of recombinant FVIIa or FFP reserved for recalcitrant bleeding events.

Sites will be required to capture details of the use of any rescue medications during the study.

Participants may be allowed to begin treatment again if, following a discussion with the Sponsor, it is agreed to be medically appropriate.

6.5.2 Surgery Guidance

Perioperative management of bleeding in study participants should follow local guidance with consultation from a hematologist if needed.

For participants undergoing minor procedures, no change in study intervention administration or reversal of study drug is recommended; however, for major surgeries with increased risk for post-operative hemorrhage or surgeries involving tissues with high fibrinolytic activity (oral mucosa or genitourinary tract), temporary discontinuation of study treatment is recommended until the participant has recovered from the procedure and the post-procedure risk of bleeding has resolved.

Additional management of participants at high risk for perioperative bleeding who have received MK-2060 is based on published experience of successful peri-surgical management of patients with inherited FXI deficiency or endogenous FXI inhibitors. In surgeries involving tissue with high fibrinolytic turnover and at risk for bleeding in the setting of reduced FXI activity, tranexamic acid alone (1 g QID) started 12 hours pre-surgery and continued for 7 days prevented bleeding events in 19 patients with FXI deficiency undergoing dental extractions [Berliner, S., et al 1992]. In similar patients undergoing major surgeries, a very low dose of recombinant factor VIIa (10 µg/kg to 15 µg/kg) given at the end of surgery along with tranexamic acid (1 g QID initiated 2 hours before surgery for 3 to 5 days) provided simple and effective control of hemostasis [Salomon, O., et al 2019]. In addition, in vitro and in vivo data have demonstrated that aPTT prolongation resulting from administration of MK-2060 is reversed with administration of FFP (see Appendix 9).

If there is a concern about the risk of bleeding in a participant who requires urgent or emergency surgery, unblinding may be considered, but should *only* be performed if knowledge of randomized treatment allocation will influence clinical management (Section 8.1.10).

6.6 Dose Modification

There are no dose modifications in this study.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

MK-2060 and placebo treatment arms are blinded but clinical supplies will be provided open label to study pharmacies for preparation. An unblinded pharmacist or qualified study site personnel will be used to blind supplies. Treatment 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 treatment/randomization schedule for the study to unblind participants and to unmask treatment.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.11.3, unless the participant has withdrawn from the study (Section 7.2).

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9 and Section 8.11.6.

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

1. The participant or participant's legally acceptable representative requests to discontinue study intervention.

2. The participant has a confirmed positive serum pregnancy test.

3. Upon site learning the participant will undergo a kidney transplant during the study.

4. The participant has a major non-traumatic bleed.

5. The participant has a medical condition or personal circumstance that, in the opinion of the investigator and/or Sponsor, places the participant at unnecessary risk through continued participation in the study, while on study treatment, or does not allow the participant to adhere to the requirements of the protocol.

6. The participant requires ongoing treatment with a prohibited medication (Section 6.5).

7. The participant permanently transitions from AVG to an alternative hemodialysis access.

8. The participant interrupted study intervention for >4 consecutive doses and is not a candidate for reloading after consultation with the Sponsor (refer to the Operations Manual for reloading).

Any time a participant's vital status is in question, the investigator should explore all possible options to contact the participant per local regulations (unless the participant has explicitly withdrawn his/her consent to any type of follow-up). The site must document all attempts to try to contact the participant in the medical records/source documents. The vital status will be collected for all randomized participants who have not withdrawn consent, irrespective of completion of study procedures.

If the participant does not attend scheduled study visits, follow-up of clinical events specified as endpoints may continue by phone, unless the participant explicitly withdraws his/her consent to any type of follow-up. In such cases, the phone contact will not be considered a protocol deviation.

In all cases, the reason for temporary interruption or permanent study intervention discontinuation must be recorded in the eCRF and in the participant's medical records.

Participants may be allowed to begin treatment again if deemed medically appropriate.

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 future biomedical research, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

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

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the

participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

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

8 STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

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

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

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

- 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 consent from each potential participant or each participant's legally

acceptable representative prior to participating in a clinical study or future biomedical research. 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 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 trial protocol number, trial 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 future biomedical research 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 future biomedical research. A copy of the informed consent will be given to the participant before performing any procedure related to future biomedical research.

8.1.1.3 Consent for PK Substudy

The investigator or medically qualified designee will explain the PK substudy 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 the PK substudy. A copy of the informed consent will be given to the participant before performing any procedure related to the PK substudy.

8.1.1.4 Consent for Quality of Life Questionnaires

At preselected sites, the investigator or qualified designee will explain the QoL questionnaires consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before administration of the QoL questionnaires. A copy of the informed consent will be given to the participant before administration of the QoL questionnaires.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed at the Screening and Randomization Visits as outlined in the SoA (Section 1.3) 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 healthcare provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

Medical history will be obtained by the investigator or qualified designee with a focus on defining the participant's history of renal disease, cardiovascular morbidities, and bleeding events.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including antiplatelet and anticoagulant medications which are protocol-specified prohibited medications (Section 6.5), and record prior medication taken by the participant within 28 days before starting the study.

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

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

Rescreening is allowed once per participant. Any participant that is rescreened, will retain the original screening number assigned at the initial Screening Visit. Specific details on the Screening Visit/ Visit 1 requirements are provided in Section 8.11.1.

8.1.7 Assignment of Treatment/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 intravenously to participants during routine hemodialysis sessions. The first 3 study intervention doses will be administered during routine hemodialysis on study Days 1, 3, and 5. This loading period will be followed by a maintenance period. During the maintenance period, participants will receive study intervention on a once weekly schedule beginning on study Day 8 following the specifications within the study pharmacy manual until the participant completes the treatment or is discontinued from the study. Timing of dose administration is found in Section 8.1.8.1.

Some administration of study intervention will take place during routine dialysis sessions that **are not** study visits. Every effort should be made to administer study intervention once weekly on the same day each week (Section 8.11.3).

8.1.8.1 Timing of Dose Administration

Study intervention will be prepared and dosed per the instructions outlined in the study pharmacy manual. All doses of study intervention will be given 30 minutes after initiation of hemodialysis and administered over approximately 60 minutes.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.11.6.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the Discontinuation Visit at the time of withdrawal. Any AEs that are

present at the time of 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 future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main 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 future biomedical research 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 prior to 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.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main 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. Prior to contacting the emergency unblinding call center to request unblinding of a participant’s intervention assignment, the investigator who is a 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 chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

In the event that 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.

Additionally, the investigator or medically qualified designee must go into the IRT system and perform the unblind in the IRT system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding in the event that this is required for participant safety.

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 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.

Critical equipment for this study includes, but it is not limited to:

- Infusion pumps
- Vital signs and ECG instruments
- All equipment to process study intervention and samples such as, but not limited to, centrifuge equipment, pipettes, and freezers for MK-2060 or placebo and sample storage.

8.1.12 Identification of External Contact Person

All participants will be asked to identify a person to be contacted by the study site to collect the participant's vital status if the participant cannot be reached (eg, spouse, family, friend, neighbor, etc.).

8.2 Efficacy Assessments

The primary endpoint for the study is the time to first occurrence of AVG thrombosis (Section 4.2.1.1). Study staff is expected to report all AVG thrombosis events as AEs and identify them as potential primary endpoints upon learning of the event's occurrence either during routine care of study participants or at study visits.

Events constituting the tertiary/exploratory endpoint of major thrombotic CV events will be reported as AEs upon study staff learning of these events' occurrence during routine care of

study participants or at study visits. These events include fatal and non-fatal MI, ischemic stroke, PE, DVT, and acute limb ischemia.

At selected study sites, KDQOL-SF and EQ-5D-5L questionnaires will be administered by the interviewer (investigator or qualified designee) at the visits outlined in the SoA. The questionnaires should be administered before administration of study intervention.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided.

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

8.3.1 Physical Examinations

Complete and directed physical examinations will be conducted during the visits outlined in the SoA (Section 1.3) by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard.

Clinically significant abnormal findings during screening should be recorded as medical history.

Directed physical examination performed throughout the treatment period will at a minimum include assessment of the cardiovascular system and hemodialysis access site.

8.3.1.1 Height

Height will be measured without shoes using a stadiometer or other appropriate device at screening/Visit 1.

8.3.1.2 Weight

Body weight will be measured without shoes, jacket or coat removed, using a standardized scale at each time point specified in the SoA (Section 1.3) post-dialysis.

8.3.2 Systemic Infusion Reaction Assessment

Participants will be monitored for up to 1 hour after the administration of study intervention during the loading phase (first 3 treatment visits) as outlined in the SoA (Section 1.3). During this time, signs and symptoms of a systemic infusion reaction including, but not limited to, fever, vital sign changes (tachycardia/hypotension), pruritis, urticarial (hives), lip swelling, angioedema, bronchospasm, stridor, hoarseness, and shortness of breath will be monitored. Infusion reactions must be assessed, managed promptly, and reported as AEs.

Infusion Reaction Management

The risk of infusion reactions to MK-2060 is considered low since the molecule contains primarily human sequences; however, infusion reactions may be observed. Due to the expected low risk and since one of the objectives of the study is to characterize the safety profile of MK-2060, no prophylactic pre-medications to reduce the minimal risk of infusion reactions will be given prior to MK-2060 administration.

Participants who experience infusion or hypersensitivity reactions in conjunction with the infusion of study intervention should receive appropriate supportive care measures as deemed necessary by the treating physician. If a reaction occurs, participants should be carefully observed until complete resolution of all signs and symptoms. Report any AEs according to the guidelines in Section 8.4.

8.3.3 Vital Signs

Vital signs will be measured at each study visit before initiation of hemodialysis and administration of study intervention as outlined in the SoA (Section 1.3). Vital signs assessed will include body temperature, respiratory rate, heart rate, and BP. Participants should be resting in the semi-recumbent position for at least 10 minutes prior to having vital signs measurements obtained.

8.3.3.1 Body Temperature

Body temperature will be a single measurement. Temperature will be measured according to standard of practice.

8.3.3.2 Heart Rate and Blood Pressure

Heart rate and BP will be performed in triplicate measurements, obtained at least 1 to 2 minutes apart and before initiation of hemodialysis and administration of study intervention. The mean of these measurements will be recorded and used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed).

The correct size of the BP cuff and the correct positioning on the participant's limb is essential to increase the accuracy of BP measurements. Whenever possible, BP measurements should be obtained using the same arm or leg, same BP monitoring device, and same examiner at each visit.

8.3.4 Electrocardiograms

A standard supine 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) at the visits outlined in the SoA (Section 1.3). The ECG should be recorded with a paper speed of 25 mm/sec and equivalence of 1 mV signal to 10 mm vertical deflection in the ECG.

Clinically significant abnormal findings during the screening period should be recorded as medical history. Assessments may be repeated during the study, as clinically indicated.

- Participants should avoid the ingestion of caffeine and nicotine-containing products for at least 30 minutes before the scheduled ECGs.

- ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position and before the assessment of blood pressure and heart rate as well as before blood collection.

All ECGs performed should be reviewed at the investigative site for participant safety monitoring. The investigator is responsible for retaining all copies of the ECG reports.

8.3.5 Clinical Safety Laboratory Assessments

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

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

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

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

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 90-days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.5.1 Serum Pregnancy Test

All WOCBP (see Section 10.5.1 for definition) participating in the study will have a serum pregnancy test at visits indicated in the SoA and when pregnancy is suspected. Participants with a positive pregnancy test must be discontinued from study treatment and followed (Section 7.1).

Germany-specific requirements are in Appendix 7.

8.3.5.2 Serum Follicle Stimulating Hormone

All WOCBP (see Section 10.5.1 for definition) participating in the study will have an FSH test at Visit 1. A second FSH test at Visit 2 is required for participants who have less than 1 year of amenorrhea.

8.3.6 Quality of Life Questionnaires

At preselected sites, the KDQOL-SF and the EQ-5D-5L questionnaires will be administered by the interviewer (investigator or qualified designee) at the visits specified in the SoA (Section 1.3). The questionnaires should be administered before administration of study intervention.

8.3.7 Vital Status Assessment

Vital status will be collected at the timepoints specified in the SoA. This assessment can also be performed at any point in the study when vital status of a participant is in question, unless the participant has specifically withdrawn consent for all further follow-up.

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

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

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

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

All 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 if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

From the time of intervention and randomization through study completion, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

Additionally, any SAEs brought to the attention of an investigator at any time outside of the time period specified in the previous paragraph 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 he/she 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 2.

Table 2 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

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:**
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential DILI - Require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days 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 **except for assessment of study endpoints**.

Participants will be directly questioned about the occurrence of AVG thrombosis or major thrombotic cardiovascular endpoints (Section 8.2) at study visits. These events will be reported as AEs or SAEs upon study staff learning of the events' occurrence during routine care of study participants or at study visits

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

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

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

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

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

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

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

Not applicable.

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

1. 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 upon 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).

8.5 Treatment of Overdose

In this study, an overdose is defined as any dose higher than the maximal target dose prescribed in the protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose in consultation with the Sponsor.

8.6 Pharmacokinetics

For the investigation of the systemic exposure to MK-2060, the plasma concentration of MK-2060 will be determined at different time points in all participants.

Blood samples for PK analysis will be collected from all randomized participants at select study visits described in the SoA (Section 1.3). Blood samples will be collected prior to hemodialysis and administration of study intervention at all specified visits, with additional blood samples collected approximately 30 minutes after study intervention administration on Day 1 and Day 85. This PK analysis is separate from the PK substudy and it is part of the main study.

A separate PK substudy will be available to all study sites (see Appendix 8). Sites should ask all main study participants to enter into the PK substudy and enroll those that consent. Approximately 100 participants will be enrolled.

Participants in the PK substudy will have all the PK samples collected per the SoA for the main study (Section 1.3), in addition to supplementary PK sample collections (Table 10). Participants in the substudy will have trough PK samples collected prior to dialysis on Day 3 and Day 5, will have PK samples collected 6 hours post-study intervention administration on Day 1 and Day 85, and will have PK samples collected prior to dialysis on the 2 dialysis visits following Day 85, and at the next dosing visit as described in Table 10, Appendix 8.

8.6.1 Blood Collection for Plasma MK-2060

Blood samples will be taken on defined study days for PK analysis from all participants (see SoA, Section 1.3). Participants enrolled in the PK substudy will have additional blood draws at additional study visits (see Appendix 8: PK Substudy). Sample collection, storage, and shipment instruction for plasma samples will be provided in a separate Study Operations Manual by the Sponsor.

Trough samples will be collected immediately pre-dialysis and before any IV heparin is administered to the participant. Peak samples will be collected approximately 30 minutes after study intervention infusion ends. If study intervention is intravenously dosed outside the hemodialysis circuit, blood draws must be taken from a separate intravenous site. If the hemodialysis circuit is used for both intervention dosing and blood draws, separate access points in the hemodialysis circuit must be used with blood draws taken from an access point earlier in the dialysis circuit than the access point used for intervention infusion to infuse study intervention or other participant medications. The access point used for blood draws must be flushed with saline before sample collection. The time samples were drawn, time infusion was started, and time the infusion ended will be recorded.

8.7 Immunogenicity Assessments

ADA samples will be collected from all randomized participants according to the ADA sampling scheme outlined in the SoA (Section 1.3). Sample collection, storage, and shipment instructions for plasma samples will be provided in the operations/laboratory manual.

8.8 Pharmacodynamics

Sample collection, storage, and shipment instructions for pharmacodynamic samples will be provided in the operations/laboratory manual.

8.9 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants as specified in the SoA (Section 1.3): Blood for Genetic Analysis.

8.9.1 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 future biomedical research if the participant provides documented informed consent for future biomedical research. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

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

8.10 Future Biomedical Research Sample Collection

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

- Leftover DNA for future research
- Leftover main study plasma from PT/aPTT/FXI activity stored for future research

8.11 Visit Requirements

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

If a participant misses a scheduled visit and study sites are unable to reach the participant, the sites will contact the 'external contact person' identified by participants during screening (Section 8.1.12) to collect participant's vital status (Section 8.3.7).

Every effort should be made to align study visits with routine hemodialysis sessions.

8.11.1 Screening

Up to 30 days prior to intervention randomization, potential participants will be evaluated to determine whether they fulfill the entry requirements outlined in Section 5.1 and Section 5.2. Informed consent must be documented prior to performing any protocol-specific procedure.

Participants may be rescreened once, after consultation with the Sponsor. Rescreening should include all screening procedures listed in the SoA, including consent review. Participants who consent to this study and for any reason do not continue to randomization, will be considered a screen failure.

Note: Local laboratories can be used at Screening.

8.11.2 Randomization

At the Randomization Visit, participants who fulfill all inclusion/exclusion criteria will be randomized in a 1:1:1 ratio to MK-2060 20 mg, MK-2060 6 mg, or matching placebo and assigned a unique randomization number. Randomization must occur ≤30 days from the Screening Visit.

At the Randomization Visit, prior to initiation of hemodialysis, participants will undergo directed physical examination, measurement of vital signs, blood draws, and complete QoL questionnaires. After initiation of hemodialysis, they will receive the first dose of study intervention as described in Section 8.1.8.1, with assessment for systemic infusion reaction for up to 1 hour after completion of the infusion.

All procedures and assessments specified for the Randomization Visit will be performed after the Screening Visit procedures are performed.

8.11.3 Treatment Period

Participants in this study are expected to be at the study site several times a week for routine hemodialysis sessions. Study Visits for this study should be aligned with ongoing dialysis sessions (see Section 1.3 for visit windows).

Throughout the treatment period, participants will receive study intervention once a week during a routine dialysis session (Section 8.1.8). Participants will maintain this weekly schedule until the required number of overall AVG thrombosis events have occurred in the study (Section 9.9.1).

After Visit 6, study visits vary in frequency **but** study intervention will **continue to be administered on a weekly basis during routine dialysis sessions** until the participant completes the treatment or is discontinued from the study. Due to the weekly dosing, there will be many dialysis sessions where study intervention is administered but there will be no per-protocol study Visit. Every effort should be made to administer study intervention once weekly on the same day each week.

8.11.4 Final Efficacy Visit

The Final Efficacy Visit will be conducted for all participants once the planned number of AVG thrombosis events is observed and the efficacy cutoff is declared by the Sponsor.

If applicable, participants will continue in the study until the Final Efficacy Visit but will no longer be administered study intervention at this visit or going forward. Participants who prematurely discontinued study intervention are required to attend the Final Efficacy Visit for collection of clinical events and all assessments and procedures outlined in the SoA.

8.11.5 Safety Follow-up Visit

The Safety Follow-up Visit will take place approximately 90 days ± 7 days after the Final Efficacy Visit to assess for clinical events, AEs, and vital status. All assessments and procedures outlined in the SoA will be performed.

8.11.6 Premature Discontinuation Visit

At the Discontinuation Visit, all laboratory testing and procedures outlined in the SoA will be completed. Discontinuation Visit procedures will be performed on participants as soon as possible after discontinuing study intervention (≤7 days).

All participants who discontinue study intervention prior to completion of the protocol-specified treatment period will continue to attend all remaining protocol-specified visits, including the Safety Follow-up Visit, which is completed approximately 3 months from the date of last dose of study medication, and perform all procedures stipulated in the SoA. In the

event a participant specifically withdraws consent for further follow-up, no additional information is permitted to be collected.

If the participant does not attend the Discontinuation Visit, a telephone contact for collection of protocol-defined endpoint events should occur. In such cases, the phone contact will not be considered a protocol deviation. If the site is unable to reach the participant, the site will contact the 'external contact person' identified by the participant during screening to collect participant's vital status (Section 8.1.12).

8.11.7 Premature Intervention Discontinuation Safety Follow-up Visit

A Safety Follow-up Visit will be conducted for all participants who discontinue study intervention prematurely. This Visit will be conducted 90 days ± 7 days after the Premature Discontinuation Visit. All assessments and procedures outlined in the SoA will be performed.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study that are considered principal in nature. If changes are made to primary and/or key secondary hypotheses or the statistical methods related to those hypotheses after the study has begun but before any unblinding, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized will be documented in a sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Other planned analyses (ie, those specific to the analysis of PK data and FBR) will be documented in separate analysis plans.

9.1 Statistical Analysis Plan Summary

Key elements of the SAP are summarized here. The comprehensive plan is provided in Sections 9.2 through 9.12.

Study Design Overview	A Randomized Parallel-group, Placebo-controlled, Double-blind, Event-driven, Multi-center Phase 2 Clinical Outcome Trial of Prevention of Arteriovenous Graft Thrombosis and Safety of MK-2060 in Patients With End Stage Renal Disease Receiving Hemodialysis
Treatment Assignment	Participants will be randomized in a 1:1:1 ratio among 3 treatment groups: (1) MK-2060 20 mg QW, (2) MK-2060 6 mg QW, and (3) matching placebo.
Primary Analysis Populations	Efficacy: ITT Safety: APaT
Event-Driven Study Duration	The study is event-driven. It will continue until ~103 or 171 events have accrued for the interim analysis or final analysis.
Primary Endpoint	Time from randomization until the first occurrence of an AVG thrombosis event

Key Secondary Endpoint	Time to each AVG thrombosis event (first and recurrent) from randomization until the efficacy cutoff date
Statistical Methods for Key Efficacy Analyses	Primary: The HR and the associated 95% CI and *p*-values will be provided (MK-2060 vs placebo; 2 pairwise comparisons) based on a stratified Cox proportional hazards model.
Statistical Methods for Key Safety Analyses	For analyses in which 95% CIs will be provided for between-treatment differences (MK-2060 minus placebo) in the percentage of participants with events, these analyses will be performed using the M&N method.
Interim Analyses	A single IA is planned to assess efficacy and futility. The IA is planned to be performed once 60% information (103 events) for the primary endpoint is available. The study may stop at the IA if the criterion for efficacy is met. At the IA, a *p*-value for the comparison of MK-2060 versus placebo <0.001 (one-sided) will be considered statistically significant. If the efficacy criterion is met at the IA, the eDMC may recommend study continuation after considering safety factors, including the type and quality of bleeding events (Section 4.2.1.3). The study may stop for futility if the posterior probability is <30% that the true HR (MK-2060 vs placebo) in time to first occurrence of an AVG thrombosis event is ≤0.75 for each dose of MK-2060.
Multiplicity	At the IA and final analysis, there are 2 pairwise treatment group comparisons that may be tested to address the primary hypothesis. Testing will be performed in order of descending randomized dose and will stop with the first comparison that has a one-sided *p*-value ≥0.001 (or 0.024) for the IA (or final analysis).
Sample Size and Power	The planned sample size is approximately 489 participants, with 163 participants in each group. This study is event-driven and will complete after accumulation of sufficient events to determine efficacy for the time from randomization to the first occurrence of an AVG thrombosis event. If the true HR is 0.6, the study will have 80% power.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

The Sponsor will generate the randomized allocation schedule for study intervention assignment for this protocol, and the randomization will be implemented in IVRS.

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

Blinding procedures related to the planned IA are described in Section 9.7.

9.3 Hypotheses/Estimation

Objectives and hypotheses are stated in Section 3.

9.4 Analysis Endpoints

9.4.1 Efficacy Endpoints

Primary Efficacy Endpoint

- Time from randomization until the first occurrence of an AVG thrombosis event

Secondary Efficacy Endpoint

- Time to each AVG thrombosis event (first and recurrent) from randomization until the efficacy cutoff date

Efficacy endpoints are further described in Section 4.2.1.1.

9.4.2 Patient-reported Outcome Endpoints

- Mean change from baseline in KDQOL-SF scale scores over time
- Mean change from baseline in EQ-5D scores over time

PRO endpoints are described in Section 4.2.1.2.

9.4.3 Safety Endpoints

- The key safety endpoint is time from randomization until the first ISTH major bleeding event or a clinically relevant non-major bleeding event

Safety and tolerability will also be assessed by clinical review of all relevant parameters including AEs, laboratory safety tests, and vital signs.

Safety parameters are described in Section 4.2.1.3.

9.4.4 Pharmacokinetic Endpoint

The key exploratory PK endpoints for MK-2060 are C_{max} and C_{trough}.

Additional details are in Section 4.2.1.4.

9.4.5 Immunogenicity Endpoints

The exploratory immunogenicity endpoints are the incidence and magnitude (titer) of ADA to MK-2060.

Additional details are in Section 4.2.1.5.

9.4.6 Pharmacodynamic Endpoints

aPTT is the key PD endpoint.

Additional details are in Section 4.2.1.6.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Population

The ITT population will serve as the population for efficacy analyses. All randomized participants will be included in this population. Participants will be included in the treatment group to which they are randomized.

9.5.2 Patient-reported Outcome Analysis Population

The PRO population will be the subset of the randomized population based on clinical sites selected for PRO administration. This population consists of all randomized participants at the selected sites who had at least 1 IV administration (including only partial) of study intervention and had completed the baseline and at least 1 post-baseline PRO assessment. The PRO population definition will be applied separately to each questionnaire. Participants will be included in the treatment group to which they are randomized.

9.5.3 Safety Analysis Population

Analyses of safety will be performed in the APaT population, consisting of all randomized participants who received at least 1 IV administration (including only partial) of study intervention. Participants will be included in the treatment group corresponding to the study intervention they received for the analysis of safety data. This will be the randomized treatment group for all participants except for those who take incorrect study intervention for the entire treatment period. Such participants will be included in the treatment group corresponding to the study intervention actually received. Any participant who receives both correct and incorrect study intervention will be analyzed according to the randomized treatment group and a narrative will be provided for any events that occur during the IV administration period for which the participant was incorrectly dosed.

At least 1 laboratory or vital sign measurement obtained after at least 1 dose of study intervention is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

9.5.4 Pharmacokinetic Analysis Population

The population for PK data analysis is defined as all participants with at least 1 measurable PK sample following treatment with MK-2060.

9.5.5 Immunogenicity Analysis Population

The population for immunogenicity analysis includes all participants with at least 1 ADA assay result following treatment with MK-2060.

9.5.6 Pharmacodynamic Analysis Population

The primary analysis population for the PD endpoints will be all randomized participants who have at least 1 infusion (including only partial) of study intervention and have at least 1 PD marker assessment. Participants will be included in the treatment group to which they are randomized.

9.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives. Methods related to the exploratory objectives will be described in the sSAP.

P-values for the key secondary efficacy endpoint may be provided as an assessment of strength of evidence without intent to make inferential claims.

For analysis purposes, the baseline assessment is considered the one closest to but before or on the day of randomization (Day 1).

For stratified analyses, the stratification factors used for randomization (Section 6.3.2) will be applied to the analysis. Small strata will be combined in a way specified by a blinded statistician before the analysis, if needed.

Event accrual will be monitored throughout the course of the study. An efficacy cutoff date for the IA or final analysis will be declared when approximately 103 or 171 events, respectively, have accrued for the primary efficacy endpoint. If the study stops at the IA, the Final Efficacy Visits will be scheduled to occur within 14 days of Sponsor's notification to stop the study. If the study continues, the Final Efficacy Visits will be scheduled to occur in the 14 days following the final analysis efficacy cutoff date. All participants still on study treatment at the time of the efficacy cutoff date (Sponsor's notification to stop the study at IA or final analysis) will attend the Final Efficacy Visit with no further administration of study treatment and will have a scheduled Safety Follow-up Visit 90 days after the Final Efficacy Visit. Two database locks will then occur: one using the efficacy cutoff date and another after all safety follow-up data are available. Analyses addressing all efficacy objectives will be performed based on data up to the efficacy cutoff date. Supportive efficacy analyses will be performed including data through the Safety Follow-up Visit. The primary assessment of safety will use all data through the Safety Follow-up Visit. Supportive safety summaries will be provided based on data through the efficacy cutoff date.

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and key secondary objectives related to the efficacy endpoints.

The primary efficacy estimand following the guidance in ICH E9 (R1) [European Medicines Agency 2020] has the following 5 attributes:

1. The **treatment** condition of interest and the alternative treatment condition to which comparison will be made: intervention with MK-2060 or placebo.

2. The **population** of participants targeted by the clinical question: individuals with ESRD.

3. The **variable** (or endpoint) to be obtained for each participant that is required to address the clinical question: first occurrence of an AVG thrombosis event.

4. The specification of how to account for **other intercurrent events** to reflect the scientific question of interest: a treatment policy approach will be used for the intercurrent events of discontinuation of study intervention and/or initiation of non-study intervention. No observed data will be excluded from analyses because of these intercurrent events.

5. The **population-level summary** for the endpoint which provides the basis for a comparison between treatment conditions: the HR (MK-2060 vs placebo) for the time to first occurrence of an AVG thrombosis event.

9.6.1.1 Primary Efficacy Endpoint

The nonparametric Kaplan-Meier method will be used to estimate the time from randomization until the first occurrence of an AVG thrombosis event curve in each treatment group. The treatment effect will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment effect (ie, HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. *P*-values will be provided to address the primary objective and associated hypothesis (2 pairwise comparisons). Kaplan-Meier figures will also be provided.

Censoring will occur at the last follow-up contact where an AVG thrombosis event could be assessed on or prior to the cutoff date. Any participant who undergoes a kidney transplant during the study will be censored on the date of the kidney transplant.

Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 9.8.

Sensitivity analyses will be described in the sSAP.

9.6.1.2 Secondary Efficacy Endpoints

Time to each AVG thrombosis event (first and recurrent)

The primary approach for time to each AVG thrombosis event analysis will be the Andersen-Gill model [Andersen, P. K. 1982] to compare the MK-2060 each dose group to placebo. The Andersen-Gill model is an extension of the Cox proportional hazard model including both first and recurrent events.

For each comparison (MK-2060 vs placebo), treatment group and the stratification factors used for randomization will be included in the model as fixed effects. Robust standard errors will be used to account for correlations of event times within a participant.

Estimates of treatment comparisons and effect size including 95% confidence intervals will be provided based on the fitted model.

The analysis strategy for key efficacy endpoints is outlined in Table 3.

Table 3 Analysis Strategy for Key Efficacy Endpoints

Endpoint	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint			
Time from randomization until the first occurrence of an AVG thrombosis event	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censor
Key Secondary Endpoint			
Time to each AVG thrombosis event (first and recurrent) from randomization until the efficacy cutoff	Andersen-Gill model[a]	ITT	Censor

AVG=arteriovenous graft; ITT=Intent-to-Treat (all randomized participants).

[a] Treatment group and the stratification factors used for randomization will be included in the model as fixed effects.

9.6.2 Analysis Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, vital signs, and ECGs. The primary approach to analysis of safety will include all data through treatment including the 3-month follow-up assessment. The analysis will compare safety events in each MK-2060 group to the placebo group.

Adverse Events

AEs will be coded using the standard MedDRA and grouped according to SOC.

The analysis of safety results will follow a tiered approach (Table 4). The tiers differ with respect to the analyses that will be performed.

For the safety analyses, any participant who undergoes a kidney transplant during the study will be censored at 3 months after the date of the kidney transplant.

Tier 1 Events

Safety parameters or AEs of special interest that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% CIs. For this protocol, the time to the composite endpoint of an ISTH major bleeding event or a clinically relevant non-major bleeding event (adjudicated) is a Tier 1 event and will be analyzed following the analysis approach for the primary efficacy analysis.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for between-treatment differences in the proportion of participants with events.

Membership in Tier 2 requires that at least 4 participants in any treatment group exhibit the event; all other AEs and PDLCs will belong to Tier 3. The threshold of at least 4 events was chosen because the 95% CI for the between-group difference in percent incidence will always include zero when the treatment groups each have fewer than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in AEs and PDLCs.

In addition, summary measures of AEs consisting of the percentage of participants with any AE, with a drug-related AE, with an SAE, with an AE which is both drug-related and serious, who discontinued due to an AE, and who died will be considered Tier 2 endpoints.

For AEs prespecified for adjudication (cardiovascular, AVG thrombotic, bleeding events, and death), results of adjudication are also considered Tier 2 endpoints.

The 95% CIs will be provided for between-treatment differences in the percentage of participants with each Tier 2 event; these analyses will be performed using the M&N method.

Tier 3 Events

Safety endpoints that are not Tier 2 events will be considered Tier 3 events. Only point estimates by treatment group will be provided for Tier 3 safety parameters.

Continuous Safety Measures

For continuous measures such as changes from baseline in laboratory and vital signs parameters, summary statistics for baseline, on treatment, and change from baseline values will be provided by treatment group.

Table 4 Analysis Strategy for Safety Parameters

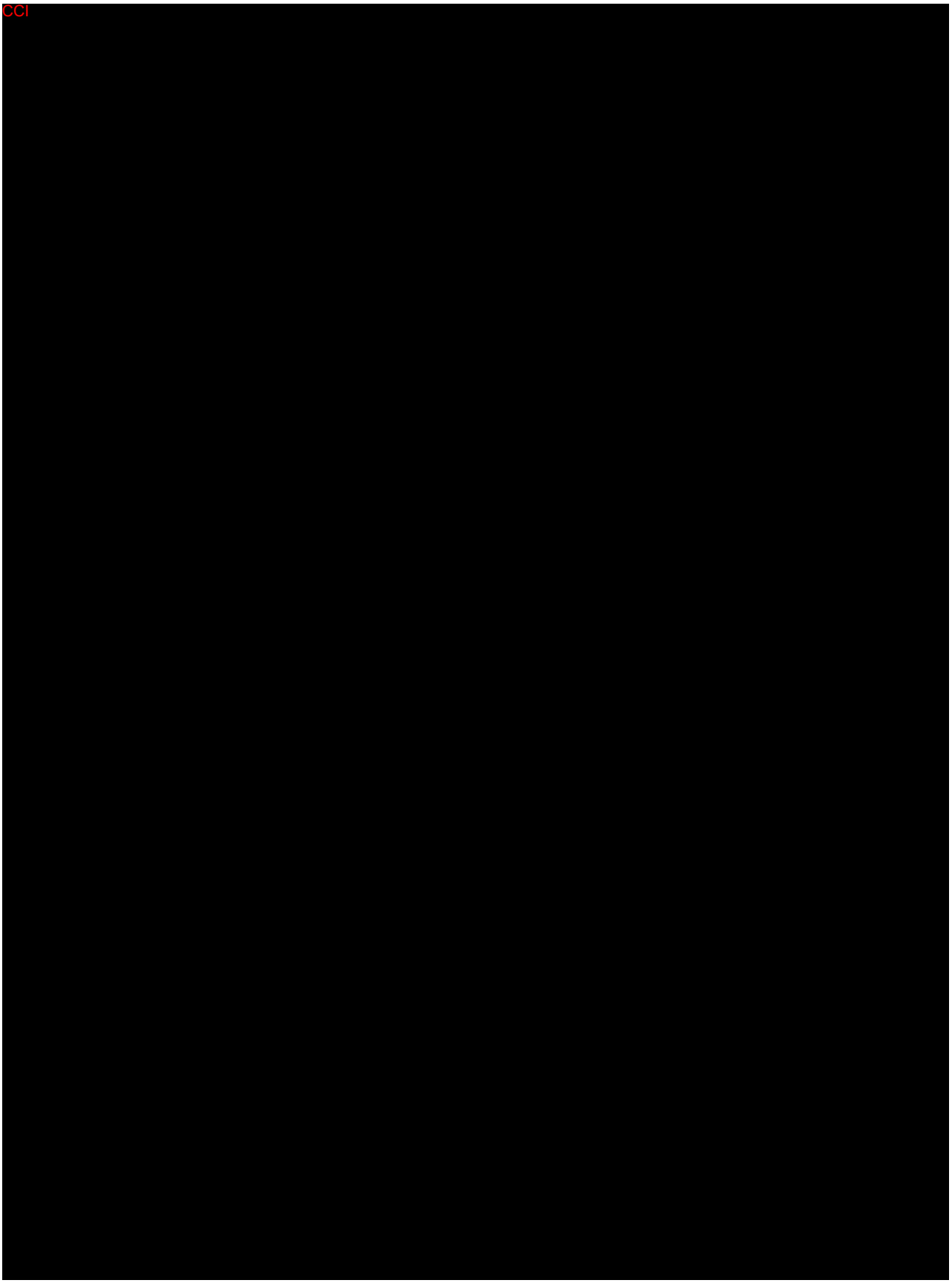
Safety Tier	Safety Endpoint	*P*-Value for Treatment Comparison	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	Time to first ISTH major bleeding event or clinically relevant non-major bleeding event (adjudicated)	X	X	X
Tier 2	Any AE		X	X
	Any serious AE		X	X
	Any drug-related AE		X	X
	Any serious and drug-related AE		X	X
	Discontinuation due to AE		X	X
	Death		X	X
	Adjudicated major thrombotic CV events		X	X
	Adjudicated AVG thrombotic events		X	X
	Adjudicated ISTH major bleeding events		X	X
	Specific AEs, SOCs, PDLCs (incidence ≥4 of participants in 1 of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs, PDLCs (incidence <4 of participants in all the treatment groups)			X
	Change from baseline results (laboratory tests, ECGs, vital signs)			X

AE=adverse event; AVG=arteriovenous graft; CI=confidence interval; CV=cardiovascular; ECGs=electrocardiogram(s); ISTH=International Society on Thrombosis and Haemostasis; PDLC=predefined limit of change; SOC=system organ class; X=results will be provided.

9.7 Interim Analyses

A single IA will be performed to assess efficacy and futility (non-binding). The IA will be conducted by an external unblinded statistician and an external unblinded programmer not otherwise involved in study conduct. Results of the IA will be reviewed by the external DMC, with recommendations provided to an internal executive oversight committee. If the eDMC recommends modifications to the design of the study or discontinuation of the study, the executive committee (and potentially other limited sponsor personnel) may be unblinded to results at the treatment level in order to act on these recommendations. The extent to which individuals are unblinded with respect to results of the IA will be documented by the unblinded statistician. Additional logistical details will be provided in the eDMC Charter.

CCI



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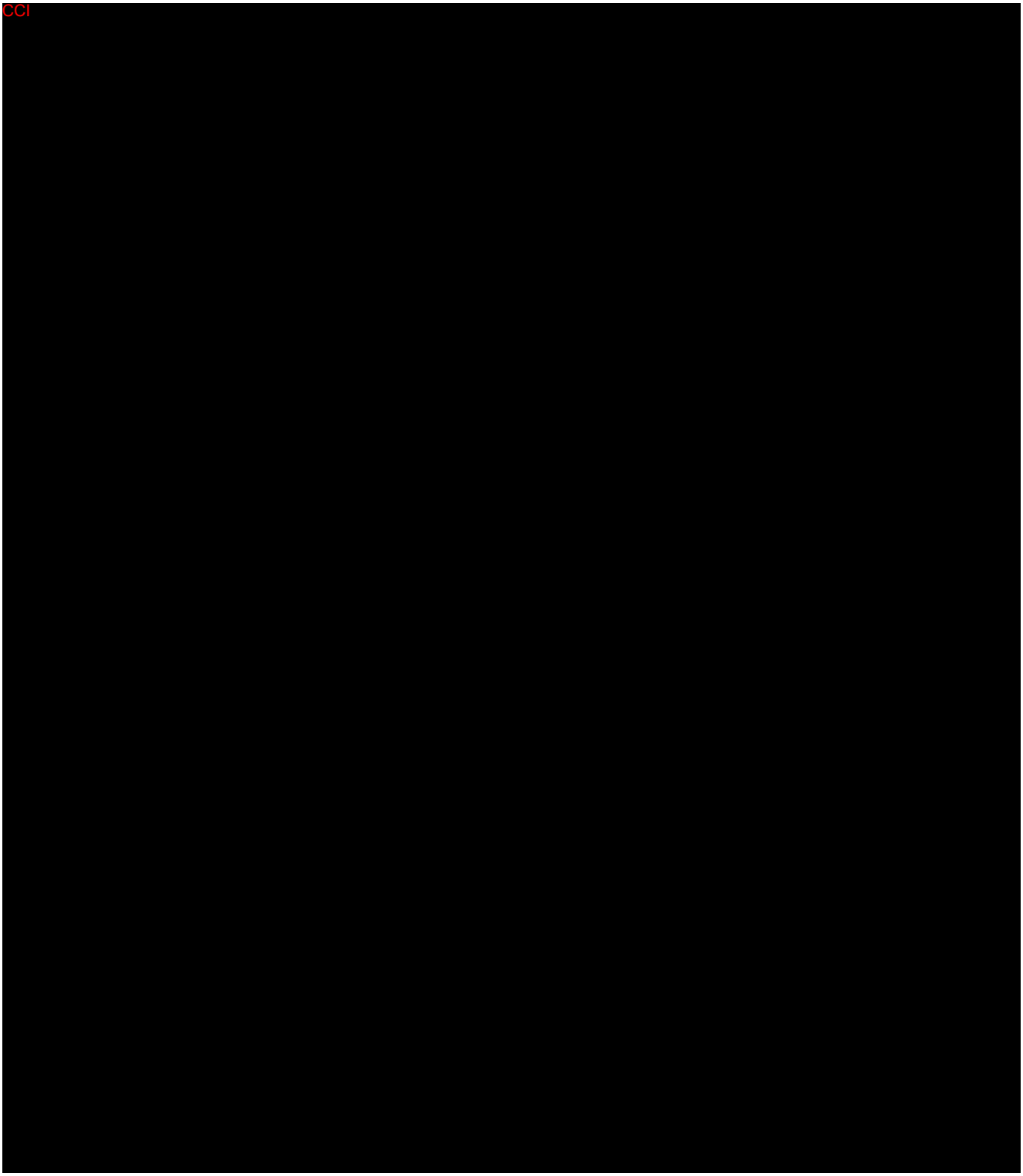

9.8 Multiplicity

At the IA and final analysis, there are 2 pairwise treatment group comparisons that may be made to test the primary hypothesis.

CCI

[redacted]

9.9 Sample Size and Power Calculations

9.9.1 Efficacy

An HR=0.6 is assumed for each MK-2060 vs placebo group comparison with respect to time to first occurrence of an AVG thrombosis event. This effect estimate is a conservative estimate based on published literature for pharmacological inhibition of FXa and FXIa. Large studies of FXa inhibitors compared to aspirin or placebo for prevention of DVT/PE in a high-risk population reported HR 0.26 to 0.36 [Agnelli, G., et al 2013] [Weitz, J. I., et al 2017]. Smaller studies of pharmacological agents targeting FXI activity compared to enoxaparin for prevention of DVTs in orthopedic surgical populations reported reductions in DVTs equivalent to RR 0.14 to 0.43 [Buller, H. R., et al 2015] [Weitz, J. I., et al 2020] (conservative estimate based on a several placebo-controlled FXa studies).

The planned sample size is approximately 489 participants, with 163 participants in each group. If the true HR is 0.6, with approximately 103 and 171 first AVG thrombosis events among 3 groups at the planned IA and final analysis, respectively, the study will have 80% power at one-sided alpha = 0.025.

Power and interim analysis calculations were performed using R ("gsDesign" package).

9.9.2 Safety

Given the sample size of 163 per group, Table 8 provides examples of minimum differences in proportions in AEs between each MK-2060 dose and placebo that would have a 95% CI that excludes zero based on the M&N method.

Table 8 Examples of AE Incidences for Which The 95% CI for the Difference Would Exclude Zero

MK-2060 n/N (%)	**Placebo** n/N (%)
4/163 (2.5%) 9/163 (5.5%) 24/163 (14.7%)	0/163 (0.0%) 2/163 (1.2%) 12/163 (7.4%)
AE= adverse event; n=number of participants with an adverse event; N=population size. Based on the M&N method	

9.10 Subgroup Analyses

The primary efficacy endpoint will be summarized for each of the following baseline defined subgroups:

- Region (US, non-US)
- Previous thrombosis of active AVG (yes/no)
- Regular aspirin use up to 150 mg daily at baseline (Yes or No)
- Concurrent diagnosis of diabetes (type 1 or type 2) at the time of randomization (Yes or No)
- Medical history of peripheral vascular disease (Yes or No)
- Age (≥65 years vs <65 years)
- Sex (male vs female)
- Race (White, Black or African American, Asian, Other)

9.11 Compliance (Medication Adherence)

A participant's percentage compliance will be calculated as the proportion of IV infusions over the total IV infusions they should have received. Summary statistics will be provided on percent compliance for the APaT population.

9.12 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in terms of number of IV infusions and duration of exposure defined as the time between first and last IV infusion. IV infusion interruption will be summarized. Summary statistics will be provided on extent of exposure for the APaT population.

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)

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. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will

support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

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

C. Confidentiality

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

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly 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 prior to transmission to the Sponsor.

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 Executive Oversight Committee

The EOC is comprised of members of the therapeutic area management. The EOC will receive and decide on any recommendations made by the DMC regarding the study.

10.1.4.2 External DMC

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the safety and efficacy data throughout the study. The voting members of the DMC are external to the Sponsor. The members of the DMC must not be involved in the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their role with respect to the study. The DMC will monitor the study at an appropriate frequency for evidence of adverse effects to study intervention and for evidence of efficacy and futility at the interim analysis (see Section 9.7), to be detailed in monitoring guidelines.

The DMC will recommend whether the study should continue (or other modifications, prespecified or otherwise, should be made) according to the protocol, considering the overall risk and benefit to study participants. The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study.

Specific details regarding the DMC's composition, responsibilities, and governance structure, including roles, responsibilities of various members, meeting facilitation, required documentation of DMC reports, and recommendations will be described in a separate charter that is reviewed and approved by the external DMC.

10.1.4.3 Clinical Adjudication Committee

A CAC will evaluate the following events for the purposes of confirming them according to the criteria in Sections 4.2.1.1 and 4.2.1.3, as well as evaluating the presence of confounding factors:

1. AVG thrombosis
2. Major thrombotic CV events
3. Bleeding events
4. Deaths

All personnel involved in the adjudication process will remain blinded to study intervention allocation throughout the study. The CAC will be comprised of an external panel of independent physicians experienced in assessing AVG thrombosis, CV events, and bleeding events. The members of the CAC will not be investigators in the MK-2060 study.

Criteria to define all these events will be detailed in the CAC charter.

10.1.4.4 Scientific Advisory Committee

This study was developed in collaboration with a SAC. The SAC is comprised of both Sponsor and non-Sponsor scientific experts who provide input with respect to study design, interpretation of study results, and subsequent peer-reviewed scientific publications.

10.1.5 Publication Policy

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

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

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical 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 trial 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.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted

standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

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

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.9 Source Documents

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

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 9 will be performed by the central laboratory. Local laboratories can be used at Screening.

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 9 Protocol-required 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	Nitrogen (BUN)	AST/ SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the ULN)
	Albumin	Bicarbonate	Chloride
	Potassium	Sodium	ALT/ SGPT
	Glucose	Calcium	Alkaline phosphatase
	Total Protein	Phosphorous	
Other Tests	• FSH (as needed for WOCBP) • Serum hCG pregnancy test (as needed for WOCBP) • Immunogenicity assay (ADA) • Coagulation test: INR, PT, aPTT • Factor XI activity • Serology (HIV antibody, hepatitis B surface antigen, and hepatitis C virus antibody)		
ADA= anti-drug antibodies; ALT= alanine aminotransferase; aPTT= activated partial thromboplastin time; AST= aspartate aminotransferase; BUN= blood urea nitrogen; FSH= follicle stimulating hormone; hCG= human chorionic antigen; HIV= human immunodeficiency virus; MCH= mean corpuscular hemoglobin; MCV= mean corpuscular volume; PT= prothrombin time; RBC= red blood cells; SGOT= serum glutamic-oxaloacetic transaminase; SGPT= serum glutamic-pyruvic transaminase; ULN= upper limit of normal; WBC= white blood cells; WOCBP= women of childbearing potential.			

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

Coagulation test results such as PT, INR, and aPTT need to remain blinded to the site and Sponsor staff involved in the study. Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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

10.3.1 Definition of AE

AE definition

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

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

- NOTE: For purposes of AE definition, study intervention 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 pre-existing 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 pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.2 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

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

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

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

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

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

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

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

f. **Other important medical events**

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

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

10.3.3 Additional Events Reported

Additional events that require reporting

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

- Is a cancer

- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

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

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

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

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

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

Assessment of intensity

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

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

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

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

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

Assessment of causality

- Did the study intervention cause the AE?

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

- **The following components are to be used to assess the relationship between the study intervention and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the 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 INTERVENTION, OR IF RE-EXPOSURE TO THE STUDY INTERVENTION POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

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

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her 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.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- 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 his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

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

Follow-up of AE and SAE

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

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

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

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

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

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

SAE reporting to the Sponsor via paper CRF

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

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

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

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

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

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

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

Women of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

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

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

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

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

10.5.2 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen- only contraceptive implant[c,d] • IUS[c,e] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen- containing) hormonal contraception[c,d] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c,d] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Acceptable Contraceptive Methods *Failure rate of >1% per year when used consistently and correctly.*
• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)[f]
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [c] Male condoms must be used in addition to hormonal contraception. [d] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [e] IUS is a progestin releasing IUD. [f] A combination of male condom with either cap, diaphragm, or sponge with spermicide are considered acceptable, but not highly effective, birth control methods. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male and female condom should not be used together (due to risk of failure with friction).

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

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

The specimens consented and/or collected in this study as outlined in Section 8.10 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 utilizing 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 future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main 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 main study use only. If specimens were collected from study participants specifically for future biomedical research, 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 prior to 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.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main 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 main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

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

operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3,4]

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

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

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

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

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

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

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

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

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

12. Questions

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

13. References

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

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

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

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

10.7 Appendix 7: Country-specific Requirements

10.7.1 Country-specific Requirements for Germany

Section 1.3 and Section 8.3.5.1

Pregnancy testing for participants in Germany must be performed prior to randomization, monthly during treatment phase, at the end of study intervention, and monthly for 120 days after the end of study intervention.

10.7.2 Country-specific Requirements for Canada

Section 5.2 Exclusion Criteria

Exclusion criterion: Participants will rare conditions that may predispose them to catastrophic bleeding events are excluded from this study.

10.8 Appendix 8: PK Substudy

The PK substudy will be available to all study sites. Sites should ask all main study participants to enter into the PK substudy and enroll those that consent. The PK substudy will enroll approximately 100 participants. The substudy will serve to improve the accuracy of the PK modeling for MK-2060 in individuals with ESRD on hemodialysis. Participants in the PK substudy will have PK samples collected in the main study (SoA, Section 1.3) and will have additional blood sampling collected for PK analysis (Table 10). Further details will be specified in a separate Site Procedure Manual and Substudy SAP.

Table 10 PK Substudy Schedule of Activities (in addition to the PK Schedule of Activities for the main study)

Study Period	Screening		Treatment Period[a]									
Visit Number/Title	1 Screen	2 Randomization	3	4	5	6	7	8	9	Visit n	Final Efficacy Visit	Safety Follow-up Visit
Scheduled Days/Month	-30 Days to Day 1	Day 1	Day 3	Day 5	Day 8	Day 15	Day 29	Day 57	Day 85	Every 3 months	Based on Efficacy Cutoff date[b]	3 months after Final Efficacy Visit
Visit Window			±1 day	±1 day	±1 days	±3 days	±3 days	±5 days	±7 days	±7 days		±7 days
PK Substudy evaluation		X[c]	X[d]	X[d]					X[c,e]			

PK= pharmacokinetics

Note: Visit windows are relative to the previous dose.

Visit n= Starting from Visit 9 (Day 85) all subsequent visits will be scheduled every 3 months until study completion is reached.

[a] Participants who discontinue study treatment will not continue to participate in the PK Substudy

[b] Efficacy Cutoff will be declared when the required number of events has accrued for the primary efficacy endpoint (see Section 9.7). If the study stops at IA, the Final Efficacy Visits will be scheduled to occur within 14 days of Sponsor's notification to stop the study. If the study continues, the Final Efficacy Visits will be scheduled to occur in the 14 days following the Final Analysis efficacy cutoff date.

[c] In addition to the main study PK draws, a third draw will be obtained 6 hours after the infusion began at Day 1 and Day 85.

[d] Trough sample collection only. To be collected pre-dialysis (before heparin is administered). Record the time the sample was drawn and the time infusion was started.

[e] PK will be collected prior to dialysis on the 2 dialysis visits post Day 85 and the next dosing visit after Day 85.

PK samples will be taken on the day the participant receives study intervention.

Note: If the participant misses a dialysis session on the day study intervention was scheduled, the participant will receive study intervention at the next hemodialysis session and resume their regular study intervention schedule the following week or as soon as possible.

10.9 Appendix 9: Hemostasis

FXI plays important roles in the coagulation cascade. FXI activation through the intrinsic pathway can initiate clot formation and activation of FXI by thrombin and facilitates further thrombin production and clot propagation. Clinical evidence from individuals with either FXI deficiency or presence of FXI inhibitors indicates that deficiencies in FXI activity lead to increased rates of bleeding in certain situations, for example oral surgeries. Prediction of an individual's bleeding risk based on the magnitude of reduction in FXI activity or associated aPTT prolongation is difficult, with poor correlation between levels of FXI activity and bleeding risk [Peyvandi, F., et al 2012] [Gailani, D. 2016] [Gomez, K. 2008].

Empirical evidence suggests that bleeding risk in surgical patients with reduced FXI activity is manageable through the addition of clotting factors in the form of either FFP or recombinant FVIIa or the use of antifibrinolytic agents, for example tranexamic acid. In individuals with FXI deficiency, perioperative infusion of FFP to provide exogenous FXI partially normalized aPTT prolongation and maintained adequate hemostasis in the setting of invasive orthopedic surgery [Sano, K., et al 2017]. In individuals undergoing major surgeries, a very low dose of recombinant FVIIa given at the end of surgery along with tranexamic acid provided simple and effective control of hemostasis [Salomon, O., et al 2019]. By extension, managing patients with reduced FXI activity from the action of MK-2060 with these therapies is expected to result in a similar reduction in bleeding risk.

The ability of human plasma, human FXI zymogen, and rhesus monkey plasma to reverse aPTT prolongation in human plasma and rhesus monkey plasma treated with MK-2060 was assessed in vitro. The aPTT prolongation was measured with varying MK-2060 concentrations: 17 nM (projected C_{min}), 30 nM (concentration leading to maximal aPTT prolongation), or 60 nM (projected C_{max}). Reversal of MK-2060 aPTT prolongation was evaluated by addition of human plasma (Figure 2, Panel A), purified human FXI zymogen (Figure 2, Panels B and D), and rhesus monkey plasma (Figure 2, Panel C). In human plasma, aPTT prolongation caused by 30 nM MK-2060 was reversed by the addition of both human plasma and FXI. The addition of 80% human plasma returned aPTT values expected from approximately 10% FXI activity levels, while 150% plasma was required to return values expected from 30% FXI activity. At 60 nM MK-2060, aPTT prolongation was reversed by the addition of 150% plasma and 200% plasma but remained at higher levels than the aPTT values expected from 10% FXI activity levels.

The effects of purified human FXI were also assessed. Previous studies have shown that in clinical practice, 2 plasma-derived factor XI concentrates could cause the reversal of aPTT prolongation: a high purity FXI protein [Bauduer, F., et al 2015] and a partially purified FX protein (Bioproducts Laboratory). Consistently, in this study, full reversal of aPTT prolongation could be achieved by the addition of purified human FXI protein: at 60 nM MK-2060, addition of FXI at concentrations > 58.1 nM resulted in a full reversal of aPTT prolongation.

Similar results were observed when additional rhesus monkey plasma or human FXI protein was added to aPTT assessed in rhesus monkey plasma. These results suggest that the impact of MK-2060-induced aPTT prolongation on hemostasis was similar in rhesus monkeys.

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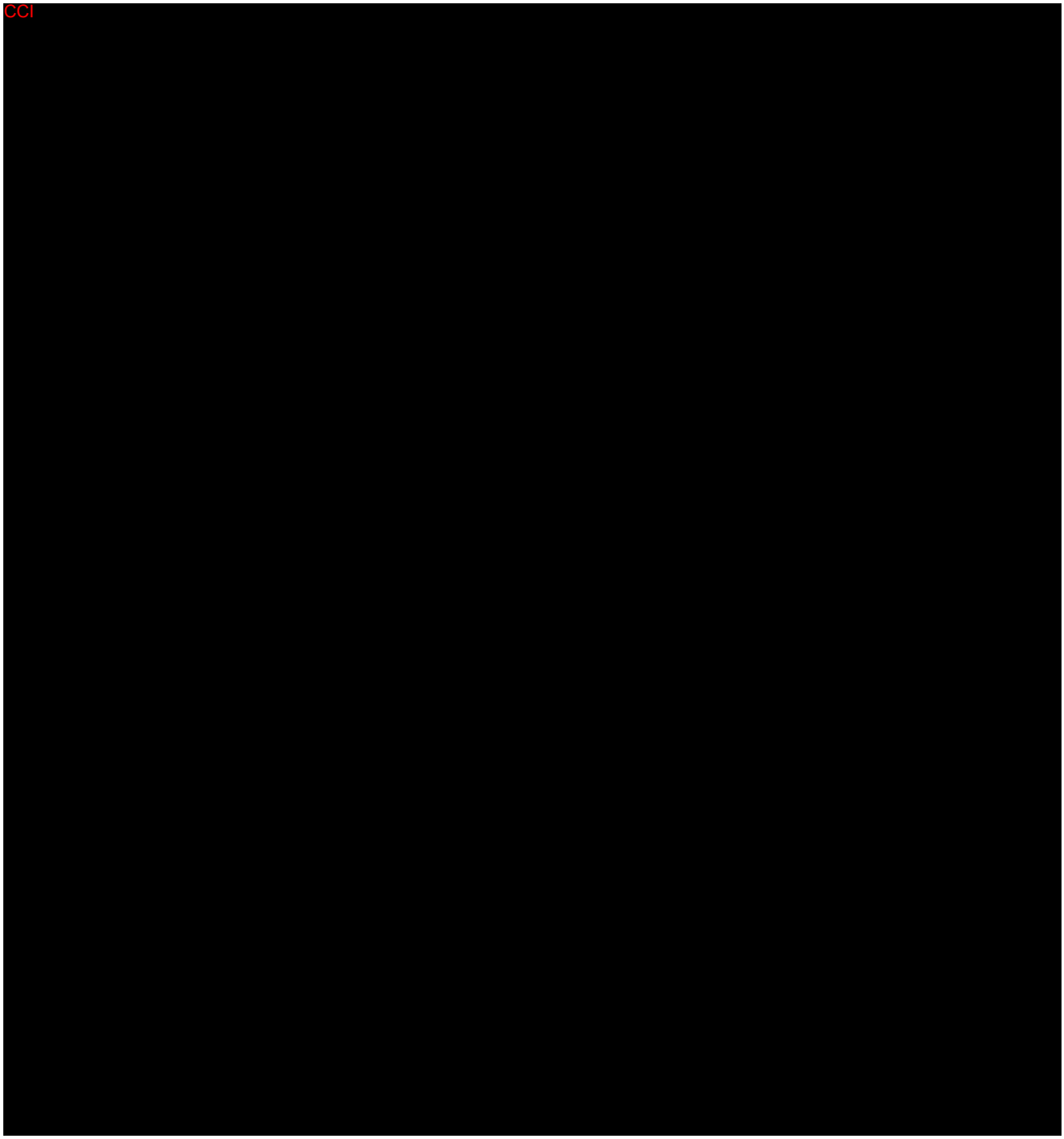

Source: Nonclinical Study Report PD008

In an in vivo study, normovolemic rhesus macaques received a single IV dose of 0.25 mg/kg MK-2060 followed, approximately 30 minutes after dosing, by a 4-hour transfusion with either FFP obtained from donor rhesus macaques or Plasma-Lyte A (control). MK-2060 administration resulted in an approximately 150% aPTT prolongation, as measured

approximately 30 minutes after dosing. A partial reversal of MK-2060-induced aPTT prolongation was achieved by the FFP transfusion but not by the Plasma-Lyte A (control) transfusion (Table 11).

Table 11 Mean aPTT Parameters in Monkeys After Dosing of MK-2060 Followed by Plasma-Lyte or Fresh Frozen Plasma Administration

	MK-2060 Dose: 0.25 mg/kg			
	Group			
	Plasma-Lyte[a]		FFP	
Time (hours)	Mean aPTT (sec)	SE (sec)	Mean aPTT (sec)	SE (sec)
-2	20.5	0.69	20.4	0.09
0	21.2	0.75	21.1	0.31
0.5[b]	50.8	2.1	50.0	1.1
2.5	51.3	1.7	46.7	0.49
4.5[c]	48.7	1.5	31.4	1.6
24	34.1	6.3	26.7	0.57

aPTT=activated partial thromboplastin time; FFP=fresh frozen plasma; IV=intravenous(ly); mg/kg=milligram per kilogram; SE=standard error; sec=seconds.

[a] Plasma-Lyte A injection pH 7.4 (multiple electrolytes injection, Type 1) is a sterile, nonpyrogenic isotonic solution in a single-dose container for IV administration. Each 100-mL container contains 526 mg sodium chloride; 502 mg sodium gluconate; 368 mg sodium acetate trihydrate; 37 mg potassium chloride; and 30 mg magnesium chloride.

[b] Time point denotes initiation of transfusion of FFP or Plasma- Lyte A.

[c] Time point denotes end of transfusion of FFP or Plasma-Lyte A.

Source: Nonclinical Study Report TT #20-4451.

The MK-2060 concentration at the beginning of the FFP transfusion (0.5 hours) was approximately 6 µg/mL (40.5 nM), which is in the range of the C_{max} values observed (28.0 to 61.3 nM) following a single dose of 20 mg or 40 mg MK-2060, respectively, in clinical study MK-2060-P004 in participants with ESRD.

These results indicate that FFP transfusion following the administration of a single 0.25 mg/kg MK-2060 IV dose to rhesus monkeys can partially reverse MK-2060-induced aPTT prolongation.

10.10 Appendix 10: Abbreviations

Abbreviation	Expanded Term
AEs	adverse event (s)
ADA	anti-drug antibodies
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
AV	arteriovenous
AVF	arteriovenous fistula
AVG	arteriovenous graft
AxMP	auxiliary medicinal product
BP	blood pressure
BUN	blood urea nitrogen
CAC	clinical adjudication committee
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum observed plasma concentration
CL	clearance
C_{min}	minimum blood plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
CORE	Center for Observational and Real-world Evidence
CrCl	creatinine clearance
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
C_{trough}	trough concentration
CV	cardiovascular
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOACs	direct oral anticoagulants
DVT	deep vein thrombosis
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
EEA	European Economic Area
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EQ-5D-5L	Euro quality of life 5-dimensional, 5-level questionnaire
ESRD	end-stage renal disease
EU CTR	European Union Clinical Trial Regulation
FDAAA	Food and Drug Administration Amendments Act
FBR	future biomedical research
FFP	fresh frozen plasma
FP	first patient
FPE	first patient enrolled
FSH	follicle stimulating hormone

Abbreviation	Expanded Term
FVIIa	factor VIIa
FXa	active factor X
FXI	factor XI
FXIa	active factor XI
GCP	Good Clinical Practice
GI	gastrointestinal
GU	genitourinary
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
ISTH	International Society on Thrombosis and Haemostasis
ITT	intent-to-treat
IUD	intrauterine device
IV	intravenous
IVRS	interactive voice response system
KDQOL-SF	kidney disease quality of life questionnaire-short form
KPS	Karnofsky performance status
LAM	lactational amenorrhoea method
LMWH	low molecular weight heparin
LPLV	last patient last visit
mAb	monoclonal antibody
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
M&N	Miettinen & Nurminen
CCI	[redacted]
NIMP	non-investigational medicinal product
NSAE	nonserious adverse event
NSAIDs	nonsteroidal anti-inflammatory drugs
NOAEL	no observed adverse effect level
NOEL	no-observed-effect-level
PD	pharmacodynamics
PDLC	predefined limits of change
pEFD	preliminary embryo-fetal development
PE	pulmonary embolism
PK	pharmacokinetic
PRO	patient-reported outcome
PT	prothrombin time
QID	four times a day
QOD	every other day
QoL	quality of life

Abbreviation	Expanded Term
QP2	department of quantitative pharmacology and pharmacometrics
QW	once a week
RBC	red blood cells
RNA	ribonucleic acid
SAC	Scientific Advisory Committee
SAEs	serious adverse event(s)
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SC	subcutaneous
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SoA	schedule of activities
SOC	system organ class
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
SW	study week
T_{max}	time to maximum plasma concentration
ULN	upper limit of normal
US	United States
USRDS	United States renal data system
VAS	visual analog scale
Vc	central volume
VTE	venous thromboembolism
WBC	white blood cells
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential
ZINB	zero inflated negative binomial

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