Official Protocol Title:	A Study to Evaluate Safety and Tolerability of Co-administration of MK-2060 and Clopidogrel in Participants with End-Stage Renal Disease on Hemodialysis
NCT number:	NCT05335005
Document Date:	09-Jun-2022

Title Page

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Protocol Title: A Study to Evaluate Safety and Tolerability of Co-administration of MK-2060 and Clopidogrel in Participants with End-Stage Renal Disease on Hemodialysis

Protocol Number: 008-01

Compound Number: MK-2060

Sponsor Name:

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

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

EudraCT	2021-005333-17
IND	142, 237

Approval Date: 09 June 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
MK-2060-008-01	09-JUN-2022	The original protocol is being amended to add standard text on photography of rash, to reflect the Sponsor's entity name and address change, and to correct typographical errors.
MK-2060-008-00	28-JAN-2022	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: [01]

Overall Rationale for the Amendments:

The original protocol is being amended to add standard text on photography of rash, to reflect the Sponsor's entity name and address change, and to correct typographical errors. These changes should not impose any undue safety risks to the participant nor have any impact on the PK/PD of MK-2060.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Title Page	IND number added	Additional clinical site in the US will be participating in the study
Title Page Section 10.1.1 Code of Conduct for Clinical Trials	Sponsor entity name and address change	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Section 3 Hypotheses, Objectives, and Endpoints	Removed "-008" from the tertiary objective "To investigate the relationship between the genetic polymorphisms of CYP2C19 and the pharmacokinetics of MK-2060."	Correction of typographical error

Section # and Name	Description of Change	Brief Rationale
Section 8.1.9 Discontinuation and Withdrawal Section 8.5 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events Section 10.3.1 Definition of AE Section 10.3.5 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor	Changed references of sections 8.4, 8.4.1, 8.4.3, and 8.4.6 to 8.5, 8.5.1, 8.5.3, and 8.5.6, respectively	Correction of typographical errors
Section 8.3.2.1 Resting Vital Signs	Revised sentence to read "The same method must be used for all measurements for each individual participant and should be the same for all participants at a given site"	Clarified that temperature measurements should be taken from the same location for all participants at a given site.
Section 8.3.6 Photograph of Rash	Added language recommending photographs of rash	Addition of Sponsor standard template text

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Added note that blood or saliva drug screen may be done for anuric participants	For participants who are unable to provide urine samples, blood or saliva samples may be used for drug screen.
Section 10.2 Clinical Laboratory Tests	Removed barbiturate testing requirement from drug screen.	There is low likelihood of drug interaction between barbiturates and either clopidogrel or MK-2060.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Study to Evaluate Safety and Tolerability of Co-administration of MK-2060 and Clopidogrel in Participants with End-Stage Renal Disease on Hemodialysis

Short Title: MK-2060 and Clopidogrel Co-administration Safety and Tolerability Study

Acronym: NA

Hypotheses, Objectives, and Endpoints:

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

This study is to be conducted in adult participants with End-Stage Renal Disease on Hemodialysis.

Objectives	Endpoints
Primary	
• Objective: To assess the safety and tolerability following multiple doses of concomitant treatment of MK-2060 and clopidogrel	• Bleeding related AEs, AEs and discontinuations due to AEs
Secondary	
• Objective: To evaluate plasma pharmacokinetics of MK-2060 following multiple doses of concomitant treatment of MK-2060 and clopidogrel	• MK-2060 plasma AUC0-168, Cmax, C168, Tmax, terminal t1/2, CL, Vz
• Objective: To evaluate the time required to achieve hemostasis following completion of dialysis in ESRD patients following concomitant treatment of MK-2060 and clopidogrel • Hypothesis: Mean time-to-hemostasis for MK-2060 treatment is less than 20 minutes	• Time to hemostasis

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Graft thrombosis
Population	Patient: adult participants with end-stage renal disease on hemodialysis
Study Type	Interventional
Intervention Model	Single Group This is a multi-site study.
Type of Control	None
Study Blinding	Unblinded Open-label
Blinding Roles	No Blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 17 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Up to 12 participants will be allocated.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Inter-vention Group Name</th><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Adminis-tration</th><th>Regimen</th><th>Use</th></tr>
<tr><td>NA</td><td>MK-2060</td><td>25 mg</td><td>Week 1: 3 doses
Week 2: 1 dose</td><td>Intravenous</td><td>Week 1: 3 doses
Week 2: 1 dose</td><td>Experimental</td></tr>
<tr><td colspan="7"></td></tr>
</table>
</td></tr>
<tr><td>Total Number of Intervention Groups/ Arms</td><td>There will be 1 intervention group with up to 12 participants.</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate in the study for approximately 21 weeks, from the time the participant provides documented informed consent through the final contact. After a screening phase of approximately 4 weeks and run-in period of approximately 2 weeks, each participant will receive assigned intervention for approximately 2 weeks. After the end-of-treatment each participant will be followed for approximately 96 days.</td></tr>
</table>

Study Governance Committees:

Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 1.	

Study Accepts Healthy Volunteers: No

A list of abbreviations is in Appendix 11.

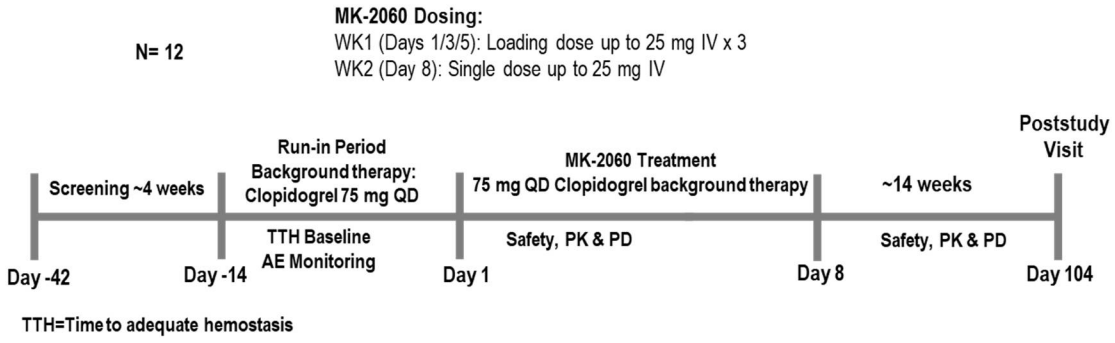
1.2 Schema

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

Table 1 Study Schema

	Week 1	Week 2
MK-2060[a]	25 mg IV MK-2060 x 3	25 mg IV MK-2060 x 1
[a] The suggested doses may be adjusted downward based on newly available safety, tolerability, pharmacokinetic and/or pharmacodynamic data observed in this study as well as other MK-2060 studies.		

Figure 1 Study Diagram



1.3 Schedule of Activities

Study Period:	Screening	Run-in [a]			Intervention														Post-study	Intervention Notes
Scheduled Day		Day -14	Day -7	Day -3	Day 1	Day2	Day 3	Day 5	Day 8	Day 9	Day 10	Day 12	Day 15	Day 21	Day 29	Day 35	Day 49	Day 67	Day 104	
Administrative Procedures																				
Informed Consent	X																			Sec. 8.1.1.1
Informed Consent for FBR	X																			Sec. 8.1.1.2
Participant ID Card	X																			Sec. 8.1.3
Inclusion/Exclusion Criteria	X	X		X	X															Sec. 5.1, 5.2, and 8.1.2 Review of IC/EC at Screening and during Run-in period; only specific criteria will be reviewed predose prior to treatment allocation on Day 1
Participant Bracelet					X															Sec. 4.3.1
Medical History	X																			Sec 8.1.4
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Sec. 6.5 & 8.1.5
Assignment of Screening Number	X																			Sec. 8.1.6
Assignment of Allocation Number					X															Sec. 8.1.7
MK-2060 Administration					X		X	X	X											Sec. 8.1.8
Record the time of the last Clopidogrel dose		X	X	X	X	X	X	X	X	X	X	X	X							
Domiciling					X	X	X	X	X											Sec. 8.1.11
On site Hemodialysis (HD) [b]		X	X	X	X		X	X	X				X							
Safety Procedures																				
Full physical examination	X				X		X	X	X				X						X	Sec. 8.3.1 To be done predose prior to HD on Days 1, 3, 5 and 8
Systemic Infusion Reaction Assessment					X	X	X	X	X	X										Sec. 8.4.1

Study Period:	Screen-ing	Run-in [a]			Intervention														Post-study	Intervention Notes
Scheduled Day		Day -14	Day -7	Day -3	Day 1	Day2	Day 3	Day 5	Day 8	Day 9	Day 10	Day 12	Day 15	Day 21	Day 29	Day 35	Day 49	Day 67	Day 104	
Local Infusion Reaction Assessment					X	X	X	X	X	X										Sec. 8.4.2
Assessment of Time to Hemostasis		X	X	X			X	X	X				X							Sec. 8.3.4. Performed immediately at the end of HD
Height	X																			Sec. 8.3.1 Height may be measured during Screening or Run-in period.
Weight	X																		X	Sec. 8.3.1, weight for BMI to be taken during Screening or Run-in period. Additional weight measurements can be taken per site SOP.
Resting Semi-Recumbent Vital Signs (blood pressure, heart rate, respiratory rate, body temperature)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X	Sec. 8.3.2.1 To be done at predose on Days 1, 3, 5 and 8
Orthostatic VS	X			X	X	X	X	X	X	X			X	X						Sec. 8.3.2.2 To be done at predose on Days 1, 3, 5 and 8. To be done before start of dialysis on Days -3 and 15.
12-lead ECG	X				X	X	X	X	X	X			X						X	Sec. 8.3.3 To be done at predose on Days 1, 3, 5 and 8
Serum FSH - (WONCBP only)	X																			
Serum or Urine Pregnancy test (WOCBP only)	X			X															X	
HIV, hepatitis B and C screen	X																			
Drug Screen and Alcohol Breath Test	X				X															Appendix 2 DS and alcohol breath test is mandatory at Screening and predose; any additional DS and alcohol breath tests are conducted per site SOP Blood or saliva DS may be used for anuric participants

Study Period:	Screen-ing	Run-in [a]			Intervention														Post-study	Intervention Notes
Scheduled Day		Day -14	Day -7	Day -3	Day 1	Day2	Day 3	Day 5	Day 8	Day 9	Day 10	Day 12	Day 15	Day 21	Day 29	Day 35	Day 49	Day 67	Day 104	
Hematology	X			X	X		X		X		X		X		X	X	X	X	X	Sec. 8.3.5 Appendix 2 To be done predose on Days 1, 3 and 8
aPTT/PT at Local Lab	X				X		X	X	X	X	X	X	X	X	X		X		X	Sec. 8.3.5 Appendix 2 Days 1, 3, 5 & 8: predose, 1h and 12h.
Chemistry [c]	X			X	X		X		X		X		X		X	X	X	X	X	Sec. 8.3.5 Appendix 2 To be done at predose on Days 1, 3 and 8
Hemoccult Test [d]				X		X		X	X		X		X		X			X		Sec. 8.3.5, 8.11.5
AE/SAE review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Sec 8.5, Appendix 3
Pharmacokinetics																				
Blood for Plasma MK-2060 Assay [e, f]					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Sec. 8.7 Days 1 & 8: predose, 1h, 12h. Days 3 &5: predose, 1h. See footnotes e, f
Blood for Clopidogrel Assay [e,f]		X	X	X	X	X	X	X	X											Sec. 8.7 See footnote e, f.
Pharmacodynamics																				
Blood for PT/aPTT/ FXI Activity by Central Lab [f]					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Sec. 8.8, Days 1 & 8: predose and 1h (within 15 min of end of infusion). Days 3 &5: predose
Biomarkers																				
Blood for Plasma ADA [f]					X								X			X		X	X	Sec. 8.9.3 Day 1: predose
Blood (DNA) for Planned Genetic Analysis					X															See section 8.8

Study Period:	Screen-ing	Run-in [a]			Intervention													Post-study	Intervention Notes
Scheduled Day		Day -14	Day -7	Day -3	Day 1	Day2	Day 3	Day 5	Day 8	Day 9	Day 10	Day 12	Day 15	Day 21	Day 29	Day 35	Day 49	Day 67	Day 104	

ADA=antidrug antibody; AE=adverse event; DNA=deoxyribonucleic acid; ECG=electrocardiogram; FBR=future biomedical research; FSH=follicle stimulating hormone; hCG=human chorionic gonadotropin; HD= hemodialysis; ID=identification; SAE=serious adverse event; SOP=standard operating procedure; VS=vital signs; WOCBP=women of childbearing potential; WONCBP= women of non-childbearing potential.

[a] Run-in period (Day -14 to Day -3) should be approximately 2 weeks before the initial dose of MK-2060.

[b] On site Hemodialysis: Pre-dose blood sample collections will be collected prior to HD initiation.

[c] Participants should fast for at least 4 hours prior to glucose measurement. Day 1 pre-dose tests can be conducted up to 24 hours prior to dosing.

[d.] Hemoccult test will be provided to subjects at Day-7 visit and participants will return the sample at Day-3. Other post-dose hemoccult test samples may be obtained within 48 hours of specified timepoint or first available sample if not within this time window.

[e] All pre-dose PK should be taken prior to initiation of dialysis on that day.

[f] Leftover main study plasma will be stored for future biomedical research if the participant (or their legally acceptable representative) provides documented informed consent for FBR.

2 INTRODUCTION

2.1 Study Rationale

MK-2060 is an anti-factor XI monoclonal antibody, being developed for prevention of thrombotic complications in end-stage renal disease (ESRD). Many ESRD patients take P2Y12 inhibitors as a concomitant antiplatelet therapy. The purpose of this study is to conduct a preliminary evaluation of the safety and tolerability of MK-2060 treatment in combination with a commonly used P2Y12 receptor inhibitor, clopidogrel, in ESRD patients.

2.2 Background

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

2.2.1 Pharmaceutical and Therapeutic Background

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

2.2.2 Ongoing Clinical Studies

MK-2060-004:

MK-2060-004 is a double-blind, randomized, placebo-controlled, multiple site, sequential panel, single and multiple dose trial of MK-2060 in adult participants (men and women of non-child bearing potential) with ESRD on HD. As of 14-Dec-2021, 41 participants have been administered at least one IV dose up to 40 mg MK-2060 or placebo. To date, single IV doses up to 40 mg in Part 1 have been generally well tolerated and there have been no treatment related SAEs and no discontinuations due to any drug-related AEs. There have been no AEs suggestive of hypersensitivity. Refer to IB Edition 5 for a detailed overview of Part 1 of the study, and available preliminary PK, PD, and safety results for Part 1.

- Updated Pharmacokinetic Data from MK-2060-004 Part 2 since IB Ed 5:

Analysis of preliminary PK from the single dose portion of MK-2060-004 (Part 1) suggested that a multiple dose regimen (25 mg dose on Day 1, 3, and 5, followed by 3 once-weekly maintenance doses of 25 mg) would result in rapid achievement of the Cmax at steady state. The projected Cmax steady state levels were comparable to what was observed for a single 40 mg IV dose and would provide sufficient PD in ESRD patients.

The IB was revised to include observed multiple dose PK parameters from Part 2 of MK-2060-004. PK parameters from 18 subjects in Part 2 are presented in [Table 2]. The observed PK concentration profiles from the Part 2 multiple-dose participants are consistent with the projected PK concentrations using the Part 1 single dose data, suggesting that the PK of MK-2060 is not time dependent.

Preliminary analysis detected no ADA positive samples over 150 days following a single dose of MK-2060 in Part 1 of MK-2060 PN004 in ERSD participants. Also, in Part 2 following multiple doses of MK-2060, no ADA positive samples were found over 111 days after initiation of dosing.

Table 2 Preliminary Part 2 Plasma Pharmacokinetic Parameters [Geometric Mean (%GCV)] of MK-2060 Following Multiple 60-minute IV infusion Doses of 25 mg QW

C_{max_day1} (nM)	C_{max_day22} (nM)	T_{max_day1} [a] (hr)	T_{max_day22} [a] (hr)	Cmax Ratio (Day 22 Day 1)	Post-wk1 $C_{predose}$ (nM)				Post-wk1 C_{eoi} (nM)		
					Day 8	Day 15	Day 22	Day 29	Day 8	Day 15	Day 22
32.4 (37.7)	93.4 (31.7)	1.00 (1.00 – 48.00) [b]	1.00 (1.00 – 24.00) [b]	2.68 (33.5)	47.1 (28.1)	44.7 (32.0)	44.8 (36.0)	44.6 (32.1)	91.4 (24.1)	96.8 (32.2)	93.5 (33.3)

[a] Median (Min-Max)

[b] On Day 1 one patient had Cmax at 48 hrs and on Day 22 five patients and one patient had Cmax at 12 and 24 hrs respectively.

- Updated Pharmacodynamic Activity Data from MK-2060-004 Part 2 since IB Ed 5:

In patients with ESRD on HD, following multiple doses of 25 mg of MK-2060, aPTT prolongation was observed with maximum mean fold change of approximately 2.95. The maximum aPTT prolongation occurred at ~ 1 hour post dose on Day 22 (end of infusion at the last dose). The multiple 25 mg doses inhibited FXI to a maximum level of approximately 2% of normal activity (based upon normal range of FXI activity standardized in the assay). The maximum inhibition of FXI activity was observed at 1 hour on Day 22.

- Updated Safety Data from MK-2060-004 Part 2 since IB Ed 5:

As of 14-Dec-2021, 20 participants have received multiple doses of MK-2060 25 mg or placebo IV, and 1 participant received only 1 dose of 25 mg IV in Part 2. This participant was discontinued from the study after the first dose due to not meeting Inclusion Criterion #1 (the participant is not being dialyzed via AVF or AVG).

Multiple IV doses of 25 mg have been generally well tolerated. There have been no deaths reported. There were no AEs suggestive of hypersensitivity. A total of two participants

discontinued the study drug due to AEs. One participant discontinued study drug due to the drug-related SAE lower gastrointestinal hemorrhage (additional information provided below) and another participant discontinued from the study drug due to a nonstudy drug related AE (COVID-19 infection). and did not receive the last dose on Day 22.

A total of 7 participants in Part 2 reported total 8 non-serious AEs (7 mild AEs, 1 moderate AE diarrhea) and 4 SAEs. Two AEs reported in one participant (mild nausea and mild sneezing) were considered as study drug related by the investigator. All other non-serious AEs were considered as not study drug related by the investigator.

A total of 4 participants in Part 2 reported total 4 SAEs, in which 1 SAE was considered as drug-related by the investigator and 3 SAEs were considered as not study drug related by the investigator. One participant reported a drug-related SAE of lower gastrointestinal hemorrhage after Day 5 dosing. This patient experienced bright red blood per rectum and was hospitalized overnight as a precaution. During the hospitalization blood counts were closely monitored and there was no decrease in hemoglobin or hematocrit, no blood transfusion or other blood products were required, and the bleeding resolved with conservative therapy. A lower gastrointestinal endoscopy revealed the source of the bleed was from internal hemorrhoids. One participant reported a nonstudy drug related SAE of pneumonia (hospitalized) approximately 6 weeks post the last dose. One participant reported a nonstudy drug related SAE of myocardial infarction (hospitalized and had triple bypass surgery coronary artery bypass graft) approximately 11 weeks post the last dose. One participant reported a nonstudy drug related SAE of arteriovenous graft thrombosis approximately 11 weeks post the last dose. All 4 participants recovered from the SAEs.

Across all treatments for 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 labs, and no changes in hematology labs suggestive of bleeding aside from the lower gastrointestinal haemorrhage summarized above. Similarly, an exploratory assessment of time to vascular access site hemostasis after removal of the hemodialysis catheters remained unchanged from baseline.

MK-2060-007:

MK-2060-007 is an event driven, randomized, placebo-controlled, parallel-group, multi-site, double-blind study of MK-2060 in participants with ESRD receiving hemodialysis via an AVG. This phase 2 study is designed to evaluate the efficacy and safety of MK-2060 20 mg QW and MK 2060 6 mg QW (with three loading doses in Week 1). As of 14-Dec-2021, 32 participants enrolled in MK-2060-007 with a maximum exposure of 78 days. MK-2060-007 is ongoing and safety data are blinded and preliminary.

2.2.3 Information on Other Study-related Therapy

Clopidogrel is an inhibitor of platelet aggregation. Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor (P2Y12) and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Biotransformation of clopidogrel is necessary to produce inhibition of platelet

aggregation, but an active metabolite responsible for the activity of the drug has not been isolated. Clopidogrel also inhibits platelet aggregation induced by agonists other than ADP by blocking the amplification of platelet activation by released ADP. Clopidogrel does not inhibit phosphodiesterase activity.

Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan. Dose dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses of clopidogrel. Repeated doses of 75 mg clopidogrel per day inhibit ADP-induced platelet aggregation on the first day, and inhibition reaches steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg clopidogrel per day was between 40% and 60%.

Platelet aggregation and bleeding time gradually return to baseline values after treatment is discontinued, generally in about 5 days. After repeated 75-mg oral doses of clopidogrel (base), plasma concentrations of the parent compound, which has no platelet inhibiting effect, are very low and are generally below the quantification limit beyond 2 hours after dosing. Clopidogrel is extensively metabolized by the liver. Administration of clopidogrel with meals did not show a meaningful effect on the bioavailability of clopidogrel as assessed by the pharmacokinetics of the main circulating metabolite. Clopidogrel is rapidly absorbed after oral administration of repeated doses of 75 mg clopidogrel, with peak plasma levels of the main circulating metabolite occurring approximately 1 hour after dosing.

The use of clopidogrel is contraindicated in hypersensitivity to it and in active pathological bleeding such as peptic ulcer or intracranial hemorrhage. Thrombotic thrombocytopenic purpura has been reported rarely following use of clopidogrel, sometimes after a short exposure (<2 weeks). Clopidogrel prolongs the bleeding time and therefore should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other pathological conditions (particularly gastrointestinal and intraocular).

2.3 Benefit/Risk Assessment

Participants in clinical studies will not receive direct benefit from treatment during participation as clinical studies are designed to provide information about the safety and properties of an investigational medicine.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

This study is to be conducted in adult participants with End-Stage Renal Disease on Hemodialysis

Objectives	Endpoints
Primary	
• Objective: To assess the safety and tolerability following multiple doses of concomitant treatment of MK-2060 and clopidogrel	• Bleeding related AEs, AEs and discontinuations due to AEs
Secondary	
• Objective: To evaluate plasma pharmacokinetics of MK-2060 following multiple doses of concomitant treatment of MK-2060 and clopidogrel	• MK-2060 plasma AUC0-168, Cmax, C168, Tmax, terminal t1/2, CL, Vz
• Objective: To evaluate the time required to achieve hemostasis following completion of dialysis in ESRD patients following concomitant treatment of MK-2060 and clopidogrel • Hypothesis: Mean time-to-hemostasis for MK-2060 treatment is less than 20 minutes	• Time to hemostasis
Tertiary/Exploratory	
• Objective: To explore the effect of concomitant treatment of MK-2060 and clopidogrel on aPTT.	• aPTT fold change from baseline
• Objective: To explore the effect of concomitant treatment of MK-2060 and clopidogrel on prothrombin time.	• Prothrombin time fold change from baseline
• Objective: To evaluate plasma pharmacokinetics of clopidogrel (clopidogrel carboxylic acid) following multiple doses of concomitant treatment of MK-2060 and clopidogrel	• Clopidogrel (clopidogrel carboxylic acid) plasma concentration
• Objective: To explore the development of ADAs measured in blood samples following multiple doses of concomitant treatment of MK-2060 and clopidogrel	• ADA

Objectives	Endpoints
• Objective: To investigate the relationship between the genetic polymorphisms of CYP2C19 and the pharmacokinetics of MK-2060. Variation in CYP2C19 may be analyzed for association with any laboratory or clinical data collected in this study	• Germline genetic variation in CYP2C19 and association to clinical data collected in this study

4 STUDY DESIGN

4.1 Overall Design

This is an open label, multi-site, multiple dose trial of MK-2060 in adult participants (men and women) with ESRD on HD to be conducted in conformance with Good Clinical Practice. The study will evaluate the safety and tolerability of MK-2060 and clopidogrel administered in combination in adult participants with ESRD on HD.

The study will enroll up to 12 ESRD participants receiving clopidogrel as background therapy. After an approximately 14-day run-in period to enable measurement of baseline time to hemostasis and AE monitoring, each participant will receive a loading dose of 25 mg IV MK-2060 for a total of 3 doses in week 1 and a single dose of 25 mg IV MK-2060 in week 2.

Participants will be closely monitored for safety and tolerability, including safety labs, local lab aPTT and PT results, physical exam to check bleeding related AEs, vital signs (VS) and 12-lead ECG, as well as local infusion site reactions and systemic reactions to MK-2060 infusion. All participants in this study will be followed through approximately 96 days after the last study dose for safety and tolerability, including all adverse experiences, safety labs, local lab aPTT and PT results, physical exam to check bleeding related AEs, VS, and 12-lead ECG.

Because this is a Phase 1 assessment of MK-2060 in humans, the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is therefore written with flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Refer to Section 8.11.6 for examples of modifications permitted within the protocol parameters.

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

4.2 Scientific Rationale for Study Design

MK-2060 has been generally well-tolerated both in GLP toxicity studies and in Phase 1 clinical trials, which have included single dose assessment in normal healthy volunteers

(PN001) and single/multiple dose assessment in ESRD/HD patients. Preliminary safety data from PN004 suggests that MK-2060 does not prolong time to hemostasis following HD catheter removal. The purpose of this study is to evaluate the safety of MK-2060 in ESRD/HD patients taking clopidogrel as concomitant antiplatelet therapy, since such patients require antiplatelet/P2Y12 inhibitor treatment for variety of comorbidities occurring in conjunction with their renal disease and hemodialysis treatment. Pertinent to this study design, a study of clopidogrel in chronic HD patients showed no impact of clopidogrel on time-to-hemostasis following removal of dialysis catheters [Kaufman, J. S., et al 2000]. Furthermore, a recent publication suggested that use of clopidogrel in patients with severe FXI deficiency/hemophilia type C does not add to the bleeding risk in that particular population [Perek, S., et al 2017]. Other FXI inhibitors in clinical development have demonstrated low risk of bleeding with FXI inhibition. Taken together, these data support conducting this study with MK-2060 in ESRD/HD patients receiving clopidogrel as background therapy.

4.2.1 Rationale for Endpoints

4.2.1.1 Safety Endpoints

Based on the data from PN001 (healthy subject study) and PN004, it is expected that multiple dose IV administration of MK-2060 will be well-tolerated in participants with ESRD on HD. However, the safety and tolerability following multiple doses of concomitant treatment of MK-2060 and clopidogrel are primary endpoints for this trial and will be carefully monitored. Physical examinations, VS, ECGs, laboratory safety tests (serum chemistry and hematology), aPTT, PT, and AEs related to bleeding will be assessed throughout the treatment period. AEs, including local infusion site reactions and systemic reactions to MK-2060 infusion, will be assessed throughout the treatment period.

Bleeding related AEs will include any sign or symptom of bleeding, even if not requiring intervention by a medical/healthcare professional, as well as clinically-relevant non major bleeding or major bleeding.

As with all biologic medications, MK-2060 carries a risk of acute reactions upon exposure, particularly with IV administration. These reactions can be categorized as common acute infusion reactions, acute hypersensitivity reactions, and high cytokine release reactions. Common acute infusion reactions are usually mild, can occur even with the first dose, and manifest with rigors, back pain, abdominal pain, nausea, vomiting, diarrhea, dyspnea, flushing, pruritus, and changes in heart rate or blood pressure. Acute hypersensitivity reactions typically occur after repeated exposures but can occur with the first dose. In addition to signs similar to common infusion reactions, participants may develop urticaria, wheezing, coughing, facial swelling, angioedema and more significant changes in VS. Cytokine release reactions are exceedingly rare but severe. They manifest as severe headache, nausea, vomiting, back pain, fever, hypotension and multiorgan failure. The risk of any of these infusion reactions to MK-2060 is considered low given its profile in preclinical safety studies. There were no infusion reactions, no acute hypersensitivity reactions, and no cytokine release reactions observed so far in any MK-2060 clinical studies (see Investigator's Brochure for more information on the Phase 1 clinical trial experience

with MK-2060). Participants will be monitored closely during the infusion with scheduled VS and physical examinations as indicated in the Schedule of Activities. In addition to monitoring for acute reactions to MK-2060, the infusion site will be assessed for signs of reactogenicity, including pain, tenderness, erythema and swelling by study staff, particularly during the first week after infusion. AEs and SAEs will be collected through Day 104.

Time to adequate hemostasis after decannulation of vascular access

A secondary objective of this study is to explore the effect of MK-2060 given as a single and multiple IV dose on time to hemostasis after decannulation of the hemodialysis vascular access site in ESRD patients on clopidogrel therapy. In the dialysis unit after the completion of hemodialysis the dialysis catheters are removed from the dialysis access site (i.e., AV fistula or AV graft). Upon decannulation, pressure is held until adequate hemostasis has been obtained for both the arterial and venous sites. In this study the process is standardized such that change in time to hemostasis from baseline (i.e., average of values obtained from the run-in period) can be assessed (see the operations manual for details).

On three dialysis visits prior to dosing, time to adequate hemostasis for both the arterial and venous sites will be assessed to establish a baseline (mean of three run-in period assessments). Should time to hemostasis be different for arterial and venous sites, the longer of the two should be recorded. This endpoint will then be assessed at the end of the dialysis sessions after each dosing days as specified in the SoA. Change from baseline will be calculated.

Anti-drug antibodies (ADAs) to MK-2060

The presence and titer of ADAs will be measured using validated assays. ADAs can develop to biologics like MK-2060. ADAs may be clinically inconsequential or may change the PK and/or drug efficacy. Moreover, ADAs may lead to safety events, such as acute or delayed hypersensitivity reactions. Thus, the titer of ADAs will be correlated with PK and safety events. If needed, positive ADAs will be further evaluated to determine whether they are able to neutralize MK-2060 activity against FXI. If MK-2060-specific antibodies are confirmed to be present, additional tests will be performed to determine if the antibodies have the ability to neutralize the action of MK-2060.

4.2.1.2 Pharmacokinetic Endpoints

Plasma PK of MK-2060

The evaluation of MK-2060 PK will include determination of non-compartmental PK parameters including AUC0-168, Cmax, C168, Tmax,terminal t1/2, CL and Vz.

4.2.1.3 Pharmacodynamic Endpoints

aPTT and FXI activity (performed by Central Lab)

In order to assess PD, this study will include an assessment of aPTT prolongation levels (relative to baseline), and FXI activity levels, with assays being performed at a Central Laboratory. For PK/PD modeling, aPTT and FXI activity levels will be related to plasma exposure. The time points for PD data collection are based on the projected PK profile of MK-2060. Estimation of the aPTT effects of MK-2060 following multiple well-tolerated doses is an exploratory objective of this study.

4.2.1.4 Planned Exploratory Biomarker Research

4.2.1.4.1 Planned Genetic Analysis

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

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

In addition to studying variation across the human genome, CYP2C19 genotyping will be specifically investigated for association of variations with any clinical data.

4.2.1.5 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.

4.3 Justification for Dose

The dosing regimen for MK-2060 (25 mg IV on days 1, 3, 5 of week 1 as loading phase, and 25 mg IV once in week 2) is the same as the first two weeks dosing of the high dose arm in the ongoing Ph2 study (PN007) and first two weeks of dosing of part 2 of MK-2060-004 in ESRD patients. This dose is projected to result in ~90% of participants with an aPTT of >1.5X baseline at Cmin during steady state (C168). The observed median Cmax is 93.4 nM and median Cmin is 44.8 nM at steady state after multiple dose of MK-2060 at 25 mg in ESRD patients receiving hemodialysis (MK-2060-004, incomplete data of Part 2) which achieved similar exposures as the projected steady state exposures of 25 mg in PN007 (median Cmax of 77 nM and median Cmin of 42 nM). As this is a Phase 1 assessment of MK-2060 in humans, and the PK, pharmacodynamic and safety profiles of the compound are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants. Details of allowed modifications are provided in Section 8.11.6.

4.3.1 Rationale for Dose Interval and Study Design

The ESRD/HD population is the target patient population for MK-2060, and a proportion of ESRD patients are taking antiplatelet therapy, such as clopidogrel. Dosing of MK-2060 with the 1 week loading regimen followed by 1 maintenance dose on Day 8 provides a duration of time where MK-2060 exposures are highest and FXI inhibition/aPTT prolongation is maximized (but not exceeding exposures observed in previous trials in ESRD/HD patients). With the slow clearance of MK-2060, there will be prolonged pharmacology during washout, during which time safety and bleeding-related AEs will continue to be monitored.

Each participant will be dosed and observed until discharge (~24 hours post-dose) for safety/tolerability. 24 hours is sufficient to monitor for initial safety/tolerability and local infusion site reactions and for systemic reactions to infusion. Following discharge, the following measures are being taken in this protocol to ensure the safety of study participants:

- Participants will be informed that they are taking an anticoagulant as a participant in this trial, and that this might increase the risk of bleeding as might occur in surgery, dental procedures, or strenuous exercise/contact sport activities.
- Participants will be excluded if they have planned significant dental procedures, including surgery, or other planned surgical procedures within duration of participation in the trial.
- Participants will be required to avoid scheduling any non-urgent/elective surgical or dental procedures, and to avoid strenuous physical activity and contact sport activities for the duration of the trial.
- Participants will be provided with an identification card and a medical alert bracelet, both of which identify them as participants in an anti-coagulant

research trial and, in the event of an emergency, will serve to notify healthcare providers that they might be at risk for provoked bleeding.

- If local lab aPTT values are > 3-fold above baseline, or local lab PT values are > 1.5 fold above baseline (at any time point), participants will be asked to remain in the clinic for at least 24 hours, and until aPTT/PT values are no longer increasing (upon retest) and at the discretion of the investigator.

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

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

A study may be paused during review of newly available preclinical/clinical safety, PK, pharmacodynamic, efficacy, or biologic data or other items of interest, prior to a final decision on continuation or termination of the study. It may be necessary to keep the study open for gathering/reviewing of additional supportive data to optimally complete the objective(s) of the study. If necessary, the appropriate amendment(s) to the protocol and/or appropriate communication(s) will be generated. If the decision has been made to end the study following this review period, the study end will be defined as the date of the Sponsor decision, and this end of study date supersedes the definitions outlined above. The Competent Authority(ies) and IRB(s)/IEC(s) will be apprised of the maximum duration of the study beyond the last participant out and the justification for keeping the study open.

4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

5 STUDY POPULATION

Male and Female participants with ESRD on HD between the ages of 18 and 80 years (inclusive) 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

A participant will be eligible for inclusion in the study if the participant meets all of the following criteria:

Type of Participant and Disease Characteristics

1. ESRD maintained on stable outpatient HD regimen at a healthcare center for > 3 months prior to dosing, using an established and normally functioning, regular flow, uninfected mature AV fistula or AV graft and skin consistent with standard chronic HD access injuries, and HD stability defined as Kt/V ≥1.2 within 3 months prior to dosing.

2. On HD regimen at least 3 times per week for a minimum of 3 hours per dialysis session, using a complication-free well-maintained AV fistula or AV graft, expected and plan to continue this throughout and at least up to poststudy.

3. Is taking clopidogrel for a minimum of 2 weeks prior to the first dosing of MK-2060 administration and will continue to take clopidogrel for at least the duration of MK-2060 treatment.

4. Have a Body Mass Index (BMI) ≥ 18 and ≤ 45 kg/m^2. BMI = weight (kg)/height $(m)^2$. Dry weight (body weight after hemodialysis) should be used for BMI calculations.

5. Baseline health is judged to be stable based on medical history, physical examination, vital sign measurements and ECG performed prior to treatment allocation.

6. Liver function test (serum alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) must be equal to or below 1.5X upper limit of normal (ULN) and deemed not clinically significant by the investigator.

7. Be willing to comply with the trial restrictions (see Section 5.3) for a complete summary of trial restrictions).

Demographics

8. Is male or female, from 18 years to 80 years of age inclusive, at the time of providing informed consent.

Female Participants

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

- Not a WOCBP

OR

- A WOCBP and:

  - Uses an acceptable contraceptive method, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix [5] during the intervention period and for at least 96 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies

  - Has a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 76 hours before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, 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 in Section 8.5.5.

  - Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

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

Additional Categories

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

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

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

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

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

5.2 Exclusion Criteria

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

Medical Conditions

1. History of any clinically significant concomitant disease or condition (including treatment for such conditions) or diseases whose current condition is considered clinically unstable that, in the opinion of the investigator, could either interfere with the study drug, compromise interpretation of study data, or pose an unacceptable risk to the patient. Participants with a remote history of uncomplicated medical events (e.g., uncomplicated kidney stones, as defined as spontaneous passage and no recurrence in the last 5 years, or childhood asthma) may be enrolled in the study at the discretion of the investigator.

2. Institutionalized, mentally or legally incapacitated at the time of prestudy (screening) visit or expected during the conduct of the study or has a history of clinically significant psychiatric disorder in the last 5 years. Participants who have had situational depression may be enrolled in the study at the discretion of the investigator.

3. History of cancer (malignancy), including adenocarcinoma,

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

4. Has blood coagulation test from local lab (aPTT, PT) ≥ 20 % outside of normal range in screening period (confirmed by recheck)..

5. Any other clinically significant abnormalities in laboratory test results at screening that would, in the opinion of the investigator, increase the patient's risk of participation, jeopardize complete participation in the study, or compromise interpretation of study data.

6. Has a history of deep vein thrombosis or pulmonary embolism. Has a history of vascular access thrombosis within 1 month prior to enrollment. Has a personal or family history of

bleeding disorder (e.g., hemophilia, Factor V Leiden, prothrombin gene mutation, protein C or S deficiency, ATIII deficiency, anti- phospholipid Ab syndrome).

7. Has a history of GI bleeding, duodenal polyps or gastric ulcer in the last 5 years or severe hemorrhoidal bleed in last 3 months prior to screening.

8. Has a clinically significant history of or current frequent epistaxis within the last 3 months or active gingivitis prior to screening.

9. At the time of screening or pre-dose, has planned significant dental procedures (including planned dental surgery), or other planned surgical procedures within duration of participation in the trial.

10. Is positive for hepatitis B surface antigen or HIV. Participants positive for hepatitis C antibodies may be enrolled with agreement of both investigator and sponsor.

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

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

13. Has a tattoo, scar, or other physical finding at the area of the infusion site that would interfere with infusion or a local tolerability assessment.

Prior/Concomitant Therapy

14. Unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs or herbal remedies (except clopodigrel) beginning approximately 2 weeks (or 5 half-lives) prior to administration of the initial dose of study intervention, throughout the study, until the poststudy visit. There may be certain medications that are permitted (see Section 6.5).

15. Has ongoing anticoagulant therapy (warfarin, apixaban, dabigatran, rivaroxaban, edoxaban, betrixaban) or antiplatelet therapy which does not include clopidogrel (ie. prasugrel, ticagrelor, ticlopidine, and aspirin). Intradialytic heparin is permitted.

16. Has a history (subject recall) of receiving any human immunoglobulin preparation such as IVIG or RhoGAM within the last year.

17. Has a history (subject recall) of receiving any biological therapy (including human blood products or monoclonal antibodies; excluding erythropoietin and insulin) within the last 3 months or 5 half-lives (whichever is longer), or vaccination within the last month.

Exceptions:

- Participants who have received seasonal flu vaccine and/or pneumococcal vaccine within one month prior to Day 1 dosing may be enrolled at the discretion of the investigator.

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

Prior/Concurrent Clinical Study Experience

18. Participated in another investigational study within 4 weeks (or 5 half-lives, whichever is greater) prior to the screening visit. The window will be derived from the date of the last dose in the previous study.

Diagnostic Assessments

19. Has a blood pressure >190 mmHg systolic or >110 mmHg diastolic.

20. Exclusion criteria for ECG:

    - Heart rate < 40 or > 110 bpm

    - QTc interval > 500 msec

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

Other Exclusions

21. Under the age of legal consent.

22. Consumes greater than 3 servings of alcoholic beverages (1 serving is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day. Participants who consume 4 servings of alcoholic beverages per day may be enrolled at the discretion of the investigator.

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

24. A regular user of cannabis, any illicit drugs or has a history of drug (including alcohol) abuse within approximately 2 years. Participants must have a negative drug screen prior to treatment allocation. Participants with a positive drug screen due to the use of

physician prescribed medications (e.g., opioids, benzodiazepines, antidepressants) may be enrolled at the discretion of the investigator. In addition, participants with a positive THC may be enrolled at the discretion of the investigator if the participants' THC use is under 4 times/month and the participants agree to not use during their study participation. Participants with positive THC on screening may have rechecks performed at the discretion of the investigator to ensure compliance with abstinence from THC use during study participation.

25. The investigator has any concern regarding safe participation in the study or for any other reason the investigator considers the participant inappropriate for participation in the study.

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

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

5.3.1.1 Diet Restrictions

Fasting requirements for laboratory safety evaluations are specified in Section 10.2.

All meals on study dosing days will be served as to not interfere with the study procedures. Meals and snack(s) will be provided by the investigator as per the CRUs standard procedures when domiciling.

Participants will be instructed to avoid ingesting certain foods (such as red meat, broccoli, turnips etc.) and certain medications and supplements (such as vitamin C supplements etc.) for about three days prior to feces sample collection to avoid false positive hemoccult test.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

5.3.2.1 Caffeine Restrictions

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

5.3.2.2 Alcohol Restrictions

Participants will refrain from consumption of alcohol 24 hours before the prestudy and poststudy visits and from 24 hours prior to and after study intervention administration. Participants will refrain from consumption of alcohol 12 hours prior to scheduled outpatient visits.

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

5.3.2.3 Tobacco Restrictions

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

5.3.3 Activity Restrictions

Participants will avoid unaccustomed strenuous physical activity (ie, weight lifting, running, bicycling, etc) from the prestudy (screening) visit throughout the study and until the poststudy visit.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen-failure information may be included, as outlined in the eCRF entry guidelines. Minimal information may include demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements.

5.5 Participant Replacement Strategy

If a participant discontinues from study intervention or withdraws from the study within 21 days after the first dosing, a replacement participant may be enrolled if deemed appropriate by the investigator and Sponsor. The replacement participant will generally receive the same intervention or intervention sequence (as appropriate) as the participant being replaced. The replacement participant will be assigned a unique treatment/randomization number.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies MK-2060 will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted before dosing the replacement participant. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 3.

Table 3 Study Interventions

Arm Name	Arm Type	Intervention Name	Inter-vention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP/ NIMP	Sourcing
MK-2060	Experi mental	MK-2060	Drug	Lyophilized Powder	7.5 mg/vial	25 mg	IV Infusion	Week 1: Days 1, 3, 5 Week 2: Day 8	Experi mental	IMP	Provided centrally by Sponsor.

EEA =European Economic Area; IMP=investigational medicinal product; IV = intravenous; NIMP=noninvestigational medicinal product.

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

All supplies indicated in Table 3 will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

Refer to Section 8.1.8 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Participants in this study will be allocated by nonrandom assignment.

6.3.2 Stratification

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

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the intervention administered.

6.4 Study Intervention Compliance

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

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during time periods specified by this protocol for that medication or vaccination. If there is a clinical indication for any medications or vaccinations specifically prohibited, 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 or vaccination 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 or vaccine (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

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

Concomitant use of the following medications will be allowed during the conduct of the study as long as the subject has been on a stable dose and treatment regimen for at least approximately 2 weeks prior to screening and is able to withhold the use within four hours

prior to administration of the first dose of study drug. The name (generic and brand), dose and regimen for all concomitant medications should be recorded on the appropriate CRF.

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

ALLOWED MEDICATIONS

Lipid Lowering Agents: Statins

Atorvastatin
Simvastatin
Pravastatin
Lovastatin
Rosuvastatin
Pravastatin

Lipid Lowering Agents: Fibrates

Fenofibrate
Gemfibrozil

Lipid Lowering Agents: Other

Ezetimibe

Anti-Hypertensive Medications:

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

Specific therapeutic categories include:

1. ACE inhibitors

Benazepril
Captopril
Enalapril
Fosinopril
Lisinopril
Moexipril
Perindopril
Quinapril
Ramipril
Trandolapril

2. Angiotensin II Receptor Antagonists

Candesartan
Eprosartan
Irbesartan
Olmesartan
Telmisartan
Valsartan

3. Diuretics

Hydrochlorothiazide
Chlorothiazide
Amiloride
Triamterene
Spironolactone
Loop-diuretics, e.g., furosemide

4. Beta-blockers

5. Calcium channel-blockers

Diabetes Medications

Specific therapeutic categories include:

1. Insulin

2. Metformin

3. Sulfonylureas

Glipizide
Glyburide
Glimepiride

4. Meglitinides

Repaglinide
Nateglinide

5. Thiazolidinediones

Pioglitazone
Rosiglitazone

6. DPP-4 Inhibitors

Linagliptin
Saxagliptin
Sitagliptin
Vildagliptin

7. GLP-1 Analogs

Exenatide
Liraglutide

Iron

Phosphate Binders

Vitamin D

Erythropoietin

PROHIBITED MEDICATIONS

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

Oral Anticoagulants (Intradialytic heparin is permitted in the study)

Warfarin
Apixaban
Dabigatran
Rivaroxaban
Edoxaban
Betrixaban

Antiplatelet Medications

Prasugrel
Ticagrelor
Ticlopidine
Aspirin

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

6.5.1 Rescue Medications and Supportive Care

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

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

6.6 Dose Modification (Escalation/Titration/Other)

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

6.6.1 Stopping Rules

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

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

1. An individual participant reports an SAE considered related to the study intervention by the investigator.

2. Two (2) or more participants report Severe Nonserious AEs considered related to the study intervention by the investigator.

3. If one or more treatment-related infusion adverse events of severe intensity occurs in 2 or more participants.

4. An increase in local lab aPTT >4.0-fold versus screening baseline as confirmed after repeat measurement in 2 or more participants. Local lab aPTT measured at the Screening Visit should be used as baseline value.

5. An increase in local lab PT >1.5-fold versus screening baseline as confirmed after repeat measurement in 2 or more participants. Local lab PT measured at the Screening Visit should be used as baseline value.

In severe FXI-deficient populations, aPTT prolongations greater than 3-fold have been observed [Asakai, R., et al 1991]. Using the same PD aPTT assay utilized in PN001 and to be used by the central lab in this study, samples of pooled normal human plasma were compared to those from FXI-deficient patients, which were tested individually [Ellsworth K 2018]. In normal human plasma, the clot time ranged between 31.8 and 36.4 seconds. In plasma from FXI deficient patients, the clot time ranged between 99.5 and 128.1 seconds, which corresponded to a range of 2.9 to 3.9-fold prolongation in aPTT compared to that of the normal human plasma. From data collected in PN001, it appears that higher doses of MK-2060 provide similar inhibition as the severe FXI-deficient phenotype, evidenced by MK-2060-associated increases in aPTT (local lab) up to 3.9-fold at the highest dose in PN001 (120 mg administered subcutaneously). These aPTT prolongations occurred in the absence

of prolongation of PT and were associated with >95% inhibition of FXI activity, with no evidence of MK-2060-related AE. Therefore, the stopping criteria based upon an aPTT is >4-fold after repeat measurement in 2 or more participants.

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

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

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study-site personnel, the Sponsor, and/or designee are not blinded. Study intervention (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

6.9 Standard Policies

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

6.9.1 Study Site Retention Samples

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period

will still continue to participate in the study as specified in Section 1.3 and Section 8.1.9, or if available, a PCL. If a participant discontinues at any point during the dosing period, all safety follow-ups and PK, PD sample collections should continue weekly post the last dose. Safety procedures include full physical examination, systemic infusion reaction assessment, semi-recumbent vital signs, orthostatic vital signs, safety lab measurements, AE reviews and assessment of time to hemostasis if on-site dialysis. The poststudy timing and assessments should be performed as outlined in Section 1.3.2

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

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- The participant has a positive drug screen at any time during the course of the study and after confirmation by recheck.

7.2 Participant Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

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

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

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

8 STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

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

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

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

The maximum amount of blood collected from each participant over the duration of the study will not exceed ~453 mL (Appendix 8).

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

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

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

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

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention allocation, site personnel will add the treatment/randomization number to the participant identification card.

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

8.1.4 Medical History

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

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

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

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

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or study staff according to the specifications within the pharmacy manual.

8.1.8.1 Timing of Dose Administration

MK-2060 will be prepared and dosed per the instructions outlined in the Study Pharmacy Manual. All doses of MK-2060 will be given 30 minutes after initiation of hemodialysis and administered over approximately 60 minutes.

8.1.9 Discontinuation and Withdrawal

The investigator or study coordinator must notify the Sponsor when a participant has been discontinued/withdrawn from the study and/or intervention. If a participant discontinues for any reason at any time during the course of the study, the participant may be asked to return to the clinic (or be contacted) for a poststudy visit as per the number of days described in Section 8.11.4 to have the applicable procedures conducted. However, the investigator may decide to perform the poststudy procedures at the time of discontinuation or as soon as possible after discontinuation. If the poststudy visit occurs prior to the safety follow-up time frame as specified in Section 8.5.1, the investigator should perform a follow-up telephone call at the end of the follow-up period (Section 8.5.1) to confirm if any AEs have occurred since the poststudy clinic visit. Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.5.

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for FBR will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed before the request being received by the Sponsor will continue to be used

as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

8.1.10 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study. The emergency unblinding call center will be available so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.11 Domiciling

Participants will report to the CRU the evening prior to the scheduled day of trial drug administration and remain in the unit for 24 hours after each MK-2060 administration. At the discretion of the investigator or at the request of the participant, participants may remain in the CRU longer.

8.1.12 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

Critical Equipment for this trial includes:

- Infusion pumps
- VS and ECG instruments
- All equipment to process study drug and samples, such as but not limited to, centrifuge equipment, pipettes, and freezers for MK-2060 and sample storage.

8.2 Efficacy/Immunogenicity Assessments

The amino acid sequence of MK-2060 is highly similar to standard human IgG4 sequences. The mechanism of action of MK-2060 is not immunomodulatory and the ESRD population is less likely to have a robust immune response.

Following analysis for ADA from PN001, one out of 45 (2.2%) had positive ADA test result (50 mg SC dose, at the Day 90 post dose time point). The presence of ADA did not appear to

have an effect on the PK of MK-2060. Determining the impact of ADA on PD was not possible as there was no measurable PD effect at the Day 90 time point.

From the ongoing PN004, no ADA positive samples were found over 150 days following a single dose of MK-2060 in Part 1 of MK-2060 PN004 in ERSD participants. In Part 2 of PN004, following multiple repeat dosing of MK-2060, no ADA positive samples were found over 111 days after initiation of dosing. Based on the PK profiles observed to date and available ADA analysis data from both PN001 and PN004, it is unlikely that ADA have affected the current PK profiles. Therefore, the overall risk of immunogenicity is expected to be low for MK-2060.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in Appendix 8.

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

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard. Height and weight will also be measured and recorded.

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

8.3.1.1 Body Weight and Height

Body height and weight will be obtained with the subjects shoes off, jacket or coat removed.

8.3.1.2 Body Mass Index (BMI)

BMI equals a person's weight in kilograms divided by height in meters squared ($BMI=kg/m^2$). BMI will be rounded to the nearest whole number according to the standard convention of 0.1 to 0.4 round down and 0.5 to 0.9 round up.

Dry weight (body weight after hemodialysis) should be used for BMI calculations.

8.3.2 Vital Signs

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

- VS will be measured in a semi-recumbent position after at least 10 minutes rest and will include temperature, systolic and diastolic BP, and pulse and RR.

8.3.2.1 Resting Vital Signs

Vital Sign Measurements (Heart Rate and Blood Pressure)

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

The Day 1 predose (baseline) resting HR and BP will be in triplicate measurements, obtained at least 1 to 2 minutes apart within 3 hours of dosing MK-2060. The median of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). All other VS measurements will be single measurements.

Participants will continue to rest semi-recumbent from dosing until 4 hours postdose except to stand for any study-related procedure.

Body Temperature

Body temperature will be measured. The same method must be used for all measurements for each individual participant and should be the same for all participants at a given site.

Respiratory Rate

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

8.3.2.2 Orthostatic Vital Signs

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

8.3.3 Electrocardiograms

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

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

The correction formula to be used for QTc is Fridericia.

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

The Day 1 predose ECGs will be obtained in triplicate at least 1 to 2 minutes apart within 3 hours before dosing MK-2060. The median of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). Unless otherwise designated in the flow chart, all other ECG measurements will be single measurements.

If a participant demonstrates an increase in QTc interval ≥60 msec compared with median predose baseline measurement, the ECG will be repeated twice within 5 minutes. The median value of the QTc interval from the 3 ECGs will represent the value at that time point. If the median QTc interval increase from baseline for any postdose time point is ≥60 msec, the participant will continue to be monitored by repeat 12-lead ECGs every 15 minutes for at least 1 hour or until the QTc is within 60 msec of baseline. If prolongation of the QTc interval ≥60 msec persists, a consultation with a study cardiologist may be appropriate and the Sponsor should be notified.

If the median QTc interval is ≥500 msec, the Sponsor should be notified and the ECGs should be reviewed by a cardiologist. The participant should be telemetry monitored (until the QTc is <500 msec) or should be considered for transfer to a location where closer monitoring and definitive care (eg, a CCU or ICU) is available.

If the participant has unstable hemodynamics, or has any clinically significant dysrhythmias noted on telemetry, the participant should be immediately transferred to an acute care setting for definitive therapy.

If prolongation of the QTc is noted, concomitant medications that prolong QTc should be held until the QTc is within 60 msec of baseline and the QTc is <500 msec.

A cardiologist will be consulted by the investigator as needed to review ECG tracings with significant abnormalities.

8.3.4 Assessment of Time to Hemostasis

Assessment of time to adequate hemostasis will be conducted at the conclusion of each onsite hemodialysis session. Procedure for assessment of time to hemostasis will be provided in a separate trial Study Operations Manual by the Sponsor. Baseline time to hemostasis will be established by the assessments performed during the Run-in period.

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

8.3.6 Photograph of Rash

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

8.4 Management of Infusion Reaction During and Post-dose

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

In rare instances, systemic infusion reactions are severe and may have a fatal outcome. It is likely that most infusion reactions will occur within the first 30-60 minutes of administration, though they may be observed up to 24-30 hours post-dose. An anaphylactic reaction is a severe type of infusion reaction that is characterized by cutaneous and mucosal symptoms, such as generalized hives, pruritis or flushing, swollen lip-tongue-uvula and angioedema, accompanied by respiratory compromise (bronchospasm, stridor or hoarseness) and/or changes in blood pressure (hypotension). Severe infusion reactions, including cytokine release syndrome and hypersensitivity reactions must be promptly treated with interruption

of the infusion, medical management, appropriate monitoring, and life-saving measures. Appropriate resuscitation equipment and a physician should be readily available during the period of drug administration. Less severe infusion reactions may respond to a reduction in the infusion rate and medical management.

8.4.1 Systemic Infusion Reaction Assessment

Participants will be monitored during the administration of MK-2060 for 24 hours post-dose at CRU after the initiation of administration. During this time, signs and symptoms of a systemic injection/infusion reaction, including but no limited to fever, VS changes (tachycardia/hypotension), pruritis, urticarial (hives), lip swilling, angioedema, bronchospasm, stridor, hoarseness, and shortness of breath will be monitored. Injection/infusion reactions must be assessed and managed promptly.

8.4.2 Local Infusion Reaction Assessment

A local infusion site examination will be obtained as outlined in Section 1.3 and will include an assessment of any pain, tenderness, erythema/redness and induration/swelling. These events will be evaluated based upon the system outlined in the guidance for the industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials in Table 4. Infusion reactions must be assessed and managed promptly per site procedure.

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

Table 4 Local Infusion Reaction Assessment

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

8.5 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 8.5.3.

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.

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

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

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

From the time of intervention allocation through ~96 days after cessation of intervention, all AEs, SAEs and other reportable safety events must be reported by the investigator.

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

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and 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 5.

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

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

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

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event.

8.5.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.5.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in allocated participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.5.4 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.

8.5.5 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.

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

Not applicable.

8.5.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.6.

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

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

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

8.6 Treatment of Overdose

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

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

8.7 Pharmacokinetics

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

8.7.1 Blood Collection for Plasma MK-2060 and Clopidogrel

Sample collection, storage, and shipment instructions for plasma samples will be provided in the Study Operations Manual by the Sponsor. Samples taken on the day of infusion will be collected in the opposite arm from the infusion site. The 1-hour PK sample will be obtained immediately prior to the end of infusion (i.e. no more than 15 min before anticipated time of the end of infusion). As plasma concentrations of the parent compound of clopidogrel are very low and are generally below the quantification limit beyond 2 hours after dosing, concentrations of the main circulating metabolite clopidogrel carboxylic acid will be assessed to monitor clopidogrel therapy.

8.8 Pharmacodynamics

Sample collection, storage, and shipment instructions for PT/aPTT/ FXI activity by central lab samples will be in the operations 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.

8.9.1 Planned Genetic Analysis Sample Collection

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

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

8.9.2 Blood Collection for PT, aPTT, FXI Activity

PT and aPTT at screening, predose, and postdose specified in the SoA will be performed locally for safety monitoring. All other predose and postdose PT and aPTT, as well as FXI activity will be performed at a central vendor for PK/PD analysis. Sample collection, storage, and shipment instructions for the PT, aPTT, FXI activity will be provided in a separate Study

Operations Manual by the Sponsor. The primary data for statistical analysis and modeling will be based on the information from the central vendor.

8.9.3 Blood for Plasma ADA

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

8.10 Future Biomedical Research Sample Collection

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

- Leftover DNA for future research.
- Leftover main study plasma for future research.

8.11 Visit Requirements

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

8.11.1 Screening and Run-in Period

Screening Visit:

Within 6 weeks before intervention allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

Participants may be rescreened after consultation with the Sponsor. Rescreening should include all screening procedures listed in the SoA, including consent review.

Run-in Period:

Approximately 14 days before intervention allocation, potential participants who meet inclusion/exclusion criteria at the Screening Visit will report to the clinical research unit to perform on site hemodialysis on the days per SoA. Baseline Time to hemostasis will be measured during the run-in period. Refer to the SoA for other procedures required for the run-in period.

8.11.2 Treatment Period

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

After all predose procedures have been completed, participants will be assigned a unique allocation number in a computer-generated allocation schedule.

Participants will be administered study drug as indicated in Section 6. Participants who on Day 1 have a significant acute illness or fever prior to the administration of study drug may be rescheduled.

8.11.3 Poststudy

The poststudy visit will occur approximately 96 days following administration of the last dose of study drug. Procedures outlined in the poststudy visit may be obtained on Day 104 (±7 days). However, follow up on any clinical or laboratory AEs should occur in person if the poststudy visit occurs prior to 96 days following administration of the last dose of study drug.

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

At any point if a participant discontinues from treatment but continues to be monitored in the study, all of study procedures specified in the SoA may be completed upon joint agreement between the investigator and the Sponsor. The subset of study procedures completed will be communicated in a PCL.

8.11.5 Critical Procedures Based on Study Objectives: Timing of Procedure

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

At any postdose time point, the blood sample for MK-2060 needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible. Study procedures can be performed before or after the prescribed/scheduled time.

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

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

The following variance in procedure collection times will be permitted.

- Postdose PK and PD sample collection, standard safety evaluations (VS, ECG, laboratory safety tests (including chemistry/hematology, aPTT, PT), physical exam (full, symptom driven, systemic injection/infusion, local injection/infusion)) as outlined in Table 6 and Table 7 below.

Table 6 Pharmacokinetic (Blood), Pharmacodynamic and Biomarker Collection Windows

PK, PD and ADA Collection	PK, PD and ADA Collection Window
Days 1, 3, 5, 8: predose	Within 2 hr of dosing (samples to be collected before dialysis)
Day 1, 3, 5, 8: 1 hr post each dose	± 15 min (within 15 min of end of infusion)
Days 1, 3, 5, 8: 12 hr post dose	± 30 min
Days 2, 9,10	± 4 hr of theoretical sampling time
Days 12, 15, 21, 29, 35	± 1 day
Days 49, 67	± 3 days
Day 104	± 7 days

- Predose standard safety evaluations: VS and ECG within 3 hours of MK-2060 dosing; laboratory safety tests (including aPTT and PT at local lab), drug screen and physical exam within 24 hours of MK-2060 dosing.

Table 7 Postdose Safety Evaluation Windows

Postdose Standard Safety Evaluations (VS, ECG, laboratory safety tests, and physical exam)	Postdose Evaluation Window
Days 1, 3, 5, and 8: all postdose	± 30 min of theoretical sampling time
Days 2, 9, and 10	± 4 hr of theoretical sampling time
Days 12, 15, 21, 29, 35	± 1 day
Days 49, 67	± 3 days
Day 104	± 7 days

- Assessment of time to adequate hemostasis: at the conclusion of the onsite hemodialysis session, after hemodialysis catheters are removed from the dialysis access site.
- Hemoccult test: samples may be obtained within 48 hours of specified timepoint or first available sample if not within the specified time window.
- Postdose evaluations: weight (Day 104), serum or urine pregnancy test (Day 104): use windows indicated in Table 7.
- Study intervention administration: +/- 1 hour relative to time of dosing on Day 1.
- Run-in (Day -14 to Day -3 Visits): ± 1 day is allowed.

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

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

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

- Decrease in the duration of study intervention administration (eg, number of days)
- Adjustment of the dosing interval (eg, divided doses [bid to qd, qd to bid, tid, or vice versa])
- Lengthening of the washout period between doses
- Addition of PK pause
- Instructions to take study intervention with or without food or drink may also be modified based on newly available data
- Modification of the PK/pharmacodynamic sample processing and shipping details based on newly available data

The PK/pharmacodynamic sampling scheme currently outlined in the protocol may be modified during the study based on newly available PK or pharmacodynamic data (eg, to obtain data closer to the time of peak plasma concentrations). If indicated, these collected samples may also be assayed in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

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

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

It is understood that the current study may use some or none of the alterations described above. Any alteration made to this protocol to meet the study objectives must be detailed by

the Sponsor in a letter to the Study File and forwarded to the investigator for retention. The letter may be forwarded to the IRB/IEC at the discretion of the investigator.

9 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

This section contains a summary of the statistical analyses for this trial. Full details can be found in the subsequent sections. Since this is an exploratory study, statistical analyses will consist of presenting the descriptive statistics in shape of appropriate plots and summary tables (mean, standard deviation, median, min, max).

9.2 Responsibility for Analyses

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

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

9.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3.

Primary Objective: To assess the safety and tolerability following multiple doses of concomitant treatment of MK-2060 and clopidogrel by measuring the bleeding related AEs

Secondary Objective 1: To evaluate plasma pharmacokinetics of MK-2060 and clopidogrel following multiple doses of concomitant treatment of MK-2060 and clopidogrel

Estimation:

- Estimate plasma AUC0-168, Cmax, C168, Tmax, terminal t1/2, CL, Vz.

Secondary Objective 2: To determine whether the increase in time required to achieve hemostasis in ESRD patients treated with MK-2060 and following completion of dialysis remains below 20 minutes

Hypothesis:

- Mean time-to-hemostasis for MK-2060 treatment is less than 20 minutes.

Tertiary/Exploratory Objective 1: To explore the effect of concomitant treatment of MK-2060 and clopidogrel on aPTT.

Estimation:

- Estimate aPTT fold change from baseline.

Tertiary/Exploratory Objective 2: To explore the effect of concomitant treatment of MK-2060 and clopidogrel on prothrombin time.

Estimation:

- Estimate PT fold change from baseline.

9.4 Analysis Endpoints

Primary Endpoints

1. Safety and tolerability following multiple doses of concomitant treatment of MK-2060 and clopidogrel are the primary endpoints. Thus all AEs including bleeding related AEs (as defined in Section 4.2.1.1) are the primary endpoints for this study.

Secondary Endpoints (Pharmacokinetic)

1. Pharmacokinetics: The pharmacokinetic variables of secondary interest for MK-2060 are plasma AUC0-168, Cmax, C168, Tmax, terminal t1/2, CL, and Vz.

2. Time to hemostasis

Exploratory Endpoints:

1. Pharmacodynamics: The PD variable of exploratory interest is aPTT (change from baseline). Baseline is defined as the pre-dose value.

2. ADA

9.5 Analysis Populations

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

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

Per-Protocol: The Per-Protocol Population consists of the set of data generated by the subset of subjects who comply with the protocol sufficiently to ensure that these data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance

covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations. Important protocol deviations will be identified to the extent possible prior to unblinding by individuals responsible for data collection/compliance, and its analysis and interpretation. Any subjects or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR. At the end of the study, all subjects who are compliant with the study procedure as aforementioned and have available data from at least one treatment will be included in the Per-Protocol dataset.

9.6 Statistical Methods

Safety

Summary statistics and plots will be generated for raw laboratory safety tests, ECGs, and/or VS as well as for change from baseline, as deemed clinically appropriate. For the primary endpoint, i.e., the bleeding related AEs, descriptive summary (total counts, percentage) will be provided. Same will be provided for all AEs as well as for the secondary and exploratory endpoints wherever appropriate. For continuous measurements, mean, standard deviation, median, min, max will be provided. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline) as appropriate. Values will be listed for each PK parameter (including Tmax and apparent terminal t1/2), and appropriate non-model based descriptive statistics will be provided.

Secondary Hypothesis:

To determine whether the mean time-to-hemostasis recorded from patients treated with MK-2060 is lower than the cut-off time of 20 minutes, a Bayesian approach will be used. Utilizing a non-informative flat prior, the posterior probability that the observed mean of time-to-hemostasis of participants is less than 20 will be calculated, and the criteria for success will be met if the following condition is satisfied.

Posterior-probability (PP) ($\mu_{TH} < 20$) ≥ 0.60

Where

μ_{TH} = mean of the time-to-hemostasis measurements for ESRD patients treated with MK-2060

MK-2060 PK parameters including plasma AUC0-168, Cmax, C168, Tmax, terminal t1/2, CL, Vz with the following (non-model-based) descriptive statistics will be provided: N (number of subjects with non-missing data), geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s2) - 1), where s2 is the observed variance on the natural log-scale).

Exploratory Estimation:

Descriptive statistics as well as appropriate plots will be displayed for aPTT fold change from baseline. To describe the subject distribution using a contingency table for various time-to-hemostasis measurements with respect to treatments by clopidogrel and clopidogrel+MK-2060, respectively.

Time-to-hemostasis (mins)	Clopidogrel	Clopidogrel + MK-2060
<10		
10-20		
> 20		

9.7 Interim Analyses

No interim analysis is planned for this study.

9.8 Multiplicity

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

9.9 Sample Size and Power Calculations

Approximately 12 subjects will be enrolled for this study. The success criterion is that the posterior probability (PP) for the mean time-to-hemostasis less than 20 min, is greater than 60%. Based on the assumed prior mean and standard deviation calculated from data for MK-2060-004, the PP is calculated based on 10,000 simulations, and is found to be reasonably high (>X%) that PP is above 60%.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (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, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this

information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names

and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

Not applicable.

10.1.5 Publication Policy

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

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.7 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

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 8 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 8 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry[a]	BUN	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is above the ULN)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose	Calcium	Alkaline phosphatase	
Other Screening Tests	• aPTT, PT (collection according to the trial schedule of activities Section 1.3 for aPTT and PT collected at local lab) • FSH (as needed in WONCBP only) • Serum or urine β human chorionic gonadotropin (β hCG) will be carried out on Day 1 predose. At all other timepoints urine or serum pregnancy test will be carried out (as needed for WOCBP) (Serum β hCG pregnancy test will be carried out if there is a positive urine test) • alcohol breath test and drug screen (to include at minimum: amphetamines, cocaine, opiates, cannabinoids and benzodiazepines) • Serology (HIV antibody, HBsAg, and hepatitis C virus antibody)]			
ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; [HBsAg=hepatitis B surface antigen]; hCG=human chorionic gonadotropin; [HIV=human immunodeficiency virus]; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WBC=white blood cell; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential				
[a] Fasting: Participants should fast for at least 4 hours prior to glucose measurement.				

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

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

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- Note: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.5.6 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:

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

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

10.3.3 Additional Events Reported

Additional events that require reporting

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

- Is a cancer
- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

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

number, will be blinded on the copies of the medical records before submission to the Sponsor.

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

Assessment of intensity /toxicity

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

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

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

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

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

Assessment of causality

- Did the Sponsor's product cause the AE?

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

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill

count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

- **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

- **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

  (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

  (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

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

- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to 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 Sponsor's product relationship).

  - Yes, there is a reasonable possibility of Sponsor's product relationship:

    - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

  - No, there is not a reasonable possibility of Sponsor's product relationship:

    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

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

SAE reporting to the Sponsor via paper CRF

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

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

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

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

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

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 for a male participant 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.
Methods That Are Not Considered Highly Effective *Failure rate of >1% per year when used consistently and correctly.*
• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods).
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly).

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

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

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

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

7. Retention of Specimens[3, 4]

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

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

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

8. Data Security[3, 4]

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

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

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

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

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

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

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

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

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

12. Questions

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

13. References

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10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: Blood Volume Table

	Prestudy	Treatment Periods	Poststudy	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Tests	2	9	1	12	12.5	150
HIV/Hepatitis Screen	1			1	5	5
FSH (Females only)	1			1	3.5	3.5
Serum β-hCG pregnancy test (Females only)	2		1	3	3.5	10.5
Blood (DNA) for genetic analysis		1		1	8.5	8.5
Blood for PT and aPTT at local lab	1	19	1	21	3	63
Blood for plasma ADA and MK-2060		4	1	5	2.7	13.5
Blood for MK-2060 only		16		16	1.8	28.8
Blood for Clopidogrel Assay	3	5		8	4	32
Blood for PT, aPTT, FXI activity by central lab		16	1	17	8.1	137.7
Total Blood Volume per Male Participant[a]						**438.5 mL**
Total Blood Volume per Female Participant[a]						**452.5 mL**

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

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

For all laboratory values obtained at prestudy (screening) visit and/or predose evaluation:

A. If all protocol-specified laboratory values are normal, the participant may enter the study.

B. If a protocol specified laboratory value is outside of the parameter(s) outlined in the inclusion/exclusion criteria (including a repeat if performed), the participant will be excluded from the study.

C. If ≥1 protocol-specified laboratory value not specified in the inclusion/exclusion criteria is outside the normal range, the following choices are available:

    a. The participant may be excluded from the study;

    b. The participant may be included in the study if the abnormal value(s) is NCS (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document).

    c. The participant may be included in the study if the abnormality is consistent with a pre-existing medical condition which is not excluded per protocol (eg, elevated eosinophil count in a participant with asthma or seasonal allergies), the medical condition should be annotated on the laboratory report.

    OR

    d. The abnormal test may be repeated (refer items a. and b. below for continuation of algorithm for repeated values).

        a. If the repeat test value is within the normal range, the participant may enter the study.

        b. If the repeat test value is still abnormal, the study investigator will evaluate the potential participant with a complete history and physical examination, looking especially for diseases that could result in the abnormal laboratory value in question. If such diseases can be ruled out, and if the abnormal laboratory value is not clinically relevant, then the participant may enter the study.

D. If there is any clinical uncertainty regarding the significance of an abnormal value, the participant will be excluded from the study.

10.10 Appendix 10: Abbreviations

Abbreviation	Expanded Term
ADA	anti drug antibodies
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
AV	arteriovenous
bid	twice daily
BMI	body mass index
BP	blood pressure
CCU	Cardiac care unit
Cmax	maximum plasma concentration
CL	clearance
CRF	Case Report Form
CRU	clinical research unit
CSR	Clinical Study Report
CYP	cytochrome P450
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
EMA	European Medicines Agency
ESRD	End-stage renal disease
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
FXI	Factor XI
FXIa	Factor XIa
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
GLP-1	Glucagon-like peptide-1
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HD	hemodialysis
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form

Abbreviation	Expanded Term
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ICU	intensive care unit
IEC	Independent Ethics Committee
IgG4	immunoglobulin G4
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
Kt/V	A number used to quantify hemodialysis. K – dialyzer clearance of urea t – dialysis time V – volume of distribution of urea, approximately equal to patient's total body water
mAb	monoclonal antibody
NCS	not clinically significant
NSAE	Nonserious adverse event
NSAID	Non-steroidal anti-inflammatory drug
OR	objective response
PCL	Protocol Clarification Letter
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
po	orally
PP	posterior probability
PT	Prothrombin time
QTc	Corrected Q-T interval
QW	Once weekly
RNA	ribonucleic acid
RR	respiratory rate
SAE	serious adverse event
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transminase
SLAB	Supplemental laboratory test(s)
SoA	schedule of activities
SOP	Standard Operating Procedures
SUSAR	suspected unexpected serious adverse reaction
THC	Tetrahydrocannabinol
Tmax	Time to maximum plasma concentration
t1/2	half life
ULN	upper limit of normal
VS	vital signs
WBC	white blood cell

Abbreviation	Expanded Term
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential

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