Official Protocol Title:	Single and Multiple Dose Clinical Trial to Study the Safety and Pharmacokinetics of MK-2060 in Older Participants with End-Stage Renal Disease on Hemodialysis
NCT number:	NCT03873038
Document Date:	02-Aug-2021

Title Page

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Protocol Title: Single and Multiple Dose Clinical Trial to Study the Safety and Pharmacokinetics of MK-2060 in Older Participants with End-Stage Renal Disease on Hemodialysis

Protocol Number: 004-06

Compound Number: MK-2060

Sponsor Name:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

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Regulatory Agency Identifying Number(s):

IND	142,237

Approval Date: 02 August 2021

Sponsor Signatory

Typed Name: Date
Title:

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: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
MK-2060-004-06	02-AUG-2021	The protocol amendment 05 is being amended to allow flexibility in the number of female participants, expand the age range (reduce lower limit to 18 years) and expand BMI range to 45 kg/m^2 for Part 2 in order to optimize recruitment in the study.
MK-2060-004-05	08-FEB-2021	The protocol amendment 04 is being amended to allow patients who have completed all procedures in Part 1 Panel C to enroll in Part 2 of the study, based on the terminal half-life of MK-2060 from preliminary PK analysis, in order to optimize recruitment in the study.
MK-2060-004-04	02-SEP-2020	The protocol amendment 03 is being amended to revise the planned dose and the dose regimen for Part 2 based on the newly available preliminary PK and PD analysis of Part 1 Panels A-C.
MK-2060-004-03	21-FEB-2020	The protocol amendment 02 is being amended to expand age range (reduce lower limit to 40 years) and expand BMI range to 42 kg/m^2 for Part 1. In addition, smoking exclusion criteria (exclusion criteria #22) has been removed in order to optimize recruitment in the study.
MK-2060-004-02	21-JAN-2020	The protocol amendment 01 is being amended to revise inclusion criteria #1 (change the references 3 months of stable dialysis prior to screening to prior to dosing) and #3 (expand BMI range to 42 kg/m^2 for Part 2) in order to optimize recruitment in the study.
MK-2060-004-01	03-DEC-2019	The original protocol is being amended to add a multiple dosing study part (Part 2) to evaluate the safety and tolerability of MK-2060 following multiple dose IV administration including an IV loading dose in older adult participants with ESRD on HD.
MK-2060-004-00	21-FEB-2019	Not applicable.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: [06]

Overall Rationale for the Amendments:

The protocol amendment 05 is being amended to allow flexibility in the number of female participants and the total number of participants enrolled in Part 2 of the study, as well as to revise inclusion criteria #7 (lower age limit to 18 for Part 2), and #3 (expand BMI range to 45 kg/m^2 for Part 2) in order to optimize recruitment in the study. 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
1.1 Synopsis 4.1 Overall Design 9.9 Sample Size and Power Calculations	Changed the total number of participants to be approximately 20 for Part 2.	Enrolling exactly 20 participants in Part 2 is not critical to meeting the primary objectives of the study.
4.1 Overall Design 4.2 Scientific Rationale for Study Design 5 Study Population 5.1 Inclusion Criteria	Changed lower age limit from 40 to 18 for Part 2. Removed the following sentence at the end of 2nd paragraph in Section 4.2: In the US population ESRD has the highest prevalence in the 65 and older age group [United States Renal Data System 2018], therefore this study is being conducted in older adult subjects ages ≥40 and ≤80 years old.	Expanding the age range is to optimize recruitment for Part 2 of the study. This change adds flexibility for participant initial screening and enrollment without imposing any undue safety risks to the participant.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Inclusion Criteria 3: Changed Body Mass Index (BMI) from "≥ 18 and ≤ 42 kg/m^2" to "≥ 18 and ≤ 45 kg/m^2".	Expand BMI range to 45 kg/m^2 for Part 2 to optimize recruitment for Part 2.
5.1 Inclusion Criteria	Inclusion Criteria 6: Removed ")" after "Section 5.3".	Correct typographic error.
5.2 Exclusion Criteria	Add the following bullet under Exclusion Criterium #16: • 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.	In the best of interest of the ESRD patient's health, the patients are recommended to receive COVID-19 vaccine. Administration of COVID-19 vaccine should not have any impact on the PK/PD of MK-2060.
6.3.2 Stratification	Revised the 2nd sentence to read "A minimum of 3 participants of each gender will be enrolled in Part 2".	Enrolling 3 participants of each gender in Part 2 is sufficient to meet the primary objectives of the study.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: Single and Multiple Dose Clinical Trial to Study the Safety and Pharmacokinetics of MK-2060 in Older Participants with End-Stage Renal Disease on Hemodialysis

Short Title: Single and Multiple Dose Study of MK-2060 in Older Participants with ESRD

Acronym: N/A

Hypotheses, Objectives, and Endpoints:

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

Primary Objectives	Primary Endpoints
- Objective: Part 1: To evaluate the safety and tolerability of MK-2060 following single dose IV administration in older adult participants with ESRD on HD. Part 2: To evaluate the safety and tolerability of MK-2060 following multiple dose IV administration including an IV loading dose in older adult participants with ESRD on HD.	- AEs (including local infusion site reactions and systemic reactions to infusion), physical examinations, vital signs, 12-lead ECGs, laboratory safety tests (serum chemistry, hematology), aPTT, PT, and endpoints related to bleeding (macroscopic bleeding, high sensitivity hemoccult) will be assessed throughout the dosing intervals.
Secondary Objectives	Secondary Endpoints
- Objective: Part 1: To evaluate plasma pharmacokinetics of MK-2060 following a single dose IV administration in older adult participants with ESRD on HD. Part 2: To evaluate plasma pharmacokinetics of MK-2060 following multiple dose IV administration including an IV loading dose in older adult participants with ESRD on HD.	- Part 1: MK-2060 plasma AUC0-∞, AUC0-168, Cmax, C168, Tmax, terminal t1/2, CL and Vz - Part 2: MK-2060 plasma AUC0-168, Cmax, C168 (Cmin), Tmax

Secondary Objectives	Secondary Endpoints
- Objective: Part 1: To evaluate the effect of MK-2060 on aPTT following single dose IV administration in older adult participants with ESRD on HD. Part 2: To evaluate the effect of MK-2060 on aPTT following multiple dose IV administration including an IV loading dose in older adult participants with ESRD on HD. - Hypothesis: Part 1: The true fold increase from baseline for aPTT 168 hours after a single well-tolerated dose of MK-2060 in older adult participants with ESRD on HD is at least 1.5. Part 2: The true fold increase from baseline for aPTT 168 hours post the last dose following an IV loading dose and three maintenance IV doses of MK-2060 in older adult participants with ESRD on HD is at least 1.5.	- aPTT fold change from baseline
Part 1: - Objective: To compare the plasma pharmacokinetics of MK-2060 following a single dose IV administration in older adult participants with ESRD on HD to participants with normal renal function (historical controls in PN001). - Estimation: In older adult participants with ESRD on HD, PK parameters (e.g. AUC0-∞, Cmax) of MK-2060 following administration of a single dose will be estimated and compared to participants with normal renal function (historical controls in PN001).	- Part 1: MK-2060 plasma AUC0-∞, AUC0-168, Cmax, C168, Tmax, terminal t1/2, CL and Vz

Overall Design:

Study Phase	Phase 1		
Primary Purpose	Treatment		
Indication	Prevention of thrombotic complications		
Population	Patient: Older adult participants with end-stage renal disease on hemodialysis		
Study Type	Interventional		
Intervention Model	Sequential This is a multi-site study.		
Type of Control	Placebo		
Study Blinding	Double-blind		
Masking	Participant or Subject	Investigator	Outcomes Assessor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 23 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.		

Number of Participants:

Approximately 44 participants will be allocated/randomized.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Part 1						
Panel A	MK-2060	8 mg	Once	IV	Single 60-minute IV infusion	Experimental
	Placebo[a]	Placebo[a]				
Panel B	MK-2060	20 mg	Once	IV	Single 60-minute IV infusion	Experimental
	Placebo[a]	Placebo[a]				
Panel C	MK-2060	40 mg	Once	IV	Single 60-minute IV infusion	Experimental
	Placebo[a]	Placebo[a]				
Part 2						
Part 2	MK-2060	Week 1: loading dose up to 25 mg x 3 Weeks 2-4: maintenance dose up to 25 mg	Week 1: 3x Week 2-4: weekly	IV	Week 1: 3x Week 2-4: weekly	Experimental
	Placebo[a]	Placebo[a]				

a. Placebo IV (0.9% sodium chloride infusion, USP sterile saline)

Total Number

Total 44 participants.

Part 1: 24 participants (3 panels of 8 participants per panel). Within each panel participants will be randomized to receive MK-2060 or placebo in a 3:1 ratio (6 active and 2 placebo). In order to ensure 24 evaluable participants with at least 21 days of follow-up, we will allow for the replacement of participants.

Part 2: Approximately 20 participants will be randomized to a once weekly dose of MK-2060 or placebo in a treatment ratio of 3:1 (15 active and 5 placebo) for 4 weeks.

In order to ensure approximately 20 evaluable participants with at least 21 days of follow-up after the last dose, replacement of participants who do not complete 21 days of follow-up may be enrolled with joint agreement of the investigator and the Sponsor.

Duration of Participation	Part 1: Each participant will participate in the study for approximately 28 weeks from the time the participant provides documented informed consent through the final contact. After a screening phase of approximately 4 weeks, each participant will receive the assigned intervention (single dose IV infusion). After study drug administration, each participant will be followed for approximately 164 days. Part 2: Each participant will participate in the study for approximately 20 weeks from the time the participant provides documented informed consent through the final contact. After a screening phase of approximately 4 weeks, each participant will receive the assigned intervention (weekly single dose IV infusion for 4 weeks). After the last dose of the study drug administration, each participant will be followed for approximately 90 days.

Study Governance Committees:

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

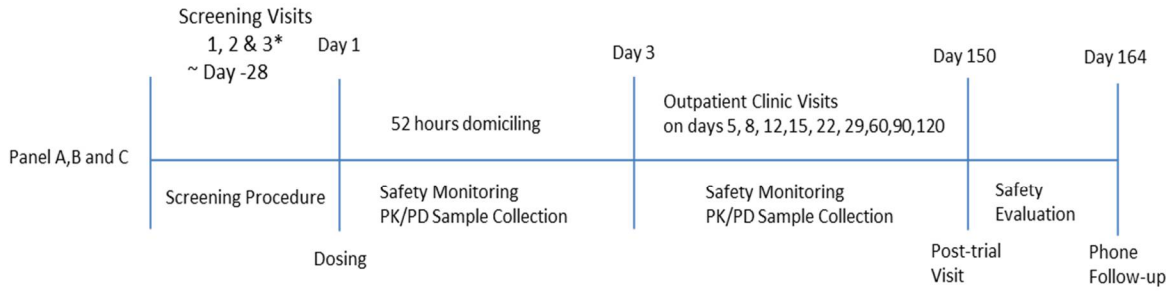
Study Accepts Healthy Volunteers: No

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

1.2 Schema

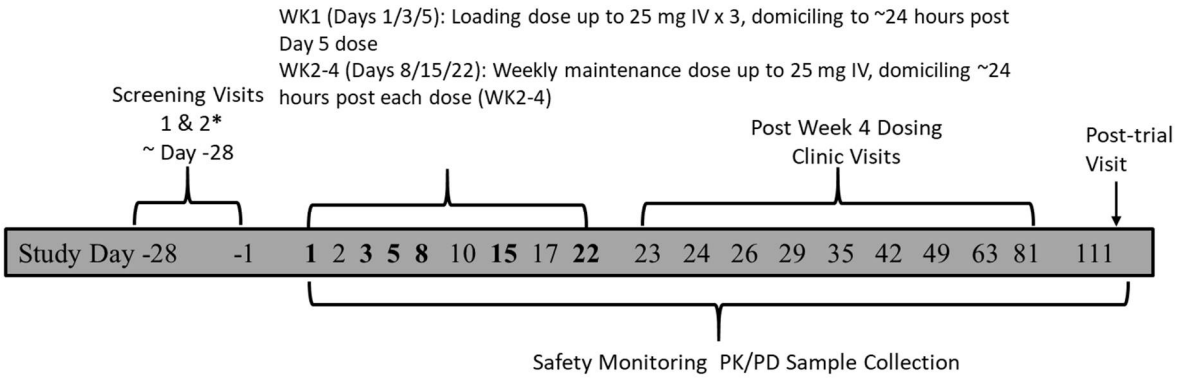
The study design is depicted in [Figure 1], [Figure 2] and [Table 1].

Figure 1 Study Design for Part 1



* Screening Visit 3: should occurs within 80 hrs prior to Day 1

Figure 2 Study Design for Part 2



* Screening Visit 2 should occur within 7 days prior to Study Day 1.

Table 1 Study Schema

Part 1			
Panel	Dose[b]		
A[a]	8 mg IV MK-2060		
	Placebo[c]		
B[a]		20 mg IV MK-2060	
		Placebo[c]	
C[a]			40 mg IV MK-2060[d]
			Placebo[c]
Part 2[e]			
Dose[f]			
Week 1		Week 2/Week 3/Week 4	
Up to 25 mg IV MK-2060 x 3		Up to 25 mg IV MK-2060	
Placebo[c]		Placebo[c]	

a. 8 older adult participants with ESRD on HD per panel. Within each panel participants will be randomized to receive a single IV infusion of MK-2060 or placebo in a 3:1 ratio (6 active and 2 placebo)
b. Part 1: There will be approximately a 28-day period (+/- 2 days) [including 21 days (+/- 2 days) safety data review and approximately 7 days for decision to dose next panel] between dosing the last participant in a panel and dose administration in the next panel to evaluate safety. The decision to proceed to the next panel will be based upon acceptable safety and tolerability data collected over at least a 21 day (+/- 2 days) observation period for at least 7 participants in the previous panel, including local lab aPTT, PT, and hemoccult test review. Plasma pharmacokinetic data will be reviewed on an ongoing basis and at least 14 days of PK data from at least 7 participants in Panel A (8 mg) will be evaluated prior to proceeding to the next panels. The suggested doses may be adjusted downward based on evaluation of safety, tolerability, pharmacokinetic and/or pharmacodynamic data observed in previous treatment panels.
c. Placebo IV (0.9% sodium chloride infusion, USP sterile saline)
d. Panel C (40 mg dose) will not be dosed until at least 21 days of safety, tolerability, PK, and PD data from the 40 mg IV dose in PN001 (Panel I) has been reviewed.
e. Approximately 20 older participants with ESRD will be randomized to receive MK-2060 or placebo in a 3:1 ration (15 active and 5 placebo).
f. Part 2 will not be dosed until at least 14 days of safety, tolerability data and available PK data from at least 6 participants in Part 1 Panel C 40 mg IV dose in this study has been reviewed.

1.3 Schedule of Activities (SoA)

1.3.1 Part 1

Study	**Panels[a] A, B, and C**																							Notes
Study Day within Period	≤28 days pre-dose[b]			Day 1 (hour post dose)						D2	D3		D5	D8	D12 [w] (±1D)	D15 [w] (±2D)	D22 [w] (±2 D)	D29 (±3 D)	D60 [w] (±5 D)	D90 [w] (±5 D)	D120 (±7 D)	D150 Post-trial[c,w] (±7 D)	D164 Phone Call (±7 D)	
Scheduled Hour	**Scn 1**	**Scn 2**	**Scn3[b]**	**Pre-dose**	**0**	**1**	**3.5**	**8**	**12**	**24**	**48**	**52**	**96**	**168**										
Administrative Procedures																								
Informed Consent	X																							
Informed Consent for Future Biomedical Research	X																							
Participant Identification Card/Bracelet[d]		X		X																				
Assignment of Screening Number	X																							
Assignment of Allocation Number[e]					X																			
Inclusion/ Exclusion Criteria	X	X	X	X																				
Clinic Procedures																								
Medical History	X																							
Prior/Concomitant Medication Review	X----------X																							
On site Hemodialysis[v]		X	X		X-------X						X---X			X				X			X			
MK-2060/Placebo					X																			

Study	**Panels[a] A, B, and C**																						Notes
Study Day within Period	≤28 days pre-dose[b]			Day 1 (hour post dose)						D2	D3		D5	D8	D12[w] (±1D)	D15[w] (±2D)	D22[w] (±2 D)	D29 (±3 D)	D60[w] (±5 D)	D90[w] (±5 D)	D120 (±7 D)	D150 Post-trial[c,w] (±7 D)	D164 Phone Call (±7 D)	
Scheduled Hour	**Scn 1**	**Scn 2**	**Scn3[b]**	**Pre-dose**	**0**	**1**	**3.5**	**8**	**12**	**24**	**48**	**52**	**96**	**168**										
Administration[f]																								
Standard Meals[g]						X----------X																		
Participant Domiciling in Clinical Research Unit				X----------X																				
Safety Procedures																								
Full Physical Examination [h]	X			X						X	X			X		X		X	X	X	X	X		
Systemic Infusion Reaction Assessment[i]						X	X	X		X	X													
Assessment of time to adequate hemostasis[u]		X	X				X					X		X				X			X			
Height	X		X																					
Weight	X		X																			X		Pre-HD
12-lead ECG[j]	X			X			X			X	X			X								X		
Semirecumbent Vital Signs (heart rate, blood pressure, respiratory rate, body temperature)[k]	X		X	X----------X					X	X	X		X	X	X						X	X		
Orthostatic Vital Signs (heartrate, blood pressure[l]	X		X	X					X	X	X													

Study	**Panels[a] A, B, and C**																						Notes
Study Day within Period	≤28 days pre-dose[b]			Day 1 (hour post dose)						D2	D3		D5	D8	D12[w] (±1D)	D15[w] (±2D)	D22[w] (±2 D)	D29 (±3 D)	D60[w] (±5 D)	D90[w] (±5 D)	D120 (±7 D)	D150 Post-trial[c,w] (±7 D)	D164 Phone Call (±7 D)	
Scheduled Hour	**Scn 1**	**Scn 2**	**Scn3[b]**	**Pre-dose**	**0**	**1**	**3.5**	**8**	**12**	**24**	**48**	**52**	**96**	**168**										
AE/SAE review[m]	X----------X																							
Serum β-Human Chorionic Gonadotropin (β-hCG)	X			X																		X		Female participants only
Serum Follicle Stimulating Hormone (FSH)	X																							Post-menopausal/ oophorectomized female participants only
Laboratory Procedures/Assessments																								
HIV/hepatitis screen	X																							Per site SOP
Serum/saliva Drug and Alcohol Breath test[n]	X		X	X																				Per site SOP
Hematology, Chemistry,[o]	X		X	X						X	X			X	X	X	X	X		X		X		
aPTT and PT at Local Lab	X					X[p]			X		X		X	X[y]	X	X	X			X				
Hemoccult Test[q]		X									X		X	X	X	X	X	X	X					
Blood for Genetic Analysis[r]				X																				
Pharmacokinetics Evaluations																								
Blood for Plasma MK-2060[s,x]				X		X[t]			X	X	X	X	X	XX	X	X	X	XX	X	X	XX	X		

Study	**Panels[a] A, B, and C**																						Notes
Study Day within Period	≤28 days pre-dose[b]			Day 1 (hour post dose)						D2	D3		D5	D8	D12 [w] (±1D)	D15 [w] (±2D)	D22 [w] (±2 D)	D29 (±3 D)	D60 [w] (±5 D)	D90 [w] (±5 D)	D120 (±7 D)	D150 Post-trial[c,w] (±7 D)	D164 Phone Call (±7 D)	
Scheduled Hour	**Scn 1**	**Scn 2**	**Scn3[b]**	**Pre-dose**	**0**	**1**	**3.5**	**8**	**12**	**24**	**48**	**52**	**96**	**168**										
Pharmacodynamic Evaluations																								
Blood for PT/aPTT/ FXI Activity by Central Lab[x]				X		X[t]			X	X	X	X	X	XX	X	X	X	XX	X	X	XX	X		
Blood for Fibrin Generation Assay[x]				X		X[t]			X	X	X	X	X	XX	X	X	X	XX	X	X	XX	X		
Blood for biomarker(s) of inflammation (e.g., hsCRP) Assay [t, x]				X		X[t]			X	X	X	X	X	XX	X	X	X	XX	X	X	XX	X		
Blood for plasma ADA				X												X	X	X	X	X	X	X		
5-D Pruritus Scale (Panel C only)																					X			

a. Participants may only participate in 1 Panel.
b. Screening 3 should occur within 80 hours prior to Day 1.
c. The Post-trial visit will occur approximately 150 days following administration of study drug. Procedures outlined in the Post-trial visit may be obtained on Day 150 (±7 days). However, follow up on any clinical or laboratory AEs should occur in person if the post-trial visit occurs prior to 150 days following administration of study drug. If a participant discontinues for any reason at any time during the course of the trial the subject may be asked to return to the clinic to complete the post-trial visit. The investigator may decide to perform the post-trial visit at the time of discontinuation or as soon as possible after discontinuation as outlined in Section 7 and 8.1.9.
d. Participants will be giving a Participants Identification Card at screening visit. In addition, participants will be given a bracelet at randomization and wear it until the post-trial visit. The bracelet is to identify participants as participants in an anti-coagulant research trial.
e. The allocation (randomization) number is assigned at the time of study drug administration.
f. MK-2060/placebo will be administered 30 minutes after the initiation of hemodialysis and will be infused over approximately1 hour. Infusion time may increase or pause, and restart based upon on tolerability. Refer to the Study Pharmacy Manual for additional information on the preparation and administration of study drug.
g. A light breakfast will be administered approximately 2 hours post-dose; a lunch and dinner will be provided at ~4 and ~10 hours post-dose respectively. Additional meals and snack(s) will be provided by the investigator (See Section 5.3.1).
h. All postdose PEs will include a local IV infusion reaction assessment for a11 panels. Refer to Section 8.4.
i. Participants will be monitored during the administration of MK-2060/placebo and after the initiation of the administration for signs and symptoms of a systemic infusion reaction. This assessment may be combined with the scheduled physical exam on Day 2 and Day 3. Note: Participants who call the CRU to report an infusion site reaction on Days 4, 5 and/or 7 may be asked to

Study	**Panels[a] A, B, and C**																						Notes
Study Day within Period	≤28 days pre-dose[b]			Day 1 (hour post dose)						D2	D3		D5	D8	D12[w] (±1D)	D15[w] (±2D)	D22[w] (±2 D)	D29 (±3 D)	D60[w] (±5 D)	D90[w] (±5 D)	D120 (±7 D)	D150 Post-trial[c,w] (±7 D)	D164 Phone Call (±7 D)	
Scheduled Hour	**Scn 1**	**Scn 2**	**Scn3[b]**	**Pre-dose**	**0**	**1**	**3.5**	**8**	**12**	**24**	**48**	**52**	**96**	**168**										

return to the CRU as soon as possible for an additional local infusion site reaction assessment.

j. Day 1 pre-dose ECGs will be obtained in triplicate at least 1-2 minutes apart (within 24 hours prior to trial drug administration). The median of these measurements will be used as the baseline. Screening and post-dose ECG measurements will be single measurements. ECG will be performed after participants have been in a semi-recumbent position for at least 10 minutes.

k. Pre-dose HR and BP will be triplicate measurements obtained at least 1-2 minutes apart within 3 hours of dosing MK-2060/placebo (i.e., within 3 hours of starting the infusion). The median of these measurements will be used as the baseline. Screening and post-dose vital sign measurements will be single measurement. HR and BP will be measured at pre- dose, 15 min, 30 min, and 1, 2, 3.5 and 12 hours post-dose on Day 1. Body temperature and respiratory rate will be single measurements per timepoint (pre-dose and post- dose).

l. Orthostatic vital sign measurements (heart rate, blood pressure) should follow the last semi-recumbent vital sign measurement. Measurements should be obtained after participants have been standing for 2 minutes.

m. All Adverse Events non-serious (NSAEs)] and serious adverse events (SAEs) will be recorded up to 164 days post-dose (inclusive).

n. Screening and pre-dose drug screen is mandatory (pre-dose drug screen may occur in the evening prior to Day 1 at the time of admission); any additional drug screen is conducted per site SOP.

o. Hematology/Chemistry will be obtained after an 8 hour fast. Pre-dose tests can be conducted up to 24 hours prior to dosing.

p. Local aPTT and PT tests will be performed on Day 1 at 1 hour (end of infusion). This sample will be obtained immediately prior to the end of infusion (i.e., no more than 5 min before anticipated time of the end of the infusion).

q. Hemoccult test will be provided to participants at screening 1 visit and participants will return the sample at screening visit 2. Other post-dose hemoccult test samples may be obtained within 48 hours of specified timepoint.

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

s. 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.

t. The 1-hour PK and PD samples will be obtained immediately prior to the end of infusion (i.e. no more than 5 min before anticipated time of the end of the infusion).

u. Assessment of time to adequate hemostasis will be conducted at the conclusion of the dialysis session.

v. Onsite hemodialysis sessions will be 4 hours in duration. Pre-dose and 48hr blood sample collections will be collected prior to HD initiation and 4hr and 52hr samples collected immediately after the conclusion of HD.

w. Day 12, 15, 22, 60, 90 and 150 clinic visits must occur within 12 hours prior to a hemodialysis session.

x. All the PK/PD draws for on-site HD on Day 8, 29 and 120 must have two draws for a pre-HD and a post-HD sample.

y. Local lab aPTT/PT will be drawn prior to initiation of onsite HD on Day 8.

1.3.2 Part 2

Study Period	Screening ≤28 days to Day 1		Intervention																		Post-study	Notes
Scheduled Week/Day	Scn1	Scn2[d]	Week 1				Week 2		Week 3		Week 4				Post Week 4						111	Sec. 8.11 for Visit Requirements and Sec. 8.11.6 for Timing of Procedure
			1	2	3	5	8	10	15	17	22	23	24	26	29	35	42	49	63	81		
Visit Window (Day)			NA	NA	NA	NA	NA	±1	NA	±1	NA	NA	NA	+1	NA	±2	±2	±2	±3	±3	±7	
Administrative Procedures																						
Informed Consent	X																					Sec. 8.1.1, 8.9 and 10.6 (Appendix 6)
Informed Consent for Future Biomedical Research	X																					
Inclusion/Exclusion Criteria	X	X	X																			Sec. 5.1, 5.2 and 8.1.2, Day 1 at predose
Participant Identification Card		X																				Sec. 8.1.3
Participant Bracelet			X																			Sec. 4.3.5
Assignment of Screening Number	X																					Sec. 8.1.6
Assignment of Allocation Number			X																			See Section 8.1.7, at Day 1 predose
Clinic Procedures																						
Medical History	X																					Sec. 8.1.4
Prior/Concomitant Medications Review	X----------																				X	Sec. 6.5 and 8.1.5
MK-2060 or Placebo Administration			X		X	X	X		X		X											Sec. 8.1.8 and 8.6
On site Hemodialysis		X	X		X	X	X		X		X						X					See footnote b
Meals			X				X		X		X											Sec. 5.3.1
Domiciling			X	X	X	X	X		X		X											Sec. 8.1.11
Safety Procedures																						
Physical Examinations	X		X	X	X		X	X	X	X	X	X	X			X		X	X	X	X	Sec. 8.3.1, include a local IV infusion reaction assessment at all postdose PE
Systemic Infusion Reaction Assessment			X	X	X	X	X	X	X	X	X	X	X									Sec. 8.4.1
Assessment of Time to Hemostasis		X	X		X	X	X		X		X						X					Sec. 8.3.4. ~4 hrs postdose on each dosing days
Height	X	X																				Sec. 8.3.1

Study Period		Screening ≤28 days to Day 1		Intervention																		Post-study	Notes
Scheduled Week/Day		Scn1	Scn2[d]	Week 1				Week 2		Week 3		Week 4				Post Week 4						111	Sec. 8.11 for Visit Requirements and Sec. 8.11.6 for Timing of Procedure
				1	2	3	5	8	10	15	17	22	23	24	26	29	35	42	49	63	81		
Visit Window (Day)				NA	NA	NA	NA	NA	±1	NA	±1	NA	NA	NA	+1	NA	±2	±2	±2	±3	±3	±7	
Weight		X	X																			X	
Resting 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	X	X	Sec. 8.3.2 Predose, 15 min, 30 min, and 1, 2, 3.5 and 12 hrs postdose on each dosing days
Orthostatic Vital Signs (blood pressure, heart rate)		X	X	X	X	X	X	X	X	X	X	X	X										Sec. 8.3.2. Predose and 12 hrs postdose on each dosing days
12-lead electrocardiogram		X		X	X	X	X	X	X	X	X	X	X			X						X	Sec. 8.3.3. Predose and 3.5 hrs postdose on each dosing days
Laboratory Procedures/Assessments																							
Safety Lab	Hematology and Chemistry	X	X	X		X		X	X	X	X	X		X			X		X	X	X	X	Sec. 8.4.3, 10.2 (Appendix 2) and 10.9 (Appendix 9).
	aPTT/PT at Local Lab	X		X(3)		X(2)	X(2)	X(2)	X	X(2)	X	X(2)	X	X	X	X	X	X		X	X	X	Day 1: Predose, 1 and 12 hrs postdose. Predose may be performed within 3 days of dosing. Days 3, 5, 8, 15 and 22: 1 and 12 hrs postdose.
	Hemoccult Test		X		X		X	X	X	X	X	X	X			X	X	X	X	X	X		Sec. 8.4.3, 8.11.6, 10.2 (Appendix 2) and 10.9 (Appendix 9).
	HIV/hepatitis Screen	X																					Per site SOP
	Serum/saliva Drug and Alcohol Breath Test	X	X	X																			Per site SOP
	Serum Follicle Stimulating Hormone (FSH)	X																					Postmeno-pausal/ oophorectomized female participants only
	Serum β-Human Chorionic Gonadotropin (β-hCG)	X																				X	Female participants only
AE/SAE review		X----------X																					Sec. 8.5 and 10.3 (Appendix 3)

Study Period	Screening ≤28 days to Day 1		Intervention																		Post-study	Notes
Scheduled Week/Day	Scn1	Scn2[d]	Week 1				Week 2		Week 3		Week 4				Post Week 4						111	Sec. 8.11 for Visit Requirements and Sec. 8.11.6 for Timing of Procedure
			1	2	3	5	8	10	15	17	22	23	24	26	29	35	42	49	63	81		
Visit Window (Day)			NA	NA	NA	NA	NA	±1	NA	±1	NA	NA	NA	+1	NA	±2	±2	±2	±3	±3	±7	
Pharmacokinetics																						
Blood for Plasma MK-2060 Assay			X(3)	X	X(2)	X(2)	X(2)	X	X(2)	X	X(3)	X	X	X	X	X	X	X	X	X	X	Sec. 8.7 Days 1 & 22: predose, 1h (within 5 min end of infusion), 12h. Days 3, 5, 8 & 15: predose, 1h (end of infusion). See footnote e, f.
Pharmacodynamics																						
Blood for PT/aPTT/ FXI Activity by Central Lab			X(2)	X	X	X	X	X	X	X	X(2)	X	X	X	X	X	X	X		X	X	Sec. 8.8, Days 1 and 22 (2 draws): predose and 1h (within 5 min end of infusion.
Blood for Fibrin Generation Assay			X(2)	X	X	X	X	X	X	X	X(2)	X	X	X	X	X	X	X		X	X	
Blood for biomarker(s) of inflammation (e.g., hsCRP) Assay			X				X		X		X				X	X	X	X		X	X	
Biomarkers																						
Blood for plasma anti-drug antibody			X						X		X							X	X	X	X	See Section 8.9 On dosing Days 1, 15, and 22: draw sample at predose.
Blood for Genetic Analysis			X																			See footnote c.
5-D Pruritus Scale													X				X					

a. Blood samples at each dosing day (i.e. Days 1, 3, 5, 8, 15 and 22 postdose will be collected in the opposite arm from the dialysis vascular access site.

b. On site Hemodialysis: Pre-dose blood sample collections will be collected prior to HD initiation and 4hr samples collected immediately after the conclusion of HD.

c. Blood for Genetic Analysis: This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at that site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the participant (or their legally acceptable representative) provides documented informed consent for future biomedical research. If the planned genetic analyses are not approved, but future biomedical research is approved and consent is given, this sample will be collected for the purpose of future biomedical research. Blood for genetic analysis should be collected only once per participant after randomization. If a participant re-enrolled into Part 2, a blood for genetic analysis sample is not needed if collected in Part 1.

d. Screening 2 may be performed within 80 hours prior to Day 1.

e. 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.

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

2 INTRODUCTION

2.1 Study Rationale

MK-2060 is an anti-FXI monoclonal antibody being developed for the prevention of thrombotic complications in end-stage renal disease (ESRD). The purpose of this study is to assess the safety, tolerability, PK, and PD of MK-2060 after IV administration of single and multiple doses in older adult participants with ESRD on HD. Data from this trial will be used to aid dose selection of MK-2060 in future trials.

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

Protocol 001

Protocol MK-2060-001 is a double-blind, randomized, placebo-controlled, single site, sequential panel study to evaluate the safety, tolerability, PK, and PD of single ascending dose administration of SC and IV doses of MK-2060 in healthy male participants. The clinical conduct of PN001 is complete. 36 healthy male participants received single SC doses of MK-2060 up to 120 mg and 24 healthy male subjects received single IV doses of MK-2060 up to 40 mg. MK-2060 was generally well-tolerated and there were no SAEs or discontinuations due to AEs. Refer to the IB Edition 4 for a detailed overview of the study, and available preliminary PK, PD, and safety results.

Protocol 004 Part 1 Panels A, B and C:

As of 09-Oct-2020, 24 participants have been administered one IV dose up to 40 mg MK-2060 or placebo. To date, single IV doses up to 40 mg have been generally well tolerated and there have been no treatment emergent SAEs and no discontinuations due to any drug-related AEs. There have been no AEs suggestive of hypersensitivity. Refer to IB Edition 4 for a detailed overview of preliminary safety, PK and PD results for Part 1 Panels A, B and C.

2.3 Benefit/Risk Assessment

Participants in clinical trials generally cannot expect to receive direct benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness 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

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

Objectives	Endpoints
Primary	
• Objective: Part 1: To evaluate the safety and tolerability of MK-2060 following single dose IV administration in older adult participants with ESRD on HD. Part 2: To evaluate the safety and tolerability of MK-2060 following multiple dose IV administration including an IV loading dose in older adult participants with ESRD on HD.	• AEs (including local infusion site reactions and systemic reactions to infusion), physical examinations, vital signs, 12-lead ECGs, laboratory safety tests (serum chemistry, hematology), aPTT, PT, and endpoints related to bleeding (macroscopic bleeding, high sensitivity hemoccult) will be assessed throughout the dosing intervals.
Secondary	
• Objective: Part 1: To evaluate plasma pharmacokinetics of MK-2060 following a single dose IV administration in older adult participants with ESRD on HD. Part 2: To evaluate plasma pharmacokinetics of MK-2060 following multiple dose IV administration including an IV loading dose in older adult participants with ESRD on HD.	• Part 1: MK-2060 plasma AUC0-∞, AUC0-168, Cmax, C168, Tmax, terminal t1/2, CL and Vz • Part 2: MK-2060 plasma AUC0-168, Cmax, C168 (Cmin), Tmax

Objectives	Endpoints
• Objective: Part 1: To evaluate the effect of MK-2060 on aPTT following single dose IV administration in older adult participants with ESRD on HD. Part 2: To evaluate the effect of MK-2060 on aPTT following multiple dose IV administration including an IV loading dose in older adult participants with ESRD on HD. • Hypothesis: Part 1: The true fold increase from baseline for aPTT 168 hours after a single well-tolerated dose of MK-2060 in older adult participants with ESRD on HD is at least 1.5. Part 2: The true fold increase from baseline for aPTT 168 hours post the last dose following an IV loading dose and three maintenance IV doses of MK-2060 in older adult participants with ESRD on HD is at least 1.5.	• aPTT fold change from baseline
<u>Part 1:</u> • Objective: To compare the plasma pharmacokinetics of MK-2060 following a single dose IV administration in older adult participants with ESRD on HD to participants with normal renal function (historical controls in PN001). • Estimation: In older adult participants with ESRD on HD, PK parameters (e.g. AUC0-∞, Cmax) of MK-2060 following administration of a single dose will be estimated and compared to participants with normal renal function (historical controls in PN001).	• Part 1: MK-2060 plasma AUC0-∞, AUC0-168, Cmax, C168, Tmax, terminal t1/2, CL and Vz

Objectives	Endpoints
Tertiary/Exploratory	
• Objective: Part 1: To explore the effect of MK-2060 given as a single IV dose on Factor XI (FXI) activity levels. Part 2: To explore the effect of MK-2060 given as multiple IV doses on Factor XI (FXI) activity levels.	a. FXI activity level fold change from baseline
• Objective: Part 1: To explore the effect of MK-2060 given as a single IV dose on fibrin generation. Part 2: To explore the effect of MK-2060 given as multiple IV doses on fibrin generation.	b. Fibrin Generation Assay (FGA)
• Objective: Part 1: To explore the effect of MK-2060 given as a single IV dose on prothrombin time (PT). Part 2: To explore the effect of MK-2060 given as multiple IV doses on prothrombin time (PT).	c. PT fold change from baseline
• Objective: Part 1: To explore the effect of MK-2060 given as a single IV dose on biomarker(s) of inflammation (e.g., hsCRP). Part 2: To explore the effect of MK-2060 given as multiple IV doses on biomarker(s) of inflammation (e.g., hsCRP).	d. hsCRP reduction from baseline

Objectives	Endpoints
• Objective: Part 1: To explore the effect of MK-2060 given as a single IV dose on time to hemostasis after decannulation of the hemodialysis vascular access site in ESRD patients. Part 2: To explore the effect of MK-2060 given as multiple IV doses on time to hemostasis after decannulation of the hemodialysis vascular access site in ESRD patients.	e. Time to adequate hemostasis after decannulation of vascular access compared to baseline
• Objective: To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study.	f. Germline genetic variation
• To explore the development of ADAs measured in blood samples after single and multiple IV doses of MK-2060 are administered in older adult participants with ESRD on HD.	g. ADA
• To explore biomarkers of pruritis in plasma samples of patients, and evaluate their relationship to patient-reported pruritic symptoms as registered by the 5-D Itch Scale.	h. biomarkers of pruritis, pruritic symptoms

4 STUDY DESIGN

4.1 Overall Design

This is a double-blind, randomized, placebo-controlled, multiple site, sequential panel, single and multiple dose trial of MK-2060 in older adult participants (age ≥40 and ≤80 for Part 1 and ≥18 and ≤80 for Part 2; men and women of non-child bearing potential) with ESRD on HD to be conducted in conformance with Good Clinical Practice. The study will evaluate the safety and tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single and multiple dose IV administration of MK-2060 in older adult participants with ESRD.

Part 1: Part 1 of the trial will consist of up to 3 panels. In all panels, 8 participants will be randomized to receive a single dose of MK-2060 or placebo (0.9% sodium chloride infusion, USP sterile saline) in a treatment ratio of 3:1 (6 active and 2 placebo). Each participant may only participate in one panel of the study.

Participants in all panels will be domiciled for ~52 hours after study drug administration for safety/tolerability monitoring. Participants in all groups/panels will be closely monitored for safety and tolerability, including safety labs, local lab aPTT and PT results, physical exam to check incidence of bleeding, vital signs (VS) and 12-lead ECG, as well as local infusion site reactions and for systemic reactions to infusion.

There will be approximately a 28-day period (+/- 2 days) [including 21 days (+/- 2 days)] safety data review and approximately 7 days for dosing escalation decision)] between dosing the last cohort in a panel and dose administration in the next panel to evaluate safety, tolerability, and available PK data. The decision to proceed to the next panel will be based upon acceptable safety and tolerability data collected over at least a 21-day (+/- 2 days) observation period for at least 7 participants in the previous panel, including local lab aPTT, PT, and hemoccult test review. Plasma pharmacokinetic data will be reviewed on an ongoing basis and at least 14 days of PK data from at least 7 participants in Panel A (8 mg dose) will be evaluated prior to proceeding to the next panels. Panel C (40 mg dose) will not be dosed until at least 21 days of safety, tolerability, PK, and PD data from the 40mg IV panel in the ongoing PN001 (Panel I) has been reviewed.

Part 2: Part 2 will be the first study of multiple dosing of MK-2060 in older adult patients with ESRD on HD. In this part, approximately 20 participants will be randomized to a 3 times per week for the 1st week and then once weekly dose for 3 weeks of MK-2060 or placebo (0.9% sodium chloride infusion, USP sterile saline) in a treatment ratio of 3:1 (15 active and 5 placebo) for total of 4 weeks of dosing. Participants will receive a loading dose up to 25 mg IV MK-2060 or placebo for a total of 3 doses in week 1 and a weekly maintenance dose up to 25 mg IV MK-2060 or placebo in weeks 2-4. Participants will not be dosed until 14 days of safety data and available PK data from at least 6 participants in the 40mg IV panel (Part 1 Panel C) of this trial has been reviewed. Participants who have completed Part 1 Panel A, B, or C may be enrolled in Part 2 of the study with joint agreement of the Investigator and the Sponsor.

Participants will be domiciled for the 1st week until ~ 24 hours post the third dose and for ~24 hours after each study drug administration in weeks 2-4 for safety/tolerability monitoring. Participants may be domiciled longer pending the investigator requirements and/or the preference of the participant. Participants will be closely monitored for safety and tolerability, including safety labs, local lab aPTT and PT results, physical exam to check incidence of bleeding, vital signs (VS) and 12-lead ECG, as well as local infusion site reactions and for systemic reactions to infusion. All participants in this study will be followed through approximately 3 months after the last study dose (Dose #6) for safety and tolerability, including all adverse experiences, safety labs, local lab aPTT and PT results, physical exam to check incidence of bleeding, vital signs (VS) and 12-lead ECG.

The trial design is depicted in [Figure 1, Figure 2 and Table 1]. For all panels in Part 1 and Part 2, participants will be followed for approximately 164 days or 90 days post the last dose of study drug respectively. Blood samples will be collected for MK-2060 plasma PK and PD to assess aPTT/PT levels, fibrin generation, and FXI activity levels.

The precise timing of safety and tolerability measurements, PK and PD samples may be altered during the course of the study based on newly available data (i.e., to obtain data closer to the time of peak concentrations or to better describe the half-life of the compound).

Because this is a Phase 1 assessment of MK-2060 in humans, the pharmacokinetic (PK), pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is therefore written with flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Refer to Section 8.11.7 for examples of modifications permitted within the protocol parameters.

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

4.2 Scientific Rationale for Study Design

The main objectives of this study are to evaluate safety, tolerability, PK, and PD of MK-2060 after IV administration of single and multiple doses in older adult (ages ≥ 40 and ≤ 80 for Part 1 and ≥ 18 and ≤ 80 for Part 2) men and women of non-child bearing potential (WONCBP) with ESRD on HD. PD effects on aPTT, PT, FXI activity, and fibrin generation will be explored. Up to approximately 44 older adult participants with ESRD on HD who meet study eligibility criteria may be enrolled in this study.

MK-2060 is being developed for the prevention of thrombotic complications in ESRD patients, thus the primary aim of this study is to evaluate safety, tolerability, PK, and PD of MK-2060 in this patient population.

We do not anticipate renal impairment, HD, or age to significantly alter the PK and PD of MK-2060. As discussed above, PN001 has demonstrated MK-2060 to be generally safe and well-tolerated in normal healthy subjects. Based on preliminary analysis, MK-2060 achieved mean maximum concentration at 1hr (end of infusion) after IV infusion, followed by a bi-phasic terminal phase with apparent mean half-life of ~29 to 39 days. MK-2060 clearance was ~0.23 L/day, consistent with reported CL of mAb. As renal elimination is typically an insignificant pathway for IgG mAbs due to their large size, the clearance of MK-2060 is not expected to change in renal impaired subjects or subjects on hemodialysis. Furthermore, assessment of the clotting cascade in subjects with ESRD has demonstrated that FXI levels are not significantly altered [Vaziri, N. D., et al 1994]. In PN001, MK-2060 volume of distribution was estimated as 11 L, slightly larger than the reported volume of distribution for mAb. [Dirks, N. L. 2010]. It could be possible that kidney failure or HD might impact volume of distribution, due to fluid retention, although we do not anticipate this to have a major effect. As MK-2060 is a monoclonal antibody age is also unlikely to alter PK and PD. The impact of renal impairment, HD, and age on MK-2060 PK and PD will be further

assessed by comparing data in this study to the data in young normal healthy subjects in PN001. IONIS has demonstrated using an FXI anti-sense oligo (ASO) that inhibition of the FXI pathway in ESRD patients on HD (mean age of 61 years) is generally safe and well-tolerated [Bethune, C., et al 2017]. Thus, the study of MK-2060 in older adult patients with ESRD on HD is well supported.

The rationale to limit recruitment to males and WONCBP is that developmental and reproductive toxicology studies in animals have not been completed.

4.2.1 Rationale for Endpoints

4.2.1.1 Safety Endpoints

This will be the first introduction of MK-2060 to participants with ESRD on HD. Based on the data from PN001, it is expected that IV administration of MK-2060 will be well-tolerated in participants with ESRD on HD. However, the safety and tolerability of MK-2060 are primary endpoints and will be carefully monitored. Physical examinations, VS, ECGs, laboratory safety tests (serum chemistry and hematology), aPTT, PT, and endpoints related to bleeding (macroscopic bleeding and high sensitivity hemoccult) will be assessed throughout the dosing intervals. AEs, including local infusion site reactions and systemic reactions to infusion, will be assessed throughout the dosing intervals.

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. However, given potential safety risks, participants will be monitored closely during the infusion with scheduled VS and physical examinations as needed. 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 164 for all panels in Part 1 and Day 111 for Part 2.

Time to adequate hemostasis after decannulation of vascular access

An exploratory 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. 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. In this study the process is standardized such that change in time to hemostasis from baseline (i.e., pre-dose) can be assessed (see the operational manual for details).

Twice for Part 1 and once for Part 2 during the screening period (i.e., prior to dosing) time to adequate hemostasis will be assessed to establish a baseline (mean of two screening period assessments; Screen 2 and Screen 3 for Part 1). 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. This exploratory analysis may allow for a very preliminary read on bleeding risk with administration of MK-2060 in the ESRD patient population.

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

In order to characterize the PK profile of MK-2060 in older adult participants with ESRD on HD, for Part 1 non-compartmental PK parameters AUC0-∞, AUC0-168, Cmax, C168hr, Tmax, apparent terminal t1/2, CL and Vz will be summarized after single dose IV administration; for Part 2, non-compartmental PK parameters AUC0-168, Cmax, C168, Tmax will be summarized for the first and last dose. Estimation of plasma PK data of MK-2060 following a single and multiple dose in older participants with ESRD on HD is a secondary objective of this study. Another secondary objective is to compare single dose plasma PK data of MK-2060 in older adult participants with ESRD on HD to participants with normal renal function studied in PN001.

4.2.1.3 Pharmacodynamic Endpoints

aPTT and FXI activity (performed by Central Lab); fibrin generation assay (FGA) and high sensitivity C-reactive protein (hsCRP)

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. FGA and hsCRP will also be measured as exploratory PD biomarkers. 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 a single and multiple well-tolerated

dose is a secondary objective of this study. For this secondary objective, the hypothesis that is being tested is: The true fold-increase in aPTT 168 hours after a single well-tolerated dose of MK-2060 in older adult participants with ESRD on HD is at least 1.5 (Part 1) and the true fold increase from baseline for aPTT 168 hours post the last dose following an IV loading dose and three maintenance IV doses of MK-2060 in older adult participants with ESRD on HD is at least 1.5 (Part 2). A 1.5-fold aPTT prolongation corresponds to the in vitro PD effect that is observed when using a concentration of MK-2060 that was demonstrated to inhibit clot formation in nonhuman primates to a similar extent as a clinically relevant comparator (apixaban, 5 mg bid). In plasma from severe FXI-deficient patients, aPTT prolongation up to 3.9-fold is observed, using the same PD assay described above [Ellsworth K 2018]. aPTT prolongation up to approximately 3.5-fold was also reported in FXI-deficient subjects in a published study [Asakai, R., et al 1991]. aPTT prolongation up to ~4-fold would be expected for almost complete FXI inhibition, and aPTT prolongation greater than 4-fold would represent unexpected pharmacology, which is part of the basis for the aPTT-based stopping rules described in Section 6.6.1

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 absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

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

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

4.2.1.5 Future Biomedical Research

The Sponsor will conduct future biomedical research 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 analyses, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from

appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research 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 future biomedical research are presented in Appendix 6.

4.2.2 Rationale for the Use of Placebo

The primary goal of the study is to evaluate the safety and tolerability of MK-2060 in older adult participants with ESRD on HD. A placebo-controlled study will allow for an unbiased assessment of safety and tolerability of MK-2060, including local infusion site reactions. Secondary and exploratory outcomes are also supported by the use of placebo, including evaluation of the effect of MK-2060 on aPTT following single and multiple dose IV administration, which should only be observed in participants with active treatment.

4.3 Justification for Dose

4.3.1 Rationale for Dose Selection/Regimen/Modification

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 8.11.7 - Study Design/Dosing/Procedures Modifications Permitted within Protocol Parameters.

The primary objective of the current study is to assess the safety and tolerability profile of MK-2060 after IV single and multiple dose administration in older adult participants with ESRD on HD under IND guidance limitations for dose. The purpose of this trial is not to determine maximum tolerated dose but rather to investigate the pharmacology of MK-2060 at relevant exposures, consistent with the guidance of the IND.

4.3.2 Starting Dose for This Study

The clinical conduct of the Phase I study in healthy male participants (PN001) evaluating safety, tolerability, and PK of MK-2060 has completed. The highest single IV dose of 40 mg has been well tolerated.

In healthy participants the 8 mg IV dose was well-tolerated and lacked a significant pharmacodynamic effect (maximum observed aPTT increase was 1.4-fold compared to baseline), thus it has been selected as the starting dose for Panel A in the current trial. Selection of this dose will allow the assessment of the impact of renal impairment and HD on MK-2060 PK by direct comparison of the data from the 8 mg IV dose in normal healthy subjects in PN001. Please refer to Section 4.2 above for further discussion of why significant PK differences with MK-2060 in older adult participants with ESRD on HD is not anticipated.

4.3.3 Maximum Dose/Exposure for This Study

The maximum dose to be administered in this study will not exceed 40 mg and will be based on review of emerging data from earlier panels within the current study, and from the ongoing PN001. Panel C (40 mg dose) will not be dosed until at least 21 days of safety, tolerability, and PK and PD data from the 40 mg IV dose in PN001 (Panel I) has been reviewed.

The safety of MK-2060 was evaluated in a cardiovascular safety pharmacology study and a 4-week repeat-dose toxicity study, both in Rhesus monkeys. The NOAEL for the multiple dose study was ≥60 mg/kg/week ($AUC_{0\text{-}168hr}$ at 60mg/kg = 7920µg/mL * day).

Assuming dose proportionality, a single dose of 40 mg MK-2060 IV is predicted to result in a mean Cmax ~80 nM (plasma concentrations of MK-2060 that does not exceed those observed in previous panels of PN001), C168 ~20 nM and a mean AUC0-168hr of 5800 nM*hr, 220-fold below the NOAEL of 7920 µg/mL*day (1.28 x 106 nM*hr) in healthy male subjects. At this dose the mean aPTT change from baseline is predicted to be ~2.75 fold at Cmax and ~2 fold at C168. Please refer to Section 4.2 above for further discussion of why significant PK differences with MK-2060 in older adult participants with ESRD on HD is not anticipated.

4.3.4 Rationale for Multiple Dose Regimen (Part 2)

The primary intent of Part 2 is to evaluate the safety, tolerability, PK, and PD of an MK-2060 multiple dose regimen that will achieve target anticoagulation. For anticoagulants, it is desirable to achieve near target anticoagulation as soon as therapy is initiated so a loading dose is being used for this portion of the study. 40 mg IV is the highest dose assessed in PN001 in NHVs and in ESRD patients in Part 1 of PN004. In PN001 with a single 40 mg IV dose Cmax and AUC0-168hr the geometric mean (GCV) were 78.2 (11.8) nM and 6350 (17.6) nM*hr , respectively. Preliminary dose modelling based on PK/PD data from the available 8, 20, and 40 mg single dose data in ESRD patients in Part 1 of PN004 projects that a regimen of 25 mg dosed on Days 1, 3, and 5 followed by 3 maintenance doses of 25 mg QW is projected to have a median Cmax (post first maintenance dose) of 91 nM and AUC0-168hr (post last dose) of 8868 nM*hr. From a safety perspective, the steady state Cmax of the 25 mg IV QW dose is projected to be ~25% higher than the Cmax achieved with the 40 mg IV single dose in PN001. Due to the slight increase in projected steady state Cmax in Part 2, the domiciling period has been increased during the first week of dosing for additional safety monitoring. As discussed above, all doses of MK-2060 have been generally well tolerated with no dose related SAEs, discontinuations due to AEs, or AEs suggestive of hypersensitivity, therefore no safety issues are anticipated in Part 2 with this slightly higher exposure. 25 mg QW is projected to result in >90% of participants with aPTT of 1.5 fold baseline at trough. The multiple dose regimen of Part 2 (3 doses for week 1 plus 3 maintenance doses) steady state is projected to be achieved by end of week 1 (concentration ~90% of steady state).

4.3.5 Rationale for Dose Interval and Study Design

MK-2060 is a fully human monoclonal antibody and is not considered a compound with high potential for risk of harm to participants according to the publication "Guideline on Strategies to Identify and Mitigate Risks for First-in-Human and Early Clinical Trials with Investigational Medicinal Products" (European Medicine Agency guidance released July 2017). The degree of uncertainty was determined by careful evaluation of the following: mode of action of MK-2060, presence or absence of biomarkers, the nature of the target, the relevance of available animal models and/or findings in nonclinical safety studies, and the study population. MK-2060 does not exhibit highly species-specific action, nor is it directed towards immune system targets. Safety assessment studies and ancillary pharmacology studies with MK-2060 provide no contraindications to the initiation of clinical studies in humans with this compound via the IV route. No dose-limiting toxicities were observed in the 4-week nonhuman primate toxicity trial, and substantial preclinical safety margins were obtained over initial human doses. These considerations suggest that the risk of unanticipated severe reactions is low. However, due to uncertainties inherent in early phase clinical testing, this study will include a period of observation on a clinical research unit (CRU) after dosing. CRUs will be staffed and equipped to manage unanticipated severe adverse effects and have appropriate access to a full service acute-care hospital to facilitate rapid institution of medical intervention as indicated.

Part 1 of the trial will include up to 3 sequential IV panels with up to 8 participants each, including up to 6 participants on active drug and up to 2 participants on placebo, per panel. The 3 panels will include dose levels administered via the IV route [Panel A: 8 mg; Panel B: 20 mg; Panel C: 40 mg] to explore the intravenous PK and PD profile of MK-2060.

Participants may only participate in one panel in Part 1 of the study. All IV doses will be delivered via a continuous infusion. In each panel, participants will be enrolled and dosed on a rolling basis. Each participant in each panel will be dosed and observed until discharge (~52 hours post-dose) for safety/tolerability. 52 hours is sufficient to monitor for initial safety/tolerability and local infusion site reactions and for systemic reactions to infusion. There will be approximately a 28-day (+/- 2 days) period between dosing the last participants in a panel and dose administration in the next panel to evaluate safety, tolerability, and available PK data.

Within each group, all participants are planned to be administered MK-2060 or placebo by Phase 1 Clinical Research standards for compounds not considered to have a high degree of uncertainty related to the potential risk of harm to participants. The dosing regimen was determined based on the following: the presence of preclinical safety margins for MK-2060, the inclusion of extensive safety monitoring in the clinic, and the fact that MK-2060 is not considered a compound with a high potential for risk of harm. There will be frequent, careful assessments of adverse events throughout the post-dose period. This recommendation is in keeping with the projected safety profile and the ability of the Phase I unit to monitor each subject closely.

In Part 1, the decision to proceed to the next panel will be based upon acceptable safety and tolerability data collected over at least a 21-day (+/- 2 days) observation period for at

least 7 participants in the previous panel, including local lab aPTT, PT, and hemoccult test review. In Part 2, participants will not be dosed until 14 days of safety data and available PK data from at least 6 participants in the 40mg IV panel (Part 1 Panel C) of this trial has been reviewed. Considering that the major safety concerns are local tolerability and acute infusion reactions, 21 days of safety data is sufficient to advance the trial between panels in Part 1. Based on observed safety from PN001 and PN004 (Panel A and B) and PK data from PN001 and PN004 (Panel A), 14 days after a single 40 mg IV dose of MK-2060 the exposure will be below the highest exposure observed with the 8 mg and 20 mg IV doses. Therefore 14 days of safety, tolerability data and available PK data from at least 6 participants in Part 1 Panel C 40 mg IV dose will be sufficient to determine the safety of proceeding to Part 2. PK and PD data will be reviewed on an ongoing basis and will be used to inform on decisions to modify the subsequent dose level. When available, plasma PK data will be reviewed to aid in dose escalation decisions; at least 14 days of PK data from at least 7 participants in Panel A (8 mg) will be evaluated prior to proceeding to the next panels. In addition, Panel C (40 mg dose) will not be dosed until 21 days of safety, tolerability, and PK and PD data from the 40 mg dose in PN001 has been reviewed.

In Part 2 (multiple dose), in order to mimic the therapeutic setting, 3 doses given on Days 1, 3, and 5 will be studied in addition to the weekly maintenance dose. A weekly maintenance dosing frequency was selected to reduce the peak to trough ratio without posing a significant burden to ESRD patients who undergo dialysis 3 times a week and can receive an IV infusion concurrent with dialysis. A less frequent dosing interval would result in higher peak concentrations and patients being sustained at maximal FXI inhibition levels longer, which could potentially increase bleeding risk in this vulnerable population. For anticoagulants, it is desirable to achieve near target anticoagulation as soon as therapy is initiated. Given the half-life of ~18 days observed in Part 1 of PN004 and the dosing frequency of QW, without the 3 doses given during week 1 (loading dose) it would take weeks to achieve steady state exposure and target anticoagulation. Thus, the 3 doses during week 1 are introduced to help achieve desired anticoagulation immediately after initiation of therapy.

Participants will be discharged following the ~52- or ~24-hour (24 hours after last dose for Week 1 and 24 hours after each dose in Weeks 2-4) in-clinic period after dosing for Part 1 or Part 2 accordingly, but they will continue to be monitored throughout the trial period and return to the site post-dose as specified in the SoA (safety evaluations as indicated in the flow chart (including repeat physical examinations, infusion reaction assessments, laboratory safety assessments, hemoccult, local lab aPTT and PT tests).

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

- Participants will be informed that they could be taking an anticoagulant as a participant in this 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 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 48 hours for Part 1 and 24 hours for Part 2, and until aPTT/PT values are no longer increasing (upon retest at 48 hours) and according to the discretion of the investigator.

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 from the study, 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 Institutional Review Board(s)/Independent Ethics Committee(s) [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 pre-specified criteria for terminating the trial early.

A primary objective of this early Phase I trial is to identify a safe and well-tolerated dose and/or dosing regimen that achieve pharmacokinetic, pharmacodynamic and/or biologic targets in humans based on preclinical or early clinical data. Therefore, it is possible that trial participants may not receive all doses specified in the protocol if this objective is achieved at lesser dose levels in this trial. This would not be defined as early termination of the trial, but rather an earlier than anticipated achievement of the trial objective(s). If a finding (e.g., pharmacokinetic, pharmacodynamic, efficacy, biologic targets, etc.) from another preclinical or clinical trial using the trial treatment(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this trial, results in the trial(s) or program being

stopped for non-safety reasons, this also does not meet the definition of early trial termination.

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

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

5 STUDY POPULATION

Male and Female of non-child bearing potential (WONCBP) participants with ESRD on HD between the ages of 18 and 80 years (ages ≥ 40 and ≤ 80 for Part 1 and ≥ 18 and ≤ 80 for Part 2) 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:

Type of Participant and Disease Characteristics

1. ESRD maintained on stable outpatient HD regimen, using an established (>3 months) 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 at a healthcare center for > 3 month from 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 for at least 3 months beyond the study.

3. Have a Body Mass Index (BMI) ≥ 18 and ≤ 45 kg/m^2. BMI = weight (kg)/height $(m)^2$.

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

5. 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 both the investigator and the Sponsor.

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

Demographics

7. Be male or female, of non-child bearing potential (WONCBP) from 40 years to 80 years of age inclusive for Part 1, and 18 years to 80 years of age inclusive for Part 2, at the time of signing the informed consent.

Male Participants

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

8. Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

Female Participants

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

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

    a. She is not a woman of childbearing potential (WOCBP), satisfying one of the two criteria below:

        i. If the participant is a postmenopausal female: she is without menses for at least 1 year and has a follicle stimulating hormone (FSH) value in the postmenopausal range upon pre-study (screening) evaluation.

        ii. If the participant is a surgically sterile female: she is status post hysterectomy, bilateral salpingectomy, oophorectomy or tubal ligation. NOTE: These procedures must be confirmed with medical records. In the absence of documentation, hysterectomy may be confirmed by pelvic exam or if necessary by ultrasound; oophorectomy may be confirmed by hormone levels, particularly follicle stimulating hormone (FSH) in the post-menopausal range, but tubal ligation without records

should be excluded. Information must be captured appropriately within the site's source documents.

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:

Medical Conditions

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

3. Has a history of cancer (malignancy), including adenocarcinoma,

   Exceptions: (1) Subjects with adequately treated non-melanomatous skin carcinoma may participate in the trial; (2) Subjects with other malignancies which have been successfully treated ≥10 years prior to the pretrial (screening) visit where, in the judgment of both the investigator and treating physician, appropriate follow-up has revealed no evidence of recurrence from the time of treatment through the time of the pretrial (screening) visit (except those cancers identified at the beginning of exclusion criterion 10); or, (3) Subjects, who, in the opinion of the trial investigator, are highly unlikely to sustain a recurrence for the duration of the trial.

4. Has blood coagulation test (aPTT, PT) ≥ 20 % outside of normal range on pretrial (screening), which are considered clinically significant by both the investigator and the sponsor.

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.

8. Has a history of or current frequent epistaxis within the last 3 months or active gingivitis.

9. Has ongoing anticoagulant therapy (warfarin, apixaban, dabigatran, rivaroxaban, edoxaban, betrixaban) or antiplatelet therapy (clopidogrel, prasugrel, ticagrelor, ticlopidine). Intradialytic heparin and aspirin are permitted.

10. 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.

11. 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.

12. Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the pre-study (screening) visits.

13. Has a history of significant multiple and/or severe allergies (e.g. food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability (i.e. systemic allergic reaction) to prescription or non-prescription drugs or food.

14. 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.

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

16. 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 1 month.

    Exceptions:

    - Participants who have received seasonal flu vaccine and pneumococcal vaccine within the last 1 month may be enrolled at the discretion of the investigator.

    - COVID-19 vaccine may be administered. 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.

17. 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.

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

Prior/Concomitant Therapy

18. Is unable to refrain from or anticipates the use of medication, including prescription and nonprescription drugs or herbal remedies beginning approximately 2 weeks (or 5 half-lives) prior to administration of the initial dose of study drug, throughout the study until

the poststudy visit. Allowed and prohibited concomitant meds are discussed in Section 6.5.

Prior/Concurrent Clinical Study Experience

19. Has participated in another investigational study within 4 weeks (or 5 half-lives, whichever is greater) prior to sponsor's investigational drug (MK2060/placebo) administration. The window will be derived from the date of the last dose in the previous study.

Diagnostic Assessments

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

Other Exclusions

21. Is under the age of legal consent.

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

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. Is a regular user of any illicit drugs or has a history of drug (including alcohol) abuse within approximately 2 years. Participants must have a negative serum or saliva drug screen prior to randomization. Participants with a positive drug screen due to the use of physician prescribed medications (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. Presents any concern by the investigator regarding safe participation in the study or for any other reason the investigator considers the participant inappropriate for participation in the study.

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

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

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

On dosing days, subjects will fast from all food and drinks, except water, for at least 8 hours prior to study drug administration. Subjects will continue to fast until 2 hours after study drug administration when they will be given a light breakfast. A lunch and dinner will be provided at time points indicated in the trial flowchart. Additional meals and snack(s) will be provided by the investigator as per the CRUs standard procedures. Subjects will fast from all food and drinks except water between meals and snacks. After 24-hour post-dose procedures on dosing days have been completed, subsequent meals and snacks will be unrestricted in caloric content, composition and timing.

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

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

5.3.2.1 Caffeine Restrictions

Participants will refrain from consumption of caffeinated beverages and xanthine-containing products from 12 hours prior to the pre- and post-trial visits, from 12 hours prior to and 12 hours after study drug administration, and 12 hours prior to scheduled outpatient visits. At all other times, caffeinated beverages or xanthine-containing products will be limited to no more than 6 units per day amounts (>6 units: 1 unit=120 mg of caffeine).

5.3.2.2 Alcohol Restrictions

Participants will refrain from consumption of alcohol 24 hours prior to the pre- and post-trial visits, from 24 hours prior to and after study drug 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 (1 glass is approximately equivalent to: beer [~355 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 pre-study (screening) visit until administration of the initial dose of study drug, 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 randomized in the study. A minimal set of screen failure information may be included, as outlined in the electronic case report forms (eCRF) entry guidelines. Minimal information may include demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements.

5.5 Participant Replacement Strategy

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

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

6 STUDY INTERVENTION

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

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

6.1 Study Intervention(s) Administered

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

Table 2 Study Intervention

Arm Name	**Arm Type**	**Intervention Name**	**Type**	**Dose Formu-lation**	**Unit Dose Strength(s)**	**Dosage Level(s)**	**Route of Administration**	**Regimen/ Treatment Period/ Vaccination Regimen**	**Use**	**IMP/ NIMP**	**Sourcing**
MK-2060	Experimental	MK-2060	Drug	Solution for Infusion	100mg/mL	8 mg 20 mg 25 mg 40 mg	IV Infusion	Part 1: Day 1 Part 2: Days 1, 3, 5, 8, 15 and 22	Experimental	IMP	Provided Centrally by sponsor
Placebo	Placebo Comparator	Placebo	Drug	Solution for Infusion	Saline	0 mg	IV Infusion	Part 1: Day 1 Part 2: Days 1, 3, 5, 8, 15 and 22	Placebo	IMP	Locally
Definition Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.											

All supplies indicated in Table 2 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (e.g., 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 in order to administer the proper dose to each subject are outlined in a separate document provided by the Sponsor.

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

In each panel in Part 1 and Part 2, participants will be assigned randomly according to a computer-generated allocation schedule. A sample allocation schedule is shown below in Table 3 and Table 4 for Part 1 and Part 2 respectively.

Table 3 Sample Allocation Schedule for Part 1

Subjects[a]	Dose[b]
Panel A	
N=6	8 mg IV
N=2	PBO
Panel B	
N=6	20 mg IV
N=2	PBO
Panel C	
N=6	40 mg IV
N=2	PBO

PBO=Placebo
[a] Subjects will be ESRD on HD and randomized to receive an intravenous (IV) dose of MK-2060 (n=6) or placebo (n=2).
[b] The suggested doses may be adjusted downward based on evaluation of safety, tolerability, pharmacokinetic, and/or pharmacodynamic data observed in previous treatment panels.

Table 4 Sample Allocation Schedule for Part 2

Subjects[a]	Dose[b]
N=15	Week 1: up to 25 mg IV x 3 / Weeks 2-4: up to 25 mg IV
N=5	PBO

PBO=Placebo
[a] Subjects will be ESRD on HD and randomized to a once weekly IV dose of MK-2060 (n=15) or placebo (n=5) for 4 weeks. Males will be assigned allocation numbers in ascending order, starting with the lowest number. Females will be assigned allocation numbers in descending order, starting with the highest number.
[b] The suggested doses may be adjusted downward based on evaluation of safety, tolerability, pharmacokinetic, and/or pharmacodynamic data observed in Part 1.

6.3.2 Stratification

A minimum of 2 participants of each gender will be enrolled in each panel in Part 1. A minimum of 3 participants of each gender will be enrolled in Part 2.

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. MK-2060 and placebo will be packaged identically by an unblinded pharmacist so that blind is maintained. The infusion bags, IV line (through which the infusion is administered) do not require opaque covering as the differences between the clinical materials are not visually distinguishable within the infusion bags, tubing or syringe. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

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

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 and is able to withhold the use within four hours prior to administration of the first dose of study drug in each panel of the study. The name (generic and brand), dose and regimen for all concomitant medications should be recorded on the appropriate CRF.

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

ALLOWED MEDICATIONS

Lipid Lowering Agents: Statins

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

Aspirin

Low-dose aspirin is permitted in the study.

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

Clopidogrel
Prasugrel
Ticagrelor
Ticlopidine

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.

Clinical Research Units (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)

Prior to each treatment, the clinical and laboratory safety parameters from the previous dose level will be reviewed by the investigator and discussed with the Sponsor to permit a decision on whether to advance to the next higher dose level. No dose escalation will occur without the joint agreement of the investigator and the Sponsor.

6.6.1 Stopping Rules

If any of the following events occur, dose escalation in Part 1 or subsequent dosing in Part 2 will be stopped to review additional safety data:

- If one or more treatment related infusion adverse events of severe intensity occurs.
- If one or more treatment related SAEs occurs, dose escalation will be stopped and a meeting to review available safety data by the investigator and Sponsor will be required.
- Two (2) or more participants within a Panel in Part 1 (at the same dose level) or Part 2 report Severe Non-Serious Adverse Events considered related to the study drug by the investigator.
- An increase in local lab aPTT > 4.0-fold versus screening baseline as confirmed after repeat measurement in 2 or more subjects in a panel in Part 1 or in Part 2. Local lab aPTT measured at Screening Visit 1 should be used as baseline value.
- An increase in local lab PT > 1.5-fold versus screening baseline as confirmed after repeat measurement in 2 or more subjects in a panel in Part 1 or in Part 2. Local lab PT measured at Screening Visit 1 should be used as baseline value.

In severe FXI-deficient populations, aPTT prolongations greater than 3-fold have been observed (050RJ8). 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 doses in PN001. 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 subjects in a panel.

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 dose escalation in Part 1 or subsequent dosing in Part 2 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 within the same panel or dose escalation will be stopped and a meeting to review 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 following the end of the study.

6.8 Clinical Supplies Disclosure

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period regimen will still continue to participate in the study as specified in Section 7.1 and Section 8.1.9, or if available, a protocol clarification letter. In Part 2, 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, semirecumbent 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 Sections 8.1.9.

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant's treatment assignment has been unblinded by the investigator, MSD, or through the emergency unblinding call center.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.

7.2 Participant Withdrawal From the Study

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

7.3 Lost to Follow-up

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

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

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

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

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized 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 500 mL for Part 1 and 563.5 mL for Part 2 (Appendix 8 and operations/laboratory manual).

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study

protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

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

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

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

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

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used 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 randomization number identifies the participant for all procedures occurring after randomization. Once a randomization number is assigned to a participant, it can never be re-assigned to another participant.

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

8.1.8 Study Intervention Administration

Administration of study medication will be witnessed by the investigator and/or study staff.

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 or placebo will be given in the morning 30 minutes after initiation of hemodialysis and after at least an 8-hour fast. The fast will be maintained until 2-hours postdose, at which time a standard light breakfast will be served. Subjects will also remain semi-recumbent for 4 hours postdose except to stand for the measurement of orthostatic VS (if needed) or other trial procedures (for example for breakfast).

8.1.9 Discontinuation and Withdrawal

The investigator or trial coordinator must notify the Sponsor when a participant has been discontinued/withdrawn from the trial. If a participant discontinues for any reason at any time during the course of the trial, the participant may be asked to return to the clinic (or be contacted) for a post-trial visit (approximately 150 or 90 days after the last dose of study drug is given for Part 1 and Part 2 respectively) to have the applicable procedures conducted.

However, the investigator may decide to perform the post-trial procedures at the time of discontinuation or as soon as possible after discontinuation. If the post-trial visit occurs prior to 150 or 90 days after the last dose of study drug is given for Part 1 and Part 2 respectively, the investigator and/or appropriately trained study site staff should perform a follow-up phone call 150 or 90 days after the last dose of study drug for Part 1 and Part 2 respectively to determine if any adverse events have occurred since the post-trial clinic visit. Any adverse events which 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 future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's consent for future biomedical research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

8.1.10 Participant Blinding/Unblinding

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

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to

him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is qualified physician should make reasonable attempts to enter the intensity of the AEs observed, the relation to study drug, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

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

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

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

8.1.11 Domiciling

Part 1: Participants will report to the clinical research unit (CRU) the evening prior to the scheduled day of trial drug administration and remain in the unit for ~ 52 hours post-dose. At the discretion of the investigator, subjects may be requested to remain in the CRU longer. If local lab aPTT values are >3-fold above baseline (as measured at Screening Visit 1), or local lab PT values are >1.5-fold above baseline (at any time point), subjects will be asked to remain in the clinic for at least 48 hours, and until aPTT/PT values are no longer increasing (upon retest at 48 hours).

Part 2: 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 post the third dose in Week 1 and for ~24 hours post-dose in Weeks 2-4. At the discretion of the investigator, subjects may be requested to remain in the CRU longer. In Part 2, Week 1, all participants will be domiciled until ~ 24 hours post the third dose on Day 5. Participants may be domiciled longer per investigator's discretion. If local lab aPTT values are >3-fold above baseline (as measured at Screening Visit 1), or local lab PT values are >1.5-fold above baseline (at any time point), subjects will be asked to remain in the clinic for at least 24 hours, and until aPTT/PT values are no longer increasing (upon retest at 24 hours postdose).

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/placebo 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. Although the samples collected for anti-drug antibody (ADA) assessment in PN001 are pending analysis, based on the PK profiles observed to date, 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 pre-study 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

The physical exam assessments will be defined and conducted per the site SOP. A symptom driven physical exam will be conducted based upon any emergent symptoms at the discretion of the investigator.

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 0.1-0.4 round down and 0.5-0.9 round up.

8.3.2 Vital Signs

8.3.2.1 Resting Vital Signs

Vital Sign Measurements (Heart Rate and Blood Pressure)

Participants should be resting in a semirecumbent for at least 10 minutes prior to having vital sign (VS) measurements obtained. Semirecumbent vital signs (VS) will include heart rate (HR) and blood pressure (BP). The correct size of the BP cuff and the correct positioning on the participants' arm is essential to increase the accuracy of BP measurements.

Pre-dose heart rate (HR) and blood pressure (BP) will be in triplicate measurements, obtained at least 1-2 minutes apart within 3 hours of dosing MK-2060/placebo. The median of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). Postdose vital sign (VS) measurements will be single measurements.

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

Body Temperature

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

Respiratory Rate

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

8.3.2.2 Orthostatic Vital Signs

Orthostatic vital signs (VS) (HR and BP) will also be obtained. Participants should be semirecumbent for at least 10 minutes and then stand upright for 2 minutes prior to 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 prior to lead placement. Participants may need to be shaved to ensure proper lead placement.

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

Participants should be resting in the semi-recumbent position for at least 10 minutes prior to ECG measurements being obtained.

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

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

Pre-dose ECGs will be obtained in triplicate at least 1-2 minutes apart within 24 hours prior to dosing MK-2060/placebo. The median of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). Unless otherwise designated in the flow chart, post-dose ECG measurements will be single measurements.

If a participant demonstrates an increase in QTc interval ≥60 msec compared with median pre-dose baseline measurement, the ECG will be repeated twice within 5 minutes. The median value of the QTc interval from the 3 ECGs will represent the value at that time point. If the median QTc interval increase from baseline for any post-dose time point is ≥60 msec, the subject 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 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 Cardiac or Intensive Care Unit) is available.

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

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

A study cardiologist should be arranged by the Principal Investigator to be available as needed to review ECG tracings with abnormalities.

8.3.4 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. In Part 1, baseline time to adequate hemostasis will be established by the mean of the assessments performed at Screen 2 and Screen 3.

In Part 2, baseline time to adequate hemostasis will be established by the assessments performed at Screen 2. After review of time to hemostasis at Day 42 or any time to hemostasis assessments beyond Day 42 and upon agreement of the both the Sponsor and investigator, the patient may return for onsite hemodialysis within 30 days until time to hemostasis returns to baseline or until the conclusion of the trial, whichever comes first.

8.4 Management of Infusion Reaction During and Post-dose

As outlined in 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, pruritus or flushing, swollen lips-tongue-uvula and angioedema, accompanied by respiratory compromise (bronchospasm, stridor or hoarseness) and/or changes in blood pressure (hypotension). Severe 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.

All participants should be evaluated for infusion-type reactions. Participants who experience infusion or hypersensitivity reactions in conjunction with the infusion of study drug should receive appropriate supportive care measures as deemed necessary by the treating physician. Participants should be carefully observed until complete resolution of all signs and symptoms, if a reaction occurs. Report any adverse experiences according to the guidelines in Section 8.5.

8.4.1 Systemic Infusion Reaction Assessment

Participants will be monitored during the administration of MK-2060/placebo for 48 hours for Part 1 (all single dose panels) and 24 hours for Part 2 (multiple doses) post-dose at CRU after the initiation of administration. During this time, signs and symptoms of a systemic injection/infusion reaction, including but not limited to fever, VS changes (tachycardia/hypotension), pruritis, urticarial (hives), lip swelling, angioedema, bronchospasm, stridor, hoarseness, and shortness of breath will be monitored. Injection/infusion reactions must be assessed and managed promptly. Such assessment and management are discussed in Section 8.4.

8.4.2 Local Infusion Reaction Assessment

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

8.4.3 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 case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

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

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

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 150 days (Part 1) or 90 days (Part 2) 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.

8.5 Adverse Events (AEs), Serious Adverse Events (SAEs), 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/randomization, must be reported by the investigator for randomized participants only if the event is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure.

From the time of intervention allocation/randomization through 164 days for Part 1 and 90 days for Part 2 following 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 of the time 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 6.

Table 6 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:**
Nonserious Adverse Event (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
Serious Adverse Event (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: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

Type of Event	**Reporting 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:
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 24 hours of learning of 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, events of clinical interest (ECIs), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.5.4 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 wth 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 suspected unexpected serious adverse reactions (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 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Not applicable

8.5.6 Events of Clinical Interest (ECIs)

Selected nonserious and SAEs 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, that is not associated with clinical symptoms or abnormal laboratory results.

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

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that must trigger 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

The participant has taken (accidentally or intentionally) any drug administered as part of the protocol that exceeds the dose as prescribed by the protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.

8.7 Pharmacokinetics

The decision as to which plasma samples collected will be assayed for evaluation of PK/pharmacodynamics will be collaboratively determined by the Department of Quantitative

Pharmacology and Pharmacometrics and the appropriate department within Early-Stage Development, (e.g., samples at lower doses may not be assayed if samples at higher doses reveal undetectable drug concentrations). Plasma samples may be tested for measurement of metabolites and/or additional PK/PD parameters.

8.7.1 Blood Collection for Plasma MK-2060

Sample collection, storage, and shipment instruction for plasma samples will be provided in a separate trial 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 5 min before anticipated time of the end of the infusion).

8.8 Pharmacodynamics

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

8.9 Biomarkers

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

8.9.1 Blood Collection for PT, aPTT, FXI Activity and FGA Assay

Part 1: PT and aPTT at screening, 1 hour, 12 hour, 48 hours, Day 5, Day 8, Day 12, Day 15, Day 22, and Day 90 post-dose will be performed locally for safety monitoring. All other pre-dose and post-dose PT and aPTT, as well as FXI activity will be performed at a central vendor for PK/PD analysis. FGA assays will be performed by the Sponsor. Sample collection, storage, and shipment instructions for the PT, aPTT, FXI activity, and FGA assays will be provided in a separate trial Study Operations Manual by the Sponsor. The primary data for statistical analysis and modeling will be based on the information from the central vendor.

Part 2: PT and aPTT at screening, predose, 1 hour, 12 hour postdose on each dosing day (Days 1, 3, 5, 8, 15 and 22), Day 10, Day 17, Day 23, Day 24, Day 26, Day 29, Day 35, Day 42, and Day 111 post-dose will be performed locally for safety monitoring. All other pre-dose and post-dose PT and aPTT, as well as FXI activity will be performed at a central vendor for PK/PD analysis. FGA assays will be performed by the Sponsor. Sample collection, storage, and shipment instructions for the PT, aPTT, FXI activity, and FGA assays will be provided in a separate trial Study Operations Manual by the Sponsor. The primary data for statistical analysis and modeling will be based on the information from the central vendor.

8.9.2 Blood for Plasma ADA

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

8.9.3 5-D Itch Scale

5-D itch scale [Elman, S., et al 2010] will be collected on Day 120 for Part 1 Panel C only and on Days 24 and 42 for Part 2 participants to collect pruritis symptoms, as indicated in the SoA.

8.9.4 Planned Genetic Analysis Sample Collection

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

Sample collection, storage, and shipment instructon for planned genetic analysis samples will be provided in the operations/laboratory manual.

8.10 Future Biomedical Research Sample Collection

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

- Leftover DNA for future research
- Leftover main study plasma from MK-2060 assay stored for future research

8.11 Visit Requirements

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

8.11.1 Screening

Approximately 4 weeks prior to intervention allocation/randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Screening 2 should occur within 80 hours prior to Day 1 for Part 2.

Participants may be rescreened after consultation with the Sponsor. Rescreening should include all screening procedures listed in the SoA, including consent review. Rescreen procedures cannot be conducted the day prior to intervention allocation/randomization if there are Day -1 procedures planned per protocol.

8.11.2 Treatment Period

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

After all pre-dose procedures have been completed; subjects will be assigned a unique randomization number associated with a specific treatment as defined by a computer-generated allocation schedule. Subjects will report to the CRU prior to the scheduled day of dosing or time specified by the investigator. On all the dosing days, subjects will fast from all food and drinks, except water, for at least 8 hours until 2 hours post study drug administration, when they will be given a light breakfast (see Section 5.3.1).

Subjects will be administered study drug as indicated in Section 6. Subjects 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 Visit

The Poststudy visit will occur approximately 150 days or 90 days following administration of the last study drug for Part 1 and Part 2 respectively. Procedures outlined in the Poststudy visit may be obtained on Day 150 (±7 days) for Part 1 and Day 111 (±7 days) for Part 2. However, follow up on any clinical or laboratory AEs should occur in person if the poststudy visit occurs prior to 150 days or 90 days following administration of the last dose of study drug for Part 1 and Part 2 respectively.

8.11.4 Discontinued Participants 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 at the discretion of the investigator and with Sponsor agreement. The subset of study procedures completed will be communicated in a PCL.

8.11.5 Safety Phone Call Follow-up (Part 1 Only)

A safety follow-up phone call will be performed approximately 14 days after the post-trial visit (within the visit windows allowed per protocol) for all panels in Part 1. The safety follow-up phone call must be performed by appropriately trained study site staff. If the initial call is unsuccessful, the study site staff should make a total of 3 attempts. All attempts to contact the subjects will be recorded in the source documents. The calls will facilitate the collection of relevant safety information. The subject will be interviewed to obtained information relating to AEs and SAEs. All safety information described by the subject must be documented in the source documents.

8.11.6 Critical Procedures Based on Study Objectives: Timing of Procedure

For this trial, the plasma sample for MK-2060 is the critical procedure.

At any post-dose timepoint, the blood sample for MK-2060 needs to be collected as close to the exact timepoint as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible. Trial procedures can be performed prior or after the prescribed/scheduled time.

The order of priority can be changed during the trial 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.

Post-dose PK and PD sample collection, standard safety evaluation (VS, ECG, laboratory safety tests (including chemistry/hematology, aPTT, PT), physical exam (full, symptom driven, systemic injection/infusion, local injection/infusion, hemoccult test): as outlined in [Table 7] below.

Table 7 Pharmacokinetic (Blood) Collection Windows

PK Collection	PK Collection Window
Part 1	
0 – 4.0 hr	5 min
4.1 - 24 hr	15 min
24.1 - 96 hr	1 hr
96.1 - 168 hr	2 hr
Day 12	1 Day and within 12 hours prior to receiving dialysis
Day 15 + Day 22	2 Days and within 12 hours prior to receiving dialysis
Day 29	3 Days and within 12 hours prior to receiving dialysis
Day 60 + Day 90	5 Days and within 12 hours prior to receiving dialysis
Day 120 + Day 150	7 Days and within 12 hours prior to receiving dialysis
Part 2	
0 – 4.0 hr post each dose	5 min
Days 1, 2, 3, 5, 8, 15, 22, 23, 24 and 29	No flexible window for the scheduled PK day
Day 26	Plus 1 day is allowed
Days 10, 17,	Plus and minus 1 day is allowed
Days 35, 42, and 49, and 63	Plus and minus 2 days is allowed
Days 81 and 111	Plus and minus 3 days is allowed

- Predose standard safety evaluations: vital signs within 3 hours and ECG, laboratory safety tests and physical exam within 24 hours

- Postdose standard safety evaluations: vital signs, ECG, laboratory safety tests, and physical exam

  - <24 hr post each dose may be obtained within 30 min of the theoretical sampling time

  - 24 hr - <48 hr post each dose may be obtained within 1 hr of the theoretical sampling time

  - 48 hr – 168 hr post each dose may be obtained within 2 hr of the theoretical sampling time

- Hemoccult Test: within 2 days of specified timepoint.

- Assessment of time to adequate hemostasis: at the conclusion of the onsite hemodialysis session, after hemodialysis catheters are removed from the dialysis access site.

- On clinic visits where onsite hemodialysis is not being conducted, visits must not occur within 8 hours of the completion of the most recent dialysis session.

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

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

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

- Repeat of or decrease in the dose of the study intervention administered in any given period/panel

- Interchange of doses between panels

- Entire panel may be omitted

- Remove a planned PK pause if agreed by Sponsor and investigator if no further increases in total daily dose

- 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.

- Decrease in the duration of study intervention administration for Part 2 (eg, number of weeks)

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

9 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

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

Statistical Analysis Plan

Safety

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

Pharmacokinetics

Model-Based PK Summary

Part 1:

For Part 1, i.e., single ascending dose, SD PK of participants with ESRD from the present study will be compared with historical SD PK data (PN001) in healthy participants.

Separately for each PK parameter, for single dose, individual values of AUC0-∞, AUC0-168hr, Cmax, and C168hr will be natural log-transformed and evaluated with a linear fixed effects model containing a categorical effect for population (ESRD on HD Part 1 single dose, healthy) and dose (8mg IV, 20mg IV and 40mg IV) and dose by population interaction. The fixed effects model will also contain a categorical effect for sex and a continuous effect for age. The present study will enroll older male and female subjects, while PN001 enrolled younger male subjects. Sex and age are not expected to impact PK. An unstructured covariance matrix will be used to allow for unequal population variances via the GROUP statement in SAS PROC MIXED. Kenward and Roger's method will be used to calculate the denominator degrees of freedom for the fixed population effect (DDFM=KR). Ninety-five percent (95%) CIs for the least squares means for each population by dose level will be constructed on the natural log scale and will reference the t-distribution. Exponentiating the least-squares means and their corresponding 95% CIs will yield estimates for the population geometric means and confidence intervals about the geometric means on the original scale.

A sample size of six subjects on active dose and two on placebo per panel is considered to be adequate to address the primary objectives of the study.

Part 2:

For Part 2 i.e., multiple IV dose administration, descriptive statistics (mean, median, standard deviation, min, max values) for AUC0-168, Cmax, C168, Tmax, terminal t1/2, CL, and Vz will be provided. In addition, graphical display such as box plot will be created for AUC0-168 and Cmax to check for possible outliers.

A sample size of fifteen subjects on active dose and five on placebo is adequate to address the primary objectives of the study.

9.2 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be conducted by, or under the direct auspices of, the 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

Secondary

1. **Hypothesis (Part 1):** The true fold increase in aPTT 168 hours after a single well-tolerated dose of MK-2060 in older subjects with ESRD on HD is at least 1.5.

2. **Hypothesis (Part 2):** The true fold increase in aPTT 168 hours after the last dose following an IV loading dose and three maintenance doses of MK-20160 in older adult participants with ESRD on HD at least 1.5.

9.4 Analysis Endpoints

Primary Endpoints

1. Safety: Primary safety endpoints will include all types of adverse experiences, in addition to laboratory safety tests, ECGs, VS. For change from baseline analyses, baseline is defined as the panel-specific pre-dose value.

Secondary Endpoints (Pharmacokinetic)

1. Pharmacokinetics (Part 1): The pharmacokinetic variables of secondary interest for single dose MK-2060 are plasma AUC0-∞, AUC 0-168hr, Cmax, C168hr, Tmax, apparent terminal t1/2, CL and Vz.

2. Pharmacokinetics (Part 2): The pharmacokinetic variables of secondary interest for multiple dose MK-2060 are plasma AUC 0-168hr, Cmax, C168hr, Tmax after the last dose.

3. Pharmacodynamics: The PD variable of secondary interest for MK-2060 is aPTT (change from baseline). Baseline is defined as the panel-specific pre-dose value.

Exploratory Endpoints:

1. FXI activity levels

2. FGA

3. PT

4. hsCRP

5. Time to hemostasis

6. 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 (PP): 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. This population will be used for the PK and PD analyses.

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. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline).

Pharmacokinetics

Model-Based PK Summary

Part 1:

SD PK of participants with ESRD from the present study will be compared with historical SD PK data (P001) in healthy participants.

Separately for each PK parameter, individual values of AUC0-∞, AUC0-168hr, Cmax, and C168hr will be natural log-transformed and evaluated with a linear fixed effects model containing a categorical effect for population (ESRD on HD, healthy) and dose (8mg IV, 20mg IV and 40mg IV) and dose by population interaction. The fixed effects model will also contain a categorical effect for sex and a continuous effect for age. The present study will enroll older male and female subjects, while PN001 enrolled younger male subjects. Sex and age are not expected to impact PK. An unstructured covariance matrix will be used to allow

for unequal population variances via the REPEATED and GROUP statement in SAS PROC MIXED. Kenward and Roger's method will be used to calculate the denominator degrees of freedom for the fixed population effect (DDFM=KR). Ninety-five percent (95%) CIs for the least squares means for each population by dose will be constructed on the natural log scale and will reference the t-distribution. Exponentiating the least-squares means, and their corresponding 95% CIs will yield estimates for the population geometric means and confidence intervals about the geometric means on the original scale.

Part 2:

Geometric means and 95% confidence intervals (based on a t-distribution) will be provided for AUC0-168, Cmax, and C168 obtained following the last multiple dose. Median, minimum, and maximum will be provided for Tmax.

Secondary Analysis: Comparison to Healthy Subjects

To compare subjects with ESRD on HD to subjects with normal renal function at the same dose level, a two-sided 90% confidence interval for the true difference in means (ESRD on HD – normal renal function, at the same dose level) will be calculated for each PK parameter using the mean square error from the PK model described above and referencing a t-distribution. For each dose level of ESRD on HD, these confidence limits will be exponentiated to obtain the 90% confidence interval for the true ratio of geometric means (ESRD on HD/normal renal function, at the same dose level) for each PK parameter.

Dose Proportionality

An exploratory analysis will be conducted to preliminarily assess dose proportionality of MK-2060 AUC0-∞, AUC0-168hr, Cmax and C168hr in ESRD on HD participants, using the power law model. Separately for each PK parameter, individual PK values will be natural log transformed and evaluated with a linear regression model having ln(dose) as an explanatory variable. A least square estimate and 95% confidence interval for the slope associated with ln(dose) will be obtained from the model.

A plot of the observed PK data versus dose will be provided along with an estimated regression line on the raw scale and a 95% Schéffe confidence band.

Descriptive Statistics

Individual values will be listed for each PK parameter (including Tmax and apparent terminal t1/2, CL, Vz) by treatment, and the following (non-model-based) descriptive statistics will be provided: N (number of subjects with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s^2) - 1), where s^2 is the observed variance on the natural log-scale).

Pharmacodynamics

Secondary Hypothesis

Part 1:

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

The posterior probability that the true fold-increase from baseline in aPTT 168 hours after a single dose is at least 1.5 will be calculated for each dose assuming normality and using a non-informative (Jeffrey's) prior. A 60% posterior probability for at least one dose level that also exhibits an acceptable safety profile will satisfy the secondary pharmacodynamics hypothesis. In addition, the proportion of subjects with a fold-increase in aPTT 168 hours after a single dose of at least 1.5 will be tabulated.

FXI activity levels, FGA and PT will be evaluated in a similar fashion. Additional model-based analysis may be employed to further explore PD endpoints over time.

Descriptive statistics will be provided for PD endpoints by treatment and time.

Part 2:

As in Part 1, individual aPTT fold-change from baseline values will be natural log-transformed and evaluated with a linear mixed effects model incorporating the longitudinal effects of measurements at the three weekly time points. An unstructured covariance matrix will be used to model the correlation between different measurements within the same subjects. Kenward and Roger's method will be used to calculate the denominator degrees of freedom for the fixed effects. Least squares mean and 95% confidence intervals for each treatment, and for the between-treatment differences (MK-2060 – placebo) and 90% CI will be obtained. These estimates will be back-transformed to obtain GM aPTT fold-change from baseline by treatment and time and the GMR (MK-2060 fold-change from baseline/placebo fold-change from baseline) by time.

The posterior probability that the true fold-increase from baseline in aPTT is at least 1.5 will be calculated at each of the three weekly time points assuming normality and using a non-informative prior. A 60% posterior probability for at least one of the three time points that also exhibits an acceptable safety profile will satisfy the secondary pharmacodynamics hypothesis. In addition, the proportion of subjects with at least 1.5 fold increase in aPTT 168 hours after the last dose will be tabulated.

FXI activity levels, FGA and PT will be evaluated in a similar fashion. Additional model-based analysis may be employed to further explore PD endpoints over time.

Descriptive statistics will be provided for PD endpoints by treatment and time.

PK-PD

The relationship between plasma concentrations and aPTT, FXI activity, FGA, and PT will be explored graphically. Upon visual inspection, additional model-based analysis may be employed to further explore the PK/PD relationship.

General

For all analyses, data will be examined for departures from the assumptions of the statistical model(s) as appropriate; e.g., heteroscedasticity, nonnormality of the error terms. Distribution-free methods may be used if a serious departure from the assumptions of the models(s) is observed, or suitable data transformations may be applied.

9.7 Interim Analyses

During the in-life portion of the trial, descriptive summary level results (PK, PD and/or safety (labs, VS, ECGs) may be prepared as needed to support dose escalation meetings. No individual level results will be provided, and the aggregate summaries will be presented in a blinded manner. There are no planned interim analyses to test any formal hypotheses.

9.8 Multiplicity

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

9.9 Sample Size and Power Calculations

A sample size of six subjects on active dose and two on placebo per panel is considered to be adequate to address the primary objectives of the study.

Pharmacokinetics

The sample size selected for each dose level to evaluate the effect of ESRD on HD on the PK of MK-2060 compared to subjects with normal renal function was not chosen to satisfy any a priori statistical requirement. Nevertheless, estimates of the expected precision of the estimates, based on these sample sizes and the variability obtained from previous studies are presented below.

The precision of the estimated ratios of geometric means (ESRD on HD/normal renal function, at the same dose level) of PK parameters obtained from this study can be assessed by calculating the half-width of the 90% CIs expected for the given sample size and assumed variability. The between-subject standard deviations (on the natural log scale) for MK-2060 AUC0-168hr and Cmax after administration of 20mg IV MK-2060 observed in a previous

study (PN001) are 0.199 ln(µM*hr) and 0.169 ln(nM), respectively. Since the between subject variability in subjects with RI has historically been seen to be 2 to 3-fold higher in many studies, the between subject variability obtained from normal renal function subjects was inflated by a factor of 2 for ESRD on HD and was used for the following calculations. With a sample size of 6 subjects per population (6 20mg IV ESRD on HD and 6 20mg IV historical normal renal function, at the same dose level) and observed between-subject SDs as given above, then the half width of the 90% CIs of GMRs for MK-2060 AUC0-168hr and Cmax on the log scale will be 0.329 and 0.279, respectively. The lower and upper 90% confidence limits for the true GMRs will be given by OBS/1.39 and OBS*1.39 for AUC0-168hr and OBS/1.32 and OBS*1.32 for Cmax, respectively, where OBS is the observed GMR. Thus, for example, if the observed GMR for AUC0-168hr was 1.50 after administration of 20mg IV MK-2060, then the 90% CI for the GMR would be 1.08 to 2.08.

Pharmacodynamics

Part 1:

If the true CV is 30%, there is approximately 72.3% probability of yielding at least 60% posterior probability that the true fold increase is at least 1.5 if the true fold increase in aPTT after 168 hours of a single well-tolerated subcutaneous dose relative to placebo is at least 1.5. The total participants per dose is 8 (active = 6, placebo = 2).

Part 2:

If the true CV is 30%, for a total of approximately 20 participants (active = 15, placebo = 5), there is approximately 84% probability of yielding at least 60% posterior probability that the true fold increase is at least 1.5. We assume that the true fold increase in aPTT after 168 hours of a single well-tolerated subcutaneous dose relative to placebo is at least 1.5.

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 and Dohme Corp., a subsidiary of Merck & Co., Inc. (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 of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (eg, International Council for Harmonisation Good Clinical Practice [ICH-GCP]) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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 to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of 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 fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues

are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the prespecified 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. Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All clinical trials will be reviewed and approved by an IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the ethics committee prior to implementation, except changes required urgently to protect participant safety that may be enacted in anticipation of ethics committee approval. For each site, the ethics committee and MSD will approve the participant informed consent form.

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. Unless required by law, only the investigator, Sponsor (or representative), 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 to identify potentially eligible participants.

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

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 International Committee of Medical Journal Editors authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

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

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 will promptly notify that study site's IRB/IEC.

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	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase	
Other Screening Tests	Follicle-stimulating hormone (as needed in women of nonchildbearing potential only) Drug screen (to include at minimum: alcohol amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) Serum β human chorionic gonadotropin (β hCG) pregnancy test (as needed for female participant) [Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)			

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, 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, or are considered clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.5.1 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:

1. **Results in death**
2. **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.
3. **Requires inpatient hospitalization or prolongation of existing hospitalization**
    - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.
4. **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.

5. Is a congenital anomaly/birth defect

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

6. 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 case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a 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 electronic data collection (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 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

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

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

Not applicable

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

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

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

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

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.

Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Pregnancy Testing

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

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

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 drugs/vaccines may interact with
- 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.

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

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participant' 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 gender, 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

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

6. Withdrawal From Future Biomedical Research

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

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

7. Retention of Specimens

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

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

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

8. Data Security

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

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

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

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@merck.com.

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10.7 Appendix 7: Country-specific Requirements

Not applicable

10.8 Appendix 8: Approximate Blood Volume

Part 1:

Part 1 Panels	Pre-study	Treatment Periods	Post-trial	Total Collection	mL Per Collection	Total mL/Test
Laboratory safety tests	2	9	1	12	12.5	150
HIV/Hepatitis screen (per site SOP)	1			1	5	5
Blood for planned genetic analysis		1		1	8.5	8.5
Blood for PT and aPTT at local lab	1	9		10	3	30
Blood for MK-2060 only		11	0	11	1.8	19.8
Blood for plasma ADA and MK-2060		7	1	8	2.7	21.6
Blood for PT, aPTT, FXI activity, hsCRP at central lab, as well as FGA		18	1	19	10	190
					Total Blood Volume Per Subject[†]	424.9 mL

[†] If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained

Part 2:

	Pre-study	Treatment Periods	Post-trial	Total Collection	mL Per Collection	Total mL/Test
Laboratory safety tests	2	12	1	15	12.5	187.5
HIV/Hepatitis screen (per site SOP)	1			1	5	5
Blood for planned genetic analysis		1		1	8.5	8.5
Blood for PT and aPTT at local lab	1	23	1	25	3	75
Blood for MK-2060 only		26	1	27	1.8	46.8
Blood for plasma ADA and MK-2060		6	1	7	2.7	18.9
Blood for PT, aPTT, FXI activity, hsCRP at central lab, as well as FGA		19	1	20	11	220
					Total Blood Volume Per Subject†	563.5 mL

†If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained

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

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

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

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

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

1. The participant may be excluded from the study;

2. The participant may be included in the study if the abnormal value(s) is not clinically significant (NCS) (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document).

3. 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

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

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

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(s)	Adverse event(s)
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC0-∞	Area under the concentration-time curve extrapolated to infinity
AUC0-168	Area under the concentration-time curve from 0 to 168 hours post-dose
AUC0-last	Area under the concentration-time curve to the last measurable concentration
AV	Arteriovenous
ASO	Anti-sense oligo
BMI	Body mass index
BP	Blood pressure
C	Plasma concentration
CL	Clearance
CFR	Code of Federal Regulations
CL/F	Apparent total clearance
Cmax	Maximum observed plasma concentration
CRU	Clinical research unit
CSR	Clinical study report
CTA	Clinical Trial Application
CV	Coefficient of variation
DEM	Dose escalation meetings
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
ER	Emergency room
ERC	Ethics review committee
ESRD	End-Stage Renal Disease
FBR	Future biomedical research
FXa	Factor Xa
FXI	Factor XI
FXIa	Factor XIa
FDAAA	Food and Drug Administration Amendments Act
FSH	Follicle stimulating hormone
FGA	Fibrin generation assay
GCP	Good Clinical Practice(s)
GCV	Geometric coefficient of variation
GM	Geometric mean
HR	Heart rate
HD	Hemodialysis
HRT	hormone replacement therapy
hsCRP	High-sentivity C-reactive protein
IB	Investigator's Brochure
IgG	Immunoglobulin
IV	Intravenous

Abbreviation	Expanded Term
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	intrauterine device
mAb	Monoclonal antibody
NHV	Normal healthy volunteer
NOAEL	no observed adverse effect level
PK	pharmacokinetic
PD	Pharmacodynamics
PI	Principal Investigator
PP	Per-protocol Population
PR	PR interval
PT	Prothrombin time
QTc	Q-T corrected (corrected Q-T interval)
RhoGAM	A brand of Rh immunoglobulin
QP2	department of quantitative pharmacology and pharmacometrics
RNA	ribonucleic acid
SAE(s)	Serious adverse event(s)
SBP	Systolic blood pressure
SC	Subcutaneous (ly)
SOP	Standard operating procedures
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
t1/2	Half-life
TGA	Thrombin generation assay
Tmax	Time to maximum observed plasma concentration
ULN	Upper limit of normal
USP	United States Pharmacopeial Convention
VS	Vital Signs
Vz/F	Apparent volume of distribution
WOCBP	woman/women of childbearing potential

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