Official Protocol Title:	An Open-Label, Single-Dose Clinical Study to Evaluate the Pharmacokinetics of MK-0616 in Participants with Varying Degrees of Renal Impairment
NCT number:	NCT05934292
Document Date:	10-AUG-2023

TITLE PAGE

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Protocol Title:

An Open-Label, Single-Dose Clinical Study to Evaluate the Pharmacokinetics of MK-0616 in Participants with Varying Degrees of Renal Impairment

Protocol Number: 020-01

Compound Number: MK-0616

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

Legal Registered Address:

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

Regulatory Agency Identifying Number(s):

NCT	To be determined
EU CT	Not applicable
EudraCT	Not applicable
JRCT	Not applicable
WHO	Not applicable
UTN	Not applicable
IND	152853

Approval Date: 10 August 2023

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 01	10-AUG-2023	The original protocol was amended to change the collection of dialysate samples from spot collections to interval collections, in an effort to align with standard practice.
Original Protocol	17-MAY-2023	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 01

Overall Rationale for the Amendment:

This protocol was amended to change spot collections for dialysate samples to interval collections.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 1.3, Schedule of Activities for Panel C	Updated original footnote 'j', now footnote 'h', to reflect that the Dialysate Samples for MK-0616 and/or Metabolites Assay are to be collected at the end of every 30-minute interval from the start of hemodialysis until immediately before completion of hemodialysis.	This change was made to address investigator/site feedback: It is understood that the collection of dialysate samples is typically an interval collection, rather than a spot collection, therefore, this update was made to comply with standard practice.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 1.3, Schedule of Activities for Panels A, B, and D	All references to BDS/UDS were changed to Drug Screen	To allow flexibility for sites to conduct a drug screen that is in alignment with their standard practice, given the participant population
Section 1.3, Schedule of Activities for Panels A, B, and D	Modified original footnote 'g', now footnote 'e'	To emphasize that the Day 1 Predose Scheduled Time is the only timepoint when triplicate semirecumbent VS (HR, BP) and 12-lead ECGs are taken
Section 1.3, Schedule of Activities for Panel C	Removed reference to '~15' under Post-study	Correction of a typo

Section Number and Name	Description of Change	Brief Rationale
Section 1.3, Schedule of Activities for Panel C	Removed Screening Visit 2	This visit is no longer necessary, given the removal of the need to calculate baseline eGFR values for participants in Panel C
Section 1.3, Schedule of Activities for Panel C	Removed original footnotes 'b' and 'c'; Footnotes 'd' through 'k' are now 'b' through 'i'	These footnotes are no longer necessary, given the removal of the need to calculate baseline eGFR values for participants in Panel C
Section 1.3, Schedule of Activities for Panel C	Removed '(ie, ~8 am in both periods)' from notes for Study Intervention Administration	To allow flexibility for sites regarding timing of study drug administration
Section 1.3, Schedule of Activities for Panel C	Updates were made to the notes for both 'On-site HD' entries (ie, Period 1 only and Period 2 only)	To reflect the fact that the length and timing of hemodialysis sessions varies from participant to participant and from session to session but needs to last a minimum of 3 hours
Section 1.3, Schedule of Activities for Panel C	All references to BDS/UDS were changed to Drug Screen	To allow flexibility for sites to conduct a drug screen that is in alignment with standard practice, given the participant population
Section 1.3, Schedule of Activities for Panel C	Specified in the Notes for Urinalysis that the urine sample is only to be collected if the participant can produce urine	To reflect that some participants with ESRD on HD are unable to produce urine and under those circumstances, would not be expected to produce urine for a urinalysis
Section 1.3, Schedule of Activities for Panel C	Removed 'Plasma' from 'Dialysate Samples for Plasma MK-0616 and/or Metabolites Assay – Period 2 Only'	Correction of a typo where 'Plasma' was included in error
Section 1.3, Schedule of Activities for Panel C	Modified original footnote 'g', now footnote 'e'	To emphasize that the Day 1 Predose Scheduled Time is the only timepoint when triplicate semirecumbent VS (HR, BP) and 12-lead ECGs are taken
Section 1.3, Schedule of Activities for Panel C	Modified original footnote 'k', now footnote 'i'	To reflect that some participants with ESRD on HD are unable to produce urine and under those circumstances, would not be expected to produce interval urine samples for PK analysis.
Section 4.1, Overall Design	Replaced '< 15 requiring HD' with 'Not applicable' in Table 1 Renal Function Group for participants in Panel C	To reflect that the calculated eGFR value is not relevant in participants with ESRD on HD, due to the fluctuation in the creatinine values between hemodialysis sessions
Section 4.1, Overall Design	Removed all reference to the timing of hemodialysis sessions	To allow flexibility in the timing of hemodialysis sessions to reflect the fact that the length and timing of hemodialysis sessions varies from participant to participant and from session to session
Section 4.1, Overall Design	Modified wording regarding dialysate sample collection, emphasizing collection at the end of every 30-minute interval from the start of hemodialysis until immediately before hemodialysis completion	To comply with standard practice regarding collection of dialysate sample for PK analysis

Section Number and Name	Description of Change	Brief Rationale
Section 5.1, Inclusion Criteria	Inclusion criterion 1 - Removed the need for the investigator to consult with the Sponsor regarding inclusion of participants with RI that have stable, chronic medical or psychiatric conditions	To allow the investigators to determine eligibility
Section 5.1, Inclusion Criteria	Inclusion criterion 5 – Removed criterion for participants with ESRD on HD (Panel C) by making it 'not applicable'	The calculated eGFR value is not relevant for participants with ESRD on HD due to the fluctuation in the creatinine values between hemodialysis sessions
Section 5.2, Exclusion Criteria	Exclusion criterion 2 – Modified exclusion of all participants with a history of renal transplant to only exclude participants with a functioning renal transplant in the past 5 years, taking transplant medication	To allow for enrollment of participants that have had a failed renal transplant
Section 5.2, Exclusion Criteria	Exclusion criterion 3 – Modified this criterion so that it only applies to participants in Panels A, B, and D	To reflect that this criterion should not apply to participants in Panel C, due to the fluctuation in the creatinine values between hemodialysis sessions
Section 5.2, Exclusion Criteria	Exclusion criterion 8 – Added '2021' before CKD-EPIcr_R and added the word 'equation' after CKD-EPIcr_R	Correction of typos where '2021' and 'equation' were previously omitted
Section 5.2, Exclusion Criteria	Exclusion criterion 21 – replaced all references to UDS with drug screen	To allow flexibility for sites to conduct a drug screen that is in alignment with their standard practice, given the participant population
Section 5.3.1.1, Diet Restrictions	Corrected '24-hr postdose' to '4-hr postdose'	Correction of a typo
Section 5.3.2.1, Caffeine Restrictions	Corrected 'Screening 2 Visit' to 'Screening Visit 2'	Correction of typos
Section 5.3.2.2, Alcohol Restrictions	Corrected 'participations' to 'participants' Corrected 'Screening 2 Visit' to 'Screening Visit 2'	Correction of typos
Section 6.5, Concomitant Therapy	Removed the requirement to consult with the Sponsor regarding participants who are taking certain prescription medications to treat manifestations of renal disease or medications needed to treat stable diseases.	The list of example medications noted in that sentence are later noted as being allowed, therefore, there is no need to consult with the Sponsor.
Section 8.1.1, Informed Consent	Moved around wording between Section 8.1.1 and 8.1.1.1	To provide further clarity
Section 8.1.1.1, General Informed Consent	Moved around wording between Section 8.1.1.1 and 8.1.1	To provide further clarity
Section 8.1.6, Assignment of Screening Number	Updated 'individual' to 'participant' Deleted 'initial' prior to 'Screening Visit'	Minor editorial changes
Section 8.1.8.1, Timing of Dose Administration	Removed all reference to the timing of hemodialysis sessions	To allow flexibility in the timing of hemodialysis sessions to reflect the fact that the length and timing of hemodialysis sessions varies from participant to participant and from session to session

Section Number and Name	Description of Change	Brief Rationale
Section 8.3.2.1, Resting Vital Signs	Specified that Screening VS measurements will be single measurements	To emphasize that the Day 1 Predose Scheduled Time is the only timepoint when triplicate semirecumbent VS (HR, BP) and 12-lead ECGs are taken
Section 8.3.3, Electrocardiograms	Removal of word 'telemetry'	Because only 12-lead ECGs are standardly taken for safety
Section 8.3.6, Photograph of Rash	Reference made to the Investigator Site Binder for additional rash guidance.	To provide the site(s) additional resources on how to manage participant rash
Section 8.6.2, Dialysate Samples for MK-0616 and/or Metabolites	Removed 'Plasma' from Section Name	Correction of a typo where 'Plasma' was included in error
Section 8.11.3, Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study	Replaced 'a PCL' with 'an official memo'	Provide more flexibility in document(s) to be used to describe subset of study procedures to be completed for participants who discontinue treatment but continue to be monitored in the study
Section 10.2, Appendix 2: Clinical Laboratory Tests	Replaced reference to serum or urine drug screen with just drug screen	To allow flexibility for sites to conduct a drug screen that is in alignment with their standard practice, given the participant population
Section 10.8, Appendix 8: Approximate Blood Volume Tables	Table for Panel C: Removed row for 'Chemistry test for Second Creatinine Value…' and re-calculated total blood volumes	This blood draw is no longer necessary, given the removal of the need to calculate baseline eGFR values for participants in Panel C
Section 10.11, Appendix 11: Abbreviations	Removed 'BDS' and 'UDS'	These abbreviations are no longer used in the document

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: An Open-Label, Single-Dose Clinical Study to Evaluate the Pharmacokinetics of MK-0616 in Participants with Varying Degrees of Renal Impairment

Short Title: MK-0616 Renal Impairment Study 2

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

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

The following objectives will be evaluated in male and female participants, 18 to 85 years of age (inclusive), with moderate RI, severe RI, ESRD on HD, and healthy adults.

Primary Objective	**Primary Endpoint**
To compare the plasma PK of MK-0616 following a single 20 mg dose in participants on a background of statin therapy with varying degrees of renal impairment (moderate, severe, ESRD) to those of healthy mean matched control participants on a background of statin therapy. Estimation: MK-0616 AUC0-inf following a single dose of MK-0616 administered to participants with varying degrees of renal impairment (moderate, severe, ESRD) will be estimated and compared to MK-0616 AUC0-inf when administered to healthy mean matched control participants.	Plasma MK-0616 AUC0-inf, AUClast, Cmax, Tmax, t1/2, CL/F, and Vz/F
Secondary Objectives	**Secondary Endpoints**
To investigate the extent MK-0616 is removed by hemodialysis. Estimation: The extent to which MK-0616 is removed from the plasma by hemodialysis [eg, CL_D, C_D, AE_D, AE_D (%dose)] will be estimated.	CL_D, C_D, Ae_D, Ae_D (%dose)

To compare the urine PK of MK-0616 following a single dose of MK-0616 to participants with varying degrees of renal impairment, where possible, to those of healthy matched control participants. Estimation: MK-0616 Ae0-24, Fe, and CLr following a single dose of MK-0616 administered to participants with varying degrees of renal impairment, as appropriate, will be estimated and compared to those estimated in healthy mean matched control participants.	Urine MK-0616 Ae0-24, Fe, and CLr
To evaluate the safety and tolerability of the administration of a single dose of MK-0616 in participants with varying degrees of renal impairment.	Adverse Events, Discontinuations due to Adverse Events

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Hypercholesterolaemia
Population	Participants with varying degrees of renal impairment and Healthy Participants
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	Active Control Without Placebo
Study Blinding	Unblinded open-label
Blinding Roles	No blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 1 year from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Up to 36 participants will be allocated as described in Section 9.4.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Moderate RI Group	MK-0616	20 mg	20 mg	Oral	Panel A: Single dose on Day 1	Test Product
Severe RI Group	MK-0616	20 mg	20 mg	Oral	Panel B: Single dose on Day 1	Test Product
ESRD on HD Group	MK-0616	20 mg	20 mg	Oral	Panel C: Single Dose on Day 1 of Periods 1 and 2	Test Product
Healthy Control Group	MK-0616	20 mg	20 mg	Oral	Panel D: Single Dose on Day 1	Test Product

Total Number of Intervention Groups/Arms	4
Duration of Participation	Each participant with moderate renal impairment, severe renal impairment, and each healthy participant will participate in the study for approximately 6 weeks from the time the participant provides documented informed consent through the final contact. Each participant with end-stage renal disease on hemodialysis will participate in the study for approximately 8 weeks from the time the participant provides documented informed consent through the final contact.

Study Governance Committees:

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

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

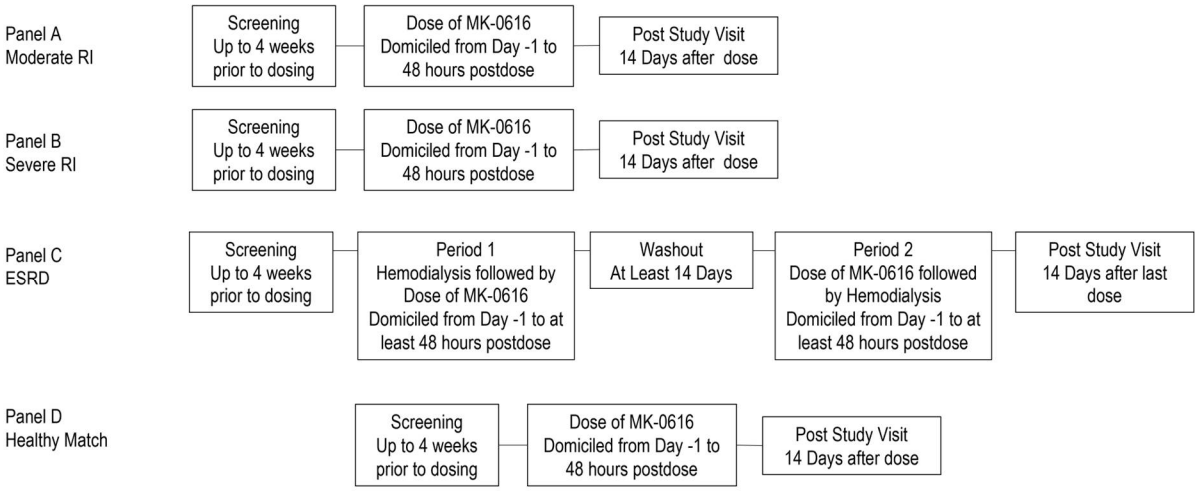
Study Accepts Healthy Participants: Yes

A list of abbreviations is in Appendix 11.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



ESRD=end-stage renal disease; RI=renal impairment

1.3 Schedule of Activities

Schedule of Activities for Panels A, B, and D

Panels A, B, and D																					
Study Period:	**Screening**			**Intervention (Period 1)**																**Post-study[a]**	**Notes**
Scheduled Day	**Up to -28**		**-1**	**1**									**2**		**3**	**4**	**6**	**8**	**11**	**~15**	
Scheduled Hour	**Screening Visit 1**	**Screening Visit 2[b]**	**Check-In**	**Pre-dose**	**0**	**0.5**	**1**	**1.5**	**2**	**4**	**8**	**12**	**24**	**36**	**48**	**72**	**120**	**168**	**240**	**Post-study**	
Administrative/Study Procedures																					
Informed Consent	X																				Sec. 5.1, 8.1.1.1
Informed Consent for FBR	X																				Sec. 5.1, 8.1.1.2
Inclusion/ Exclusion Criteria	X[c]	X[c]	X[c]																		Review to occur at Screening and after predose procedures. Sec. 5.1, 5.2, 8.1.2
Participant ID Card	X																				Sec. 8.1.3
Medical History	X			X																	Includes history of illicit drug, alcohol, tobacco, and caffeine use. Sec. 8.1.4
Prior/ Concomitant Medication Review	X----------X																				Sec. 5.2, 6.5, 8.1.5

Panels A, B, and D																					
Study Period:	**Screening**			**Intervention (Period 1)**																**Post-study[a]**	**Notes**
Scheduled Day	**Up to -28**		**-1**	**1**									**2**		**3**	**4**	**6**	**8**	**11**	**~15**	
Scheduled Hour	**Screening Visit 1**	**Screening Visit 2[b]**	**Check-In**	**Pre-dose**	**0**	**0.5**	**1**	**1.5**	**2**	**4**	**8**	**12**	**24**	**36**	**48**	**72**	**120**	**168**	**240**	**Post-study**	
Assignment of Screening Number	X																				Sec. 8.1.6
Assignment of Treatment/ Allocation Number			X																		Within 24 hours prior to study intervention administration. Sec. 5.5, 8.1.7
Study Intervention Administration					X																Sec. 8.1.8
Participant Visit to CRU	X	X[c]	X													X	X	X	X	X	
Domiciling[d]			X----------X																		Sec. 8.1.11
Standard Meals[e]						X----------X															Sec. 5.3.1
Safety Procedures																					
Full physical examination	X		X[f]										X							X	Sec. 8.3.1
Height	X																				Sec. 8.3.1
Weight	X																			X	BMI and BSA to be assessed only at Screening. Sec. 8.3.1
Semirecumbent VS (HR, BP)	X			X[g]					X				X							X	Sec. 8.3.2, Sec. 8.3.2.1
VS (RR, BT)	X			X[g]					X				X							X	Sec. 8.3.2, Sec. 8.3.2.1
Orthostatic VS (HR, BP)	X			X[g]					X				X								Sec. 8.3.2.2

Panels A, B, and D																					
Study Period:	**Screening**			**Intervention (Period 1)**																**Post-study[a]**	**Notes**
Scheduled Day	**Up to -28**		**-1**	**1**									**2**		**3**	**4**	**6**	**8**	**11**	**~15**	
Scheduled Hour	**Screening Visit 1**	**Screening Visit 2[b]**	**Check-In**	**Pre-dose**	**0**	**0.5**	**1**	**1.5**	**2**	**4**	**8**	**12**	**24**	**36**	**48**	**72**	**120**	**168**	**240**	**Post-study**	
12-lead ECG	X			X[g]					X				X							X	Sec. 8.3.3
Serum or Urine hCG – POCBP only	X		X[f]																	X	Result to be reviewed prior to dosing on Day 1. Sec. 5.1, Sec. 8.3.5, Appendix 2
Serum FSH – postmenopausal PONCBP only	X																				Appendix 2
HIV, hepatitis B and C screen (per site SOP)	X																				Sec. 8.3.4, Appendix 2
Drug Screen (per site SOP)	X		X[f]																		Sec. 8.3.4, Appendix 2
Hematology/ Chemistry	X	X[c]	X[c,f]										X							X	Fast for at least 8 hours prior to sample collection. Sec. 8.3.4, Appendix 2
Urinalysis	X		X[f]										X							X	Sec. 8.3.4
AE/SAE review	X----------X																				Sec. 8.4
Pharmacokinetics																					
Blood for Plasma MK-0616 and/or Metabolites Assay				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[h]	Sec. 8.6.1

Panels A, B, and D																					
Study Period:	**Screening**			**Intervention (Period 1)**																**Post-study[a]**	**Notes**
Scheduled Day	**Up to -28**		**-1**	**1**									**2**		**3**	**4**	**6**	**8**	**11**	**~15**	
Scheduled Hour	**Screening Visit 1**	**Screening Visit 2[b]**	**Check-In**	**Pre-dose**	**0**	**0.5**	**1**	**1.5**	**2**	**4**	**8**	**12**	**24**	**36**	**48**	**72**	**120**	**168**	**240**	**Post-study**	
Urine for Urinary MK-0616 and/or Metabolites Assay[i]				X	X----------X----X---X---X--------X																Sec. 8.6.3
Pharmacodynamics																					
Blood for Plasma for PCSK9 (free) Assay				X									X		X	X				X[h]	Sec. 8.7
Biomarkers																					
Blood for Genetic Analysis				X																	Collect predose on Day 1, but may be collected at the next scheduled blood draw, if needed from enrolled participants only. Sec. 8.8.

AE=adverse event; BMI=body mass index; BP=blood pressure; BSA=body surface area; BT=body temperature; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; CRU=clinical research unit; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; FBR=future biomedical research; FSH=follicle-stimulating hormone; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; HR=heart rate; ID=identification; PCSK9=proprotein convertase subtilisin/kexin type 9; POCBP=participant of childbearing potential; PONCBP=participant of non-childbearing potential; RR=respiratory rate; SAE=serious adverse event; SOP=standard operating procedure; VS=vital signs.

[a] Poststudy Visit should occur approximately 14 days postdose. If the visit occurs prior to 14 days postdose, verbal contact should be made to assess for AEs 14 days postdose.

[b] Screening Visit 2 is optional. If Screening Visit 2 is conducted, it must occur at least 72 hours after Screening Visit 1.

[c] Baseline eGFR will be obtained twice (at least 72 hours apart as part of participant screening) based on the 2021 CKD-EPI Creatinine (CKD-EPIcr_R) equation. This second baseline eGFR may be obtained at the optional Screening Visit 2 or on Day -1 within 24 hours of dosing (Predose Day 1 chemistry labs) but data must be available before dosing on Day 1 to ensure eligibility.

[d] Participants will report to the CRU on Day -1, at the time indicated by the CRU (~24 hours prior to dosing on Day 1). Participants will be discharged after completion of the 48-hour postdose procedures on Day 3.

[e] A standard meal will be provided as follows relative to study intervention administration: breakfast at least 30 minutes postdose, lunch at approximately 4 hours postdose. After the 4-hour postdose standard meal is completed, subsequent meals and snacks will be unrestricted in terms of caloric content, composition, and timing.

[f] Predose full physical examination, Drug Screen, serum or urine hCG for POCBP only, hematology/chemistry, and urinalysis may be conducted/collected upon admission to the CRU on Day -1 but within 24 hours of study drug administration. Results must be back prior to study intervention administration to confirm eligibility.

[g] Predose VS and 12-lead ECG to be measured within 3 hours prior to study intervention administration. Semirecumbent predose VS (HR and BP) and ECG measurements will be done in triplicate. All other scheduled timepoints and measurements, including Screening VS and Screening 12-lead ECG, and Predose RR and BT, will be single measurements.

[h] The sample drawn at the Poststudy Visit corresponds to the Day 1 336 hour postdose sample.

[i] Urine samples will be collected at predose (baseline) and at the following intervals postdose: 0 to 4 hours, 4 to 8 hours, 8 to 12 hours, 12 to 24 hours, and 24 to 48 hours.

Schedule of Activities for Panel C

All Participants in Panel C																					
Study Period:	**Screening**		**Intervention (Periods 1 and 2)**																	**Post-study[a]**	**Notes**
Scheduled Day	**Up to -28**	**-1**	**1**										**2**		**3**	**4**	**6**	**8**	**11**		
Scheduled Hour	**Screening Visit 1**	**Check-In**	**Pre-dose**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**8**	**12**	**24**	**36**	**48**	**72**	**120**	**168**	**240**	**Post-study**	
Administrative/Study Procedures																					
Informed Consent	X																				Sec. 5.1, 8.1.1.1
Informed Consent for FBR	X																				Sec. 5.1, 8.1.1.2
Inclusion/Exclusion Criteria	X	X																			Review to occur at Screening and after predose procedures in both periods. Sec. 5.1, 5.2, 8.1.2
Participant ID Card	X																				Sec. 8.1.3
Medical History	X		X																		Includes history of illicit drug, alcohol, tobacco, and caffeine use. Sec. 8.1.4
Prior/Concomitant Medication Review	X----------																			----------X	Sec. 5.2, 6.5, 8.1.5
Assignment of Screening Number	X																				Sec. 8.1.6
Assignment of Treatment/ Allocation Number		X																			To be assigned within 24 hours prior to study intervention administration in Period 1 only. Sec. 5.5, 8.1.7

All Participants in Panel C																					
Study Period:	**Screening**		**Intervention (Periods 1 and 2)**																	**Post-study[a]**	**Notes**
Scheduled Day	**Up to -28**	**-1**	**1**										**2**		**3**	**4**	**6**	**8**	**11**		
Scheduled Hour	**Screening Visit 1**	**Check-In**	**Pre-dose**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**8**	**12**	**24**	**36**	**48**	**72**	**120**	**168**	**240**	**Post-study**	
Study Intervention Administration				X																	After at least an 8-hour overnight fast; to be dosed immediately following HD session in Period 1 and ~ 0.5 hours prior to HD in Period 2. Sec. 8.1.8
Participant Visit to CRU	X	X														X	X	X	X	X	
Domiciling[b]		X----------X																			Sec. 8.1.11
Standard Meals[c]					X----------X																Starting at least 30 minutes after study intervention administration. Sec. 5.3.1
On-Site HD – Period 1 Only			X-----X													X	X				HD to last a minimum of 3 hours on Days 1, 4, and 6. Day 1 to occur on either a Friday or Saturday. Sec. 4.1

All Participants in Panel C																					
Study Period:	**Screening**		**Intervention (Periods 1 and 2)**																	**Post-study[a]**	**Notes**
Scheduled Day	**Up to -28**	**-1**	**1**										**2**		**3**	**4**	**6**	**8**	**11**		
Scheduled Hour	**Screening Visit 1**	**Check-In**	**Pre-dose**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**8**	**12**	**24**	**36**	**48**	**72**	**120**	**168**	**240**	**Post-study**	
On-Site HD – Period 2 Only					X----------X											X	X				HD starting ~ 0.5 hours postdose on Day 1. HD to last a minimum of 3 hours on Days 1, 4, and 6. Day 1 to occur on either a Friday or Saturday. Sec. 4.1
Safety Procedures																					
Full physical examination	X	X[d]											X							X	Sec. 8.3.1
Height	X																				Sec. 8.3.1
Weight	X																			X	BMI to be assessed only at Screening. Sec. 8.3.1
Semirecumbent VS (HR, BP)	X		X[e]					X					X							X	Sec. 8.3.2, Sec. 8.3.2.1
VS (RR, BT)	X		X[e]					X					X							X	Sec. 8.3.2, Sec. 8.3.2.1
Orthostatic VS (HR, BP)	X		X[e]					X					X								Sec. 8.3.2.2
12-lead ECG	X		X[e]					X					X							X	Sec. 8.3.3
Serum or Urine hCG – POCBP only	X	X[d]																		X	Result to be reviewed prior to dosing on Day 1, both periods. Sec. 5.1, Sec. 8.3.5, Appendix 2

All Participants in Panel C																					
Study Period:	**Screening**		**Intervention (Periods 1 and 2)**																	**Post-study[a]**	**Notes**
Scheduled Day	**Up to -28**	**-1**	**1**										**2**		**3**	**4**	**6**	**8**	**11**		
Scheduled Hour	**Screening Visit 1**	**Check-In**	**Pre-dose**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**8**	**12**	**24**	**36**	**48**	**72**	**120**	**168**	**240**	**Post-study**	
Serum FSH – postmenopausal PONCBP only	X																				Appendix 2
HIV, hepatitis B and C screen (per site SOP)	X																				Sec. 8.3.4, Appendix 2
Drug Screen (per site SOP)	X	X[d]																			Sec. 8.3.4, Appendix 2
Hematology/ Chemistry	X	X[d]											X							X	Fast for at least 8 hours prior to sample collection. Sec. 8.3.4, Appendix 2
Urinalysis	X	X[d]											X							X	Only if participant is able to produce urine. Sec. 8.3.4
AE/SAE review	X----------X																				Sec. 8.4
Pharmacokinetics																					
Blood for Plasma MK-0616 and/or Metabolites Assay[f]			X		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X[g]	Sec. 8.6.1
Dialysate Samples for MK-0616 and/or Metabolites Assay – Period 2 Only[h]			X----------X[h]																		Sec. 4.1, Sec. 8.6.2
Urine for Urinary MK-0616 and/or Metabolites Assay[i]			X	X----------X--X---X---X--------X																	Sec. 8.6.3

All Participants in Panel C																				
Study Period:	**Screening**		**Intervention (Periods 1 and 2)**																**Post-study[a]**	**Notes**
Scheduled Day	**Up to -28**	**-1**	**1**										**2**		**3**	**4**	**6**	**8**	**11**	
Scheduled Hour	**Screening Visit 1**	**Check-In**	**Pre-dose**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**8**	**12**	**24**	**36**	**48**	**72**	**120**	**168**	**240**	**Post-study**	
Pharmacodynamics																					
Blood for Plasma for PCSK9 (free) Assay			X										X		X	X				X[i]	Sec. 8.7
Biomarkers																					
Blood for Genetic Analysis			X																		Collect predose on Day 1 of Period 1 only, but may be collected at the next scheduled blood draw, if needed from enrolled participants only. Sec. 8.8.

All Participants in Panel C																					
Study Period:	**Screening**		**Intervention (Periods 1 and 2)**																	**Post-study[a]**	**Notes**
Scheduled Day	**Up to -28**	**-1**	**1**										**2**		**3**	**4**	**6**	**8**	**11**		
Scheduled Hour	**Screening Visit 1**	**Check-In**	**Pre-dose**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**8**	**12**	**24**	**36**	**48**	**72**	**120**	**168**	**240**	**Post-study**	

AE=adverse event; BMI=body mass index; BP=blood pressure; BSA=body surface area; BT=body temperature; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; CRU=clinical research unit; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; FBR=future biomedical research; FSH=follicle-stimulating hormone; hCG=human chorionic gonadotropin; HD=hemodialysis; HIV=human immunodeficiency virus; HR=heart rate; ID=identification; PCSK9=proprotein convertase subtilisin/kexin type 9; PK=pharmacokinetic; POCBP=participant of childbearing potential; PONCBP=participant of non-childbearing potential; RR=respiratory rate; SAE=serious adverse event; SOP=standard operating procedure; VS=vital signs.

[a] Poststudy Visit should occur approximately 14 days postdose. If the visit occurs prior to 14 days postdose, verbal contact should be made to assess for AEs 14 days postdose.

[b] Participants will report to the CRU on Day -1, at the time indicated by the CRU (~24 hours prior to dosing on Day 1). Participants will be discharged after completion of the 48-hour postdose procedures on Day 3.

[c] A standard meal will be provided as follows relative to study intervention administration: breakfast at least 30 minutes postdose, lunch at approximately 4 hours postdose. After the 4-hour postdose standard meal is completed, subsequent meals and snacks will be unrestricted in terms of caloric content, composition, and timing.

[d] Predose full physical examination, Drug Screen, serum or urine hCG (POCBP only), hematology/chemistry, and urinalysis may be conducted/collected upon admission to the CRU on Day -1 but within 24 hours of study drug administration. Results must be back prior to study intervention administration to confirm eligibility.

[e] Predose VS and 12-lead ECG to be measured within 3 hours prior to study intervention administration. Semirecumbent predose VS (HR and BP) and ECG measurements will be done in triplicate. All other scheduled timepoints and measurements, including Screening VS and Screening 12-lead ECG, and Predose RR and BT, will be single measurements.

[f] In addition to the PK sampling timepoints noted, one Pre-HD PK sample and one Post-HD PK sample must be drawn in Period 1 on Study Days 4 and 6 and one Pre-HD PK sample and one Post-HD PK sample must be drawn in Period 2 on Study Days 1, 4, and 6.

[g] The sample drawn at the Poststudy Visit corresponds to the Period 2 Day 1 336 hour postdose sample.

[h] The duration of the HD session will vary from participant to participant, based on individual needs, but should last at minimum 3 hours. A Pre-HD dialysate sample is to be collected at the start of HD. During the HD session, dialysate samples to be collected at the end of every 30-minute interval as follows: 0 to 0.5 hours, 0.5 to 1 hour, 1 to 1.5 hours, 1.5 to 2 hours, 2 to 2.5 hours, 2.5 to 3 hours, 3 to 3.5 hours, 3.5 to 4 hours, 4 to 4.5 hours, etc…from the start of HD until immediately before HD completion.

[i] Urine samples will be collected at predose (baseline) and at the following intervals postdose: 0 to 4 hours, 4 to 8 hours, 8 to 12 hours, 12 to 24 hours, and 24 to 48 hours, only if the participant can produce urine.

2 INTRODUCTION

2.1 Study Rationale

MK-0616 is a small molecule cyclic peptide inhibitor of PCSK9 being developed for the treatment of hypercholesterolemia. MK-0616 is a low clearance drug which is excreted as unchanged parent peptide in rat and cynomolgus monkeys predominately by renal clearance. As such, this study is being conducted to assess the impact of moderate renal impairment, severe renal impairment, and end-stage renal disease on the PK of MK-0616.

2.2 Background

Refer to the IB for detailed background information on MK-0616.

2.2.1 Pharmaceutical and Therapeutic Background

MK-0616 is a cyclic peptide inhibitor of PCSK9 being developed for reduction of LDL-C.

2.2.2 Information on Other Study-related Therapy

There is no other study-related therapy in this protocol.

2.3 Benefit/Risk Assessment

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

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

The following objectives will be evaluated in male and female participants, 18 to 85 years of age (inclusive), with moderate RI, severe RI, ESRD on HD, and healthy adults.

Primary Objective	**Primary Endpoint**
To compare the plasma PK of MK-0616 following a single 20 mg dose in participants on a background of statin therapy with varying degrees of renal impairment (moderate, severe, ESRD) to those of healthy mean matched control participants on a background of statin therapy. Estimation: MK-0616 AUC0-inf following a single dose of MK-0616 administered to participants with varying degrees of renal impairment (moderate, severe, ESRD) will be estimated and compared to MK-0616 AUC0-inf when administered to healthy mean matched control participants.	Plasma MK-0616 AUC0-inf, AUClast, Cmax, Tmax, t1/2, CL/F, and Vz/F
Secondary Objectives	**Secondary Endpoints**
To investigate the extent MK-0616 is removed by hemodialysis. Estimation: The extent to which MK-0616 is removed from the plasma by hemodialysis [eg, CL_D, C_D, AE_D, AE_D (%dose)] will be estimated.	CL_D, C_D, Ae_D, Ae_D (%dose)
To compare the urine PK of MK-0616 following a single dose of MK-0616 to participants with varying degrees of renal impairment, where possible, to those of healthy matched control participants. Estimation: MK-0616 Ae0-24, Fe, and CLr following a single dose of MK-0616 administered to participants with varying degrees of renal impairment, as appropriate, will be estimated and compared to those estimated in healthy mean matched control participants.	Urine MK-0616 Ae0-24, Fe, and CLr

To evaluate the safety and tolerability of the administration of a single dose of MK-0616 in participants with varying degrees of renal impairment.	Adverse Events, Discontinuations due to Adverse Events
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
To explore the relationship between genetic variation and response to the treatment administered. Variation across the human genome will be analyzed for association with clinical data collected in this study	Germline genetic variation and association to clinical data collected in this study
To explore the % change in plasma free PCSK9 from baseline following administration of a single oral 20 mg dose of MK-0616 in participants on a background of statin therapy with varying degrees of renal impairment (moderate, severe, ESRD), compared to healthy mean matched control participants on a background of statin therapy.	Percent reduction in free PCSK9 from baseline

4 STUDY DESIGN

4.1 Overall Design

This is a nonrandomized, parallel-group, multi-site, open-label study of MK-0616 in adult male and female participants with moderate renal impairment (Panel A; n=8), severe renal impairment (Panel B; n=8), end-stage renal disease on HD (Panel C; n=8), and healthy mean matched control participants (Panel D; n=8 to 12), all on a background of statin therapy. Healthy control participants will be matched for mean age (± 15 years) and BMI (± 3.5 kg/m^2) of participants with RI. In addition, the ratio of males and females of the healthy participants will be generally matched to the ratio of males and females of RI participants. Enrollment into the healthy mean matched control panel (Panel D) will begin once 8 participants with RI have been enrolled across all RI panels (8 participants from Panels A, B, and C combined). Up to an additional 4 healthy participants may be enrolled as needed, to maintain the mean-matching of the healthy participant panel to the RI panels. If additional healthy matched control participants are enrolled (beyond the minimum 8 participants), the overall ratio of males and females in the healthy panel should be as close as possible to the overall ratio of males and females in the RI panels.

The study will evaluate safety, PK, and pharmacodynamic effects of a single oral 20 mg dose of MK-0616. The dose of MK-0616 will be administered in a fasted state (ie, following an overnight fast of at least 8 hours, with no food for at least 30 minutes following the oral dose).

Assignment to a renal function group will be as shown in Table 1:

Table 1 Renal Function Group

Panel	Renal Impairment Stage	n	eGFR (mL/min)[a,b]
A	Moderate	8	≥ 30 but ≤ 60[c]
B	Severe	8	≥ 15 but < 30 not on dialysis
C	ESRD requiring HD	8	Not applicable
D	Healthy	8 to 12[d]	≥ 90

BSA=body surface area; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; cr=creatinine; eGFR=estimated glomerular filtration rate; ESRD=end-stage renal disease; HD=hemodialysis

[a] eGFR based on the 2021 CKD-EPI Creatinine (CKD-EPIcr_R) equation that does not require use of race. Baseline eGFR will be obtained twice (at least 72 hours apart as part of participant screening) and the mean of the 2 values will be used for group assignment. The second baseline eGFR sample may be obtained on Day -1 but within 24 hours of study intervention administration, as long as data are available in time to confirm eligibility.

[b] eGFR criteria will use de-indexed values to correct for participant BSA. To convert indexed eGFR expressed as mL/min/1.73 m^2, this value will be divided by 1.73 and multiplied by participant BSA.

[c] Reasonable efforts will be made to enroll at least 2 participants in the moderate renal impairment group who have eGFR values of 30 to 40 mL/min.

[d] May need to enroll more than 8 to enable mean matching of the healthy mean match controls to the participants with RI.

Participants with moderate RI (Panel A), participants with severe RI (Panel B), and healthy mean matched control participants (Panel D), will receive a single oral dose of 20 mg MK-0616, followed by PK sampling until 48 hours postdose in the clinic. There will be additional outpatient visits through 240 hours postdose for PK assessments and a follow up visit approximately 14 days postdose. Safety will be monitored throughout the study by repeated clinical and laboratory evaluations.

ESRD participants (Panel C), will receive a single oral dose of 20 mg MK-0616 on 2 separate occasions. In Period 1 on Day 1, ESRD participants will receive a single oral dose of 20 mg MK-0616 immediately following completion of the scheduled HD, followed by PK sampling until 48 hours postdose in the clinic. There will be additional outpatient visits through 240 hours postdose for PK assessments and HD sessions. For participants following a Monday, Wednesday, Friday HD schedule, MK-0616 will be administered immediately following the Friday HD session (Study Day 1). For participants following a Tuesday, Thursday, Saturday HD schedule, study intervention will be administered immediately following their Saturday HD session (Study Day 1). The participant's next scheduled HD sessions will occur either Monday or Tuesday (Study Day 4) and either Wednesday or Thursday (Study Day 6). A PK sample for MK-0616 analysis will be collected prior to HD (Pre-HD) and after HD (Post-HD) on Study Days 4 and 6. There will be a washout period of at least 14 days between MK-0616 administrations in each period, due to the need to collect PK samples out to 240-hours postdose in each period and to stay on the HD schedule.

In Period 2 on Day 1, ESRD participants (Panel C) will receive a single oral dose of 20 mg MK-0616 approximately 0.5 hours prior to their scheduled HD followed by PK sampling until 48 hours postdose in the clinic. There will be additional outpatient visits through 240 hours postdose for PK assessments of MK-0616 and HD sessions. For participants following a Monday, Wednesday, Friday HD schedule, MK-0616 will be administered approximately 0.5 hours prior to the Friday HD session (Study Day 1). For participants following a Tuesday, Thursday, Saturday HD schedule, MK-0616 will be administered approximately 0.5 hours prior to the Saturday HD session (Study Day 1). The HD session should initiate immediately following the 0.5-hour PK blood draw. The participant's next scheduled HD sessions will occur either Monday or Tuesday (Study Day 4) and either Wednesday or Thursday (Study Day 6). A PK sample for MK-0616 analysis will be collected prior to HD (Pre-HD) and after HD (Post-HD) on Study Days 1, 4, and 6. A Pre-HD dialysate sample will be collected at the start of HD. During the HD session, dialysate samples will be collected at the end of every 30-minute interval from the start of HD until immediately before HD completion, for MK-0616 analysis.

Because this is a Phase 1 assessment of MK-0616 in humans, the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is therefore written with flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Refer to Section 8.11.6 for examples of modifications permitted within the protocol parameters.

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

4.2 Scientific Rationale for Study Design

MK-0616 is likely to be used in patients with varying degrees of RI. The primary purpose of this trial is to understand the impact of moderate RI, severe RI and ESRD on the PK of MK-0616. CCI [redacted] CCI [redacted] This study will evaluate and compare MK-0616 PK in participants with moderate RI, severe RI and ESRD patients requiring HD to healthy control participants with normal renal function that are reasonably matched to the mean demographic parameters of participants with varying degrees of RI to control for the influence of covariates. In addition, the impact of HD on MK-0616 PK will also be assessed.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

No efficacy endpoints will be evaluated.

4.2.1.2 Safety Endpoints

Safety will be assessed by monitoring AEs, physical examinations, VS, 12-lead ECGs, and laboratory safety tests (chemistry, hematology, urinalysis). Based on the data from preclinical safety studies and clinical studies to date, no specific concerns or target organ toxicities have been identified. Therefore, standard safety monitoring has been deemed adequate.

4.2.1.3 Pharmacokinetic Endpoints

Pharmacokinetic parameters selected for evaluation in this study will effectively inform the pharmacokinetic profile of MK-0616 and include the following: AUC0-inf, AUClast, Cmax, Tmax, t1/2, CL/F, Vz/F, CLr (renal clearance), Ae (amount excreted).

4.2.1.4 Pharmacodynamic Endpoints

Reduction of free PCSK9 relative to baseline will be included as an exploratory endpoint. Inhibition of PCSK9 results in reduction of plasma LDL-C, therefore the percent reduction of plasma LDL-C from baseline/pre-dose levels will be used as a pharmacodynamic endpoint.

4.2.1.5 Planned Exploratory Biomarker Research

4.2.1.5.1 Planned Genetic Analysis

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

DNA samples may be used for research related to the study intervention(s), the disease under study, or related diseases. They may also be used to develop tests/assays including diagnostic

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

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

4.2.1.6 Future Biomedical Research

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

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

4.2.2 Rationale for Control

Healthy participants with normal renal function, matched by mean age, mean BMI, and sex, will serve as the control group. Comparison of data from participants with renal impairment to data from healthy participants will effectively inform the differences of safety and PK between the groups.

4.3 Justification for Dose

The proposed clinical dose for MK-0616 is 20 mg taken once daily, which will be evaluated in this study. Single doses of 20 mg MK-0616 will be sufficient to characterize the impact of RI on the PK of MK-0616.[redacted]

In healthy controls, a single oral dose of 20 mg is anticipated to result in plasma AUC0-inf of [redacted] This projection is based upon observed 18 to 20 mg fasted PK in normal healthy participants from previous Phase 1 studies (ie, P005, P009), with the additional assumption of [redacted] With above assumptions regarding severe/ESRD, the MK-0616 AUC0-inf could be up to [redacted] with a 20 mg single dose. In the FIH study (P001), single doses of 300 mg were associated with mean plasma AUC0-inf of 2260 nM*hr and were well-tolerated, so it is

anticipated that existing clinical safety is sufficient to justify the 20 mg dose in this study across all renally impaired groups.

In the Phase 2b study, plasma levels of [redacted] The target population for MK-0616 will be on standard of care/statin therapy, and a large proportion of renally impaired patients are receiving concomitant medications, including statins.

Participants will not be limited to any particular type of statin (atorvastatin, rosuvastatin, etc), which is a similar approach as used in previous studies with MK-0616. In P008 (Ph2b study), at the 18 mg dose, [redacted] Therefore, we do not plan to limit or restrict participants to a particular dose level (ie, high/medium/low intensity statin).

As this is a Phase 1 assessment of MK-0616 in humans, and the PK, pharmacodynamic and safety profiles of the compound are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants. Details of allowed modifications are provided in Section 8.11.6.

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

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

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

4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

5 STUDY POPULATION

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

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

5.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. Be in good health based on medical history, physical examination, VS measurements, and ECGs performed before allocation, with the exception of RI for participants in Panels A, B, and C. **Participants with RI** that have stable, chronic medical or psychiatric conditions, including but not limited to hypertension, hypercholesterolemia, diabetes mellitus, hyper- or hypothyroidism, gout, and chronic anxiety or depression may be included at the discretion of the investigator.
   Appendix 9 provides a table of the 12-Lead Electrocardiogram Evaluation Criteria, to be used for **healthy participants only (Panel D)**.
2. Be in good health based on laboratory safety tests obtained at the screening visit and prior to study intervention administration (Period 1 only for **ESRD participants, Panel C**), with the exception of RI for participants in Panels A, B, and C. Appendix 2 provides a table of laboratory safety tests to be performed. Appendix 10 provides an algorithm for the assessment of out-of-range laboratory values.
3. BMI $\geq$ 18 kg/m^2 and $\leq$ 40 kg/m^2, inclusive. See Section 8.3.1 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height (m)^2.
   For participants with **ESRD (Panel C)**, dry weight (body weight after hemodialysis) should be used for BMI calculation.
   Healthy Mean Matched Controls (Panel D): BMI must be ± 3.5 kg/m^2 of the mean BMI of participants within the RI panels.
4. Be on a stable dose of any statin therapy defined as: no changes to dose or type of statin therapy for at least 2 months prior to Screening Visit 1 and participant anticipates no changes to statin therapy throughout the study until the poststudy visit.
5. Has a baseline eGFR as follows based on 2021 CKD-EPI Creatinine equation [Inker, L. A., et al 2021] [Delgado, C., et al 2021]:
   For participants with moderate RI (Panel A): $\geq$ 30 mL/min but $\leq$ 60 mL/min;
   For participants with severe RI (Panel B): $\geq$ 15 mL/min but < 30 mL/min (but not on dialysis);

For participants with ESRD on HD (Panel C): not applicable;

2021 CKD-EPI Creatinine (CKD-EPIcr_R) Equation:

$eGFR = 142 \times \min(Scr/k,1)^{\alpha} \times \max(Scr/k,1)^{-1.200} \times 0.9938^{age} \times 1.012$ [if female]

where Scr is serum creatinine, k is 0.7 for females and 0.9 for males, α is -0.241 for females and -0.302 for males, min indicates the minimum of Scr/k or 1, max indicates the maximum of Scr/k or 1.

Baseline eGFR will be obtained twice (at least 72 hours apart as part of participant screening), and the mean of the two values will be used. The second baseline eGFR sample may be obtained at the time of check-in as long as the result is available in time to determine eligibility prior to study intervention administration.

eGFR values indexed to BSA 1.73 m^2 will be de-indexed by dividing the value obtained from the equation by 1.73 and then multiplying by participant BSA.

6. For participants with **ESRD (Panel C)**, participant has ESRD maintained on stable outpatient regimen at a healthcare center for > 3 months prior to dosing, using an established and normally functioning, regular flow, uninfected mature AV fistula or AV graft and skin consistent with standard HD access injuries, and HD stability defined as Kt/V ≥ 1.2 within 3 months prior to the initial administration of the study intervention.
7. For participants with **ESRD (Panel C)**, participant is on a 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 planning to continue this during the study and at least up to the poststudy visit.

Demographics

8. Is an individual of any sex/gender, from 18 years to 85 years of age inclusive, at the time of providing the informed consent.

   Healthy Mean Matched Controls (Panel D): Age must be within ± 15 years of the mean age of participants within the RI panels.

Female Participants

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

- Is not a POCBP
  OR

- Is a POCBP and:
  - Uses an acceptable contraceptive method, or is abstinent from penile-vaginal intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 8 weeks after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by POCBPs should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.
  - Has a negative highly sensitive pregnancy test (urine or serum) as required by local regulations within 24 hours (for a urine test) or 72 hours (for a serum test) before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.5.
  - Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a POCBP with an early undetected pregnancy.

Informed Consent

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

Other Inclusion Criteria

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

5.2 Exclusion Criteria

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

Medical Conditions

1. History or presence of renal artery stenosis.
2. Had a functioning renal transplant in the past 5 years and is taking transplant medication.
3. **Participants in Panels A, B and D:** Has rapidly fluctuating renal function as determined by historical measurements. Rapidly fluctuating renal function is defined as > 30 % difference between two measurements of eGFR taken at least 72 hours apart as part of participant screening.

4. Has a history of gastrointestinal disease which might affect food and drug absorption, as determined by the investigator, or has had gastric bypass or similar surgery. For example, recurrent vomiting, inflammatory bowel disease, chronic intestinal disease accompanied by a disturbance in digestion and absorption, Roemheld's syndrome, severe hernia, etc.
5. **Healthy Participants (Panel D):** History of clinically significant endocrine, GI, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or diseases. Participants with a remote history of uncomplicated medical events (eg, uncomplicated kidney stones, as defined as spontaneous passage and no recurrence in the last 5 years, or childhood asthma) may be enrolled in the study at the discretion of the investigator.

   Participants with RI (Panels A, B, and C): History of any illness, other than RI, that, in the opinion of the Investigator, might confound the results of the study or poses an additional risk to the participant by their participation in the study.
6. Mentally or legally incapacitated, has significant emotional problems at the time of prestudy (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.
7. History of cancer (malignancy). Participants with adequately treated disease deemed as "cured," or who, in the opinion of the study investigator, are highly unlikely to sustain a recurrence for the duration of the study may be enrolled at the discretion of the investigator.
8. **Healthy Participants (Panel D):** Estimated eGFR ≤ 90 mL/min based on the 2021 CKD-EPIcr_R equation (see Section 5.1 for equation and de-indexing values to correct for participant BSA).
9. History of significant multiple and/or severe allergies (eg, food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability (ie, systemic allergic reaction) to prescription or nonprescription drugs or food.
10. Has a known hypersensitivity to the active substance or any of the excipients of the study drug.
11. Has received an anti-PCSK9 small molecule treatment, mAb, or small interfering siRNA or RNAi (ie, Inclisiran) within 12 months prior to Screening Visit 1.
12. Positive test(s) for HBsAg, hepatitis C antibodies or HIV. Note: Participants with a documented cure and/or a positive serologic test for HCV with a negative HCV viral load may be included upon consultation with the Sponsor.
13. The participant had a major surgery and/or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the prestudy (screening) visit.

Prior/Concomitant Therapy

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

Participants with RI (Panels A, B, and C): Taking medications to treat chronic medical conditions and/or conditions associated with renal disease, if participant has not been on a stable regimen for at least 1 month (other than statins, which require a stable dose for at least 2 months) prior to administration of the initial dose of study intervention, and/or is unable to withhold the use of the medication(s) within 4 hours prior to and 4 hours after administration of study intervention. Exceptions may be granted for participants in whom a medication regimen has been adjusted within a one-month window prior to administration of the initial dose of study intervention, at the discretion of the Investigator and following consultation with the Sponsor. See Section 5.1.2 for allowed medical conditions, and Section 6.5 for allowed medications.

Prior/Concurrent Clinical Study Experience

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

Diagnostic Assessments

16. **Healthy Participants (Panel D):** QTc interval ≥ 470 msec (for males) or ≥ 480 msec (for females).

    Participants with RI (Panels A, B, and C): The participant meets the following 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 participant.
    - Non-sustained or sustained ventricular tachycardia (> 2 consecutive ventricular ectopic beats at a rate of > 1.7/second).

Other Exclusions

17. Under the age of legal consent.
18. **Healthy participants (Panel D):** The participant is a smoker and/or has used nicotine or nicotine-containing products (eg, nicotine patch and electronic cigarette) within 3 months of screening.

    Participants with RI (Panels A, B, and C): Does not agree to follow the smoking restrictions as defined by the CRU.
19. Consumes greater than 3 servings of alcoholic beverages (1 serving is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day. Participants who consume 4 servings of alcoholic beverages per day may be enrolled at the discretion of the investigator.

20. 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.
21. **Healthy participants (Panel D):** A regular user of cannabis, any illicit drugs or has a history of drug (including alcohol) abuse within approximately 3 months. Participants must have a negative drug screen prior to allocation.

    Participants with RI (Panels A, B, and C): A regular user of cannabis (refer to exception below for use of cannabis) or any illicit drugs or has a history of drug (including alcohol) abuse within approximately 3 months. Participants must have a negative drug screen prior to treatment allocation, but may be allowed for inclusion with a positive drug screen due to the use of physician-prescribed medications (eg., opioids, benzodiazepines, antidepressants) 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 participant agrees to not use during 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.

22. Is unwilling to comply with the study restrictions (see Section 5.3 for a complete summary of study restrictions).
23. The investigator has any concern regarding safe participation in the study or for any other reason the investigator considers the participant inappropriate for participation in the study.

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

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

5.3.1.1 Diet Restrictions

Participants will fast from all food and drinks, except water, for at least 8 hours before study intervention administration. Participants will fast from all food and drinks, except water, between study intervention administration and the first scheduled meal. Meals and snack(s) will be provided by the site staff at time points indicated in the SoA. Participants will fast from all food and drinks, except water, between meals and snacks. The caloric content and composition (macronutrients) of meals will be approximately the same in each treatment period for Panel C. The meal content should be consistent within a given clinical site. After the 4-hour postdose procedures have been completed, subsequent meals and snacks will be unrestricted in caloric content, composition, and timing.

Approximately 240 mL of water will be provided during study intervention administration. Additional water may be provided in 50-mL increments if desired. Water will be restricted 1 hour before and 1 hour after study intervention administration.

Approximately 30 minutes after study intervention administration, participants will begin to consume a breakfast. The contents of the breakfast are listed below.

The nutritional content of the breakfast is as follows:

- ~15% to 19% kcal from fat

The exact meal contents may be substituted with agreement between Sponsor and investigator, and must be documented in an administrative letter.

This breakfast should be consumed in its entirety in 30 minutes or less. The start and stop time of the breakfast will be recorded.

Instructions on whether to take MK-0616 with or without food and/or drink may be modified during the study based on newly available data.

Fasting requirements for laboratory safety evaluations are at least 8 hours prior to collection.

5.3.1.2 Fruit Juice Restrictions

Participants will refrain from the consumption of grapefruit juice, grapefruits, and grapefruit products beginning approximately 2 weeks before administration of the initial dose of study intervention, throughout the study including the washout interval between treatment periods (Panel C only) and until the poststudy visit.

Participants also will refrain from the consumption of all fruit juices 24 hours before and after study intervention administration. On all other days during the study, consumption of fruits and fruit juices (except for grapefruit, grapefruit juices, and grapefruit products) is allowed.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

5.3.2.1 Caffeine Restrictions

Participants are advised to refrain from consumption of caffeinated beverages or xanthine-containing products from 12 hours prior to the Screening Visit 1. A recheck may be needed if participants did not refrain from consuming caffeinated beverages or xanthine-containing products 12 hours prior to the Screening Visit 1.

Participants will refrain from consumption of caffeinated beverages or xanthine-containing products from:

- 12 hours before the Screening Visit 2.
- 12 hours before and after study intervention administration (for Panel C, applies to each treatment period).
- 12 hours before poststudy visit.

At all other times, caffeinated beverages or xanthine-containing products will be limited to no more than 6 units per day (1 unit = 120 mg of caffeine).

5.3.2.2 Alcohol Restrictions

Participants are advised to refrain from consumption of alcohol 24 hours prior to the Screening Visit 1. A recheck may be needed if participants did not refrain from consuming alcohol 24 hours prior to the Screening Visit 1.

Participants will refrain from consumption of alcohol from:

- 24 hours before the Screening Visit 2.
- 24 hours before and after study intervention administration (for Panel C, applies to each treatment period).
- 24 hours before poststudy visit.

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

5.3.2.3 Tobacco Restrictions

Healthy Mean Matched Control Participants (Panel D): Smoking (and/or the use of nicotine/nicotine-containing products) is not permitted during the study.

Moderate RI, Severe RI, and ESRD Participants (Panels A, B, and C): Participants will follow the smoking restrictions (and if applicable, the use of nicotine/nicotine-containing products) defined by the CRU.

5.3.3 Activity Restrictions

Participants in Panels A, B, and D will avoid unaccustomed strenuous physical activity (ie, weightlifting, running, bicycling, etc) from the prestudy (screening) visit until administration of the dose of study intervention, throughout the study, and until the poststudy visit.

ESRD participants in Panel C will avoid unaccustomed strenuous physical activity (ie, weightlifting, running, bicycling, etc) from the prestudy (screening) visit until administration of the initial dose of study intervention, throughout the study (including the washout interval between treatment periods), and until the poststudy visit.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

If a participant discontinues from study intervention or withdraws from the study, 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/allocation number.

The study site should contact the Sponsor for the replacement participant's treatment/allocation number.

6 STUDY INTERVENTION

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

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

6.1 Study Intervention(s) Administered

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

Country-specific requirements are noted in Appendix 7.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Moderate RI Group	Experimental	MK-0616	Drug	Tablet	20 mg	20 mg	Oral	Panel A: Single dose on Day 1	Test Product	IMP	Provided centrally by Sponsor
Severe RI Group	Experimental	MK-0616	Drug	Tablet	20 mg	20 mg	Oral	Panel B: Single dose on Day 1	Test Product	IMP	Provided centrally by Sponsor
ESRD on HD Group	Experimental	MK-0616	Drug	Tablet	20 mg	20 mg	Oral	Panel C: Single Dose on Day 1 of Periods 1 and 2	Test Product	IMP	Provided centrally by Sponsor
Healthy Control Group	Experimental	MK-0616	Drug	Tablet	20 mg	20 mg	Oral	Panel D: Single Dose on Day 1	Test Product	IMP	Provided centrally by Sponsor

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

All supplies indicated in Table 2 will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is in Section 4.3.

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Participants in this study will be allocated by nonrandom assignment.

A sample allocation table is provided below in Table 3.

Table 3 Allocation of Participants to Treatment

Panel	Renal Impairment Stage	N	Period 1	Period 2[a]
A	Moderate	8	20 mg MK-0616	Not applicable
B	Severe	8	20 mg MK-0616	Not applicable
C	ESRD on HD	8	20 mg MK-0616 (immediately after HD)	20 mg MK-0616 (approximately 30 minutes prior to HD)
D	Healthy	8 to 12	20 mg MK-0616	Not applicable

ESRD=end-stage renal disease; HD=hemodialysis

[a] There will be at least 14 days of washout between study intervention administration in each period

6.3.2 Stratification

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

6.3.3 Blinding

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

6.4 Study Intervention Compliance

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

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

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant ID will be confirmed at the time of dosing by a member of the study-site staff other than the person administering the study intervention. Study-site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5 Concomitant Therapy

If a participant does not discontinue all prior medications within 14 days or 5 half-lives of the first dose of study intervention, they may be included in the study if the investigator can rationalize that the specific use of a prior medication is not clinically relevant within the context of the study.

Concurrent use of any prescription or nonprescription medication, or concurrent vaccination, during the ongoing study (ie, after intervention allocation) must first be discussed between the investigator and Sponsor before administration, unless appropriate medical care necessitates that therapy or vaccination should begin before the investigator and Sponsor can consult. The participant will be allowed to continue in the study if both the Sponsor and the investigator agree.

Paracetamol/acetaminophen (up to 2 g total per day for participants with RI or up to 4 g total per day for healthy participants) may be used for minor ailments without prior consultation with the Sponsor.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are not to be used without prior consultation with the Sponsor.

In addition, the following concomitant medications/vaccinations are permitted:

- 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.
- Hormone replacement therapy
- Contraceptives
- Statins (any statin, any dose), but must be on a stable, unchanged dose for at least 2 months prior to screening

In addition, for participants with RI (Panels A, B, and C):

Medications specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medications specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy rests with the investigator and/or the participant's primary physician. For ESRD participants (Panel C), however, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Participants who are taking certain prescription medications to treat manifestations of renal disease or medications needed to treat stable diseases (eg, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers, diuretics) may be allowed to participate in the study at the discretion of the investigator. Participants must be on a stable regimen for at least 2 weeks (or 5 half-lives of the concomitant medication, whichever is longer) prior to administration of study intervention and be able to withhold the use for 4

hours prior to and 4 hours after study intervention administration. If a participant is prescribed prohibited medication, upon discussion between the Sponsor and the investigator, the investigator may substitute the previously prescribed medication to an allowed one for the purpose of this study. Examples of the types of medications that would be allowed include (but are not limited to) the following:

- Angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, diuretics
- Beta blockers
- Metformin, thiazolidinediones, sulfonylureas, DPP-4 inhibitors, alpha-glucosidase inhibitors, incretin mimetics
- Synthroid
- Colchicine, allopurinol
- SSRIs, tricyclic antidepressants
- Proton pump inhibitors

Participants using medical marijuana will be allowed to participate in the study at the discretion of the investigator, however, the use of medical marijuana should be restricted during study participation.

Any medication (including over-the-counter) that would significantly alter eGFR, which, by the determination of the investigator, might interfere with the study (eg, cimetidine) must be discontinued at least 2 weeks (or 5 half-lives of the compound, whichever is longer) prior to administration of study intervention.

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

6.5.1 Rescue Medications and Supportive Care

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

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

6.6 Dose Modification

Dose modifications are not applicable to this study.

6.6.1 Stopping Rules

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

If any of the below stopping rules are met, the study will be paused, and no further dosing will occur until the Sponsor has reviewed the totality of data available. To continue the study

(on joint agreement with the Sponsor and investigator), a substantial amendment will be submitted for approval.

1. An individual participant reports an SAE considered related to the study intervention by the investigator.
2. Two (2) or more participants within a Panel (at the same dose level) report Severe Nonserious AEs considered related to the study intervention by the investigator.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

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

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

In clinical studies with a single intervention, discontinuation of study intervention can only occur before the intervention. Therefore, participants who receive a single-dose intervention cannot discontinue study intervention (ie, participants in Panels A, B, and D).

For ESRD Participants only (Panel C):

Discontinuation of study intervention does not represent withdrawal from the study. As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.1.9, or if available, a PCL.

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

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a positive drug screen at any time during the course of the study (with the exception for positive drug screen due to prescription drug use that is approved by the investigator and Sponsor). The drug screen can be confirmed by a recheck at the discretion of the investigator after discussion with the Sponsor.

7.2 Participant Withdrawal From the Study

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

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

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

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

8 STUDY ASSESSMENTS AND PROCEDURES

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

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 their legally acceptable representative) and of the person conducting the consent discussion.

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

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

Specifics about the study and the study population are to be included in the ICF.

The participant (or their 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.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review before medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 14 days before first dose of study intervention.

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

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

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

8.1.7 Assignment of Treatment/Allocation Number

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

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

8.1.8 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or an appropriately qualified designee.

8.1.8.1 Timing of Dose Administration

Participants with moderate RI (Panel A), severe RI (Panel B), and healthy participants (Panel D):

On Day 1, 20 mg (1 x 20 mg tablet) MK-0616 will be given to participants at Hour 0.

Participants with ESRD:

On Day 1 of Period 1, 20 mg (1 x 20 mg tablet) MK-0616 will be given to participants at Hour 0, immediately following completion of the scheduled HD session. On Day 1 of Period 2, 20 mg (1 x 20 mg tablet) MK-0616 will be given to participants at Hour 0, approximately 0.5 hours prior to the scheduled HD session.

All participants:

The study interventions will be administered with approximately 240 mL of water following at least an 8-hour fast and participants will continue to fast for at least 30 minutes postdose. See Section 5.3.1 for additional information on meal restrictions throughout the study.

The exact clock time of study intervention administration will be recorded.

8.1.9 Discontinuation and Withdrawal

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

8.1.9.1 Withdrawal From Future Biomedical Research

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

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

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

8.1.10 Participant Blinding/Unblinding

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

8.1.11 Domiciling

All participants (Panels A to D) will be admitted to the CRU on Day -1, at the time indicated by the CRU, and will be housed until after the 48 hours postdose study procedures are completed on Day 3. Panel C participants with ESRD will follow the same domiciling schedule in a 2nd treatment period.

At all times, a participant may be required to remain at the CRU for longer at the discretion of the investigator or designee.

8.1.12 Calibration of Equipment

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

8.2 Efficacy/Immunogenicity Assessments

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

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard. Height and weight will also be measured and recorded at the timepoints listed in the SoA (Section 1.3).

Symptom-driven physical examinations may be performed at other times, if deemed necessary by the investigator or designee.

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

BMI

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

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

BSA

In order to correct eGFR for individual BSA, the DuBois formula will be used to calculate BSA:

$BSA\ (m^2) = Weight\ (kg)^{0.425} \times Height\ (cm)^{0.725} \times 0.007184$

8.3.2 Vital Signs

- Body temperature, HR, RR, and BP will be assessed.
- Body temperature will be measured with an appropriate thermometer.
- BP and HR measurements will be assessed in a semirecumbent position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- BP and HR measurements should be preceded by at least 10 minutes of rest for the participant in a quiet setting without distractions.

8.3.2.1 Resting Vital Signs

Vital Sign Measurements (Heart Rate and Blood Pressure)

Participants should be resting in a quiet setting without distractions in a semirecumbent position for at least 10 minutes before having VS measurements obtained. Semirecumbent VS will include HR, systolic and diastolic BP, RR, and body temperature at timepoints

indicated in the SoA. The correct size of the BP cuff and the correct positioning on the participant's arm is essential to increase the accuracy of BP measurements.

The predose (baseline) HR and BP will be triplicate measurements, obtained at least 1 to 2 minutes apart within 3 hours of dosing MK-0616. The mean of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). Screening and postdose VS measurements will be single measurements.

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

Body Temperature

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

8.3.2.2 Orthostatic Vital Signs

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

8.3.3 Electrocardiograms

- Triplicate 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. For healthy participants (Panel D), refer to Appendix 9 for evaluation and potentially significant findings.
- At each time point when triplicate ECG are required, 3 individual ECG tracings should be obtained at least 1 minute apart. The full set of triplicates should be completed in no more than 6 minutes.

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

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

The correction formula to be used for QTc is Fridericia.

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

Before each period, predose ECGs will be obtained in triplicate at least 1 minute apart within 3 hours before dosing MK-0616. The mean of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed).

During the treatment period, if a participant demonstrates an increase in QTc interval ≥60 msec compared with mean predose baseline measurement, the ECG will be repeated twice within 5 minutes. The mean value of the QTc interval from the 3 ECGs will represent the value at that time point. If the mean QTc interval increase from baseline for any postdose time point is ≥60 msec, the participant will continue to be monitored by repeat 12-lead ECGs every 15 minutes for at least 1 hour or until the QTc interval 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.

During each treatment period, if a participant demonstrates a QTc interval ≥500 msec on a postdose ECG, the ECG will be repeated twice within 5 minutes. The mean value of the QTc interval from the 3 ECGs will represent the value at that time point. If the mean 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 interval is <500 msec) or should be considered for transfer to a location where closer monitoring and definitive care (eg, a CCU or ICU) is available.

If at any time the QRS interval is prolonged ≥200 msec (and change is not considered rate related or pacing induced), then the Sponsor should be notified. The ECGs should be reviewed by a cardiologist and the participant should be considered for transfer to a location where closer monitoring and definitive care (eg, a CCU or ICU) is available.

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

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

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

8.3.4 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the 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 14 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.5 Pregnancy Testing

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3.6 Photograph of Rash

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

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

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

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

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

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

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

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

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

From the time of intervention allocation through 14 days after cessation of intervention, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

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

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 4.

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

Table 4 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

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

Type of Event	Reporting Period: Consent to Allocation	Reporting Period: Allocation through Protocol-specified Follow-up Period	Reporting Period: After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor
Cancer	Report if: – due to intervention – causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: – receiving placebo run-in or other run-in medication	Report all	Not required	Within 24 hours of learning of event

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

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

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

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

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

Not applicable to this study.

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.5.
2. Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
   *Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

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

8.5 Treatment of Overdose

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

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

8.6 Pharmacokinetics

The decision as to which plasma and/or urine samples collected will be measured for evaluation of PK/pharmacodynamics will be collaboratively determined by the Sponsor. If indicated, these samples may also be measured and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

Blood samples collected may be stored and further analysis may be performed, if required.

8.6.1 Blood Collection for Plasma MK-0616 and/or Metabolites

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

8.6.2 Dialysate Samples for MK-0616 and/or Metabolites

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

8.6.3 Urine Collection for Urinary MK-0616 and/or Metabolites

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

8.7 Pharmacodynamics

Sample collection, storage, and shipment instructions for pharmacodynamic samples (free PCSK9) will be in the Operations Manual.

8.8 Biomarkers

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

- Blood for genetic analysis
- Blood for Plasma for PCSK9 (free) Assay

8.8.1 Planned Genetic Analysis Sample Collection

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

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

8.9 Future Biomedical Research Sample Collection

All sample collections for study-specific assessments shown in the SoA are described within the main Informed Consent.

If the participant has provided documented informed consent for FBR, leftover samples will be used for FBR. The following specimens will be included for FBR:

- Leftover samples from Section 8.8

8.10 Health Economics, Medical Resource Utilization and Health Economics

Health Economics, Medical Resource Utilization and Health Economics are not evaluated in this study.

8.11 Visit Requirements

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

8.11.1 Screening

Within approximately 4 weeks; before intervention allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

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

8.11.2 Treatment Period Visit

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

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

At any point if a participant discontinues from treatment but continues to be monitored in the study, all study procedures specified in the SoA may be completed at the discretion of the investigator and with Sponsor agreement. The subset of study procedures completed will be communicated in an official memo.

8.11.4 Poststudy

Participants will be required to return to clinic approximately 14 days after the last dose of study intervention for the poststudy visit. If the poststudy visit occurs less than 14 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at 14 days post the last dose of study intervention to determine if any AEs have occurred since the poststudy clinic visit.

8.11.5 Critical Procedures Based on Study Objectives: Timing of Procedure

For this study, the blood sample for MK-0616 is the critical procedure.

At any postdose time point, the blood sample for MK-0616 needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible. Study procedures can be performed before or after the prescribed/scheduled time.

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

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

The following variance in procedure collection times will be permitted.

- PK Collection as outlined in Table 5.

Table 5 Pharmacokinetic (Blood/Urine) Collection Windows

PK Collection	PK Collection Window
0 to <1 h	5 min
1 to <24 h	15 min
24 to <48 h	1 h
48 to 168 h	2 h
>168 h	24 h

h=hour, min=minute; PK=pharmacokinetic.

Predose and Postdose Procedures

- Predose standard safety evaluations: VS and ECG within 3 hours; laboratory safety tests and physical examination within 24 hours
- Postdose standard safety evaluations: VS, ECG, laboratory safety tests, and physical examination
  - Procedures scheduled within the 24-hours after dosing may be obtained within 15 minutes of the theoretical sampling time
  - Procedures scheduled between 24-hours and 48-hours postdose may be obtained within 1 hour of the theoretical sampling time
  - Procedures scheduled from 48-hours postdose to 168-hours postdose may be obtained within 2 hours of the theoretical sampling time

  Note: Visit windows defined by ±1 day refers to calendar days.

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

This is a Phase 1 assessment of MK-0616 in humans, and the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently outlined may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants.

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

- Decrease in the dose of the study intervention administered in any given period/panel
- Entire period(s) or panel(s) may be omitted
- Lengthening of the washout period between doses
- Addition of PK pause

- Instructions to take study intervention with or without food or drink may also be modified based on newly available data
- Modification of the PK/pharmacodynamic sample processing and shipping details based on newly available data

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

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

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

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

9 KEY STATISTICAL CONSIDERATIONS

This section contains a brief summary of the statistical analyses for this trial. Full detail is in the Statistical Analysis Plan (SAP) (Section 9.2 through 9.9).

If a different group of healthy matched control participants is needed to match the mean age and BMI for the RI and ESRD groups, then separate analyses will be performed for the populations as follows:

• Moderate RI versus an appropriate group of healthy matched control participants;

• Severe RI versus an appropriate group of healthy matched control participants;

• ESRD participants versus an appropriate group of healthy matched control participants.

If a single set of healthy matched control participants can be used for comparison with all RI and ESRD groups, the following analysis pooled over all populations will be used.

Separately for each pharmacokinetic parameter, individual values of plasma MK-0616 AUC0-inf and Cmax will be natural log-transformed and evaluated with a linear mixed-effects model containing a fixed effect for populations. An unstructured covariance matrix will be used to allow for unequal population variances and to model the correlation between repeated measures (before and after HD) within each ESRD participant via the REPEATED statement in SAS PROC MIXED.

Ninety-five percent (95%) CIs for the least squares means for each population 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 GMs and CIs about the GMs on the original scale.

To compare participants with RI in each of the renal categories (moderate RI, severe RI, ESRD before HD and ESRD after HD) to matching participants with normal renal function, a 2- sided 90% CI for the true difference in means (RI - normal renal function) will be calculated for each PK parameter (AUC0-inf and Cmax) using the mean square error from the model and referencing a t-distribution. For each of the RI populations, these confidence limits will be exponentiated to obtain the 90% CI for the true GMRs (RI/normal renal function) for each PK parameter.

The same approach will be used to address the secondary estimation objective. The extent to which MK-0616 is removed from plasma by HD will be evaluated with the difference in means (ESRD before HD – ESRD after HD), the geometric mean ratio (ESRD before HD/ESRD after HD) and their 90% CIs.

A natural log transformation will be applied to AUC0-inf and Cmax. For each PK parameter, 95% confidence intervals for the least squares means 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 GMs and CIs about the GMs on the original scale. A 2-sided 90% CI for the true difference in means (before HD –after

HD) will be calculated for each pharmacokinetic parameter (AUC0-inf and Cmax) using the mean square error from the model and referencing a t-distribution. These confidence limits will be exponentiated to obtain the 90% confidence interval for the true ratio (GMR) of geometric means (before HD/ after HD) for each PK parameter. A scatter plot of AUC0-inf and Cmax by renal function will also be provided.

Urine PK: MK-0616 Ae0-24, Fe, and CLr following a single dose of MK-0616 administered to participants with moderate and severe renal impairment and ESRD, will be estimated and compared to those estimated in healthy matched control participants.

Separately for each urine PK parameter, where possible, individual values of Ae0-24, Fe and CLr will be natural log-transformed and evaluated with a linear fixed-effects model, which is described in the primary analysis. Ninety five percent CIs intervals for the least square means for each population will be constructed. To compare participants with varying degrees of RI (moderate, severe and ESRD) to matching participants with normal renal function, a 2-sided 90% CI for the true ratio of means (RI/normal renal function) will be calculated for each urine PK parameter (Ae0-24, Fe and CLr).

9.1 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.

9.2 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3

9.3 Analysis Endpoints

9.3.1 Primary Endpoints

Pharmacokinetics: The primary PK endpoints are plasma MK-0616 AUC0-inf, AUClast, Cmax, Tmax, t1/2, CL/F and Vz/F following a single dose of MK-0616 administered to participants with varying degrees of renal impairment (moderate, severe, ESRD) and healthy matched control participants.

9.3.2 Secondary Endpoints

The secondary PK endpoints are MK-0616, CL_D, C_D, Ae_D, Ae_D (%dose)] and urine MK-0616 Ae0-24, Fe, and CLr following a single dose of MK-0616 administered to participants with varying degrees of renal impairment (moderate, severe, ESRD) and healthy matched control participants.

The secondary safety endpoints are Adverse Events, Discontinuations due to Adverse Events.

9.4 Analysis Populations

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

9.4.1 All Participants as Treated (APaT) Population

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

9.4.2 Per-Protocol (PP) Population

The Per-Protocol Population consists of the set of data generated by the subset of participants who comply with the protocol sufficiently to ensure that these data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations. Important protocol deviations will be identified to the extent possible prior to unblinding by individuals responsible for data collection/compliance, and its analysis and interpretation. Any participant or data value excluded from analysis will be identified, along with their reason for exclusion, in the CSR. At the end of the study, all participants who are compliant with the study procedure as aforementioned and have available data from at least one treatment will be included in the Per-Protocol dataset. This population will be used for the PK analyses.

9.5 Statistical Methods

9.5.1 Statistical Methods for Pharmacokinetic Analyses

If a different group of healthy matched control participants is needed to match the mean age and BMI for the RI and ESRD groups, then separate analyses will be performed for the populations as follows:

• Moderate RI versus an appropriate group of healthy matched control participants;

• Severe RI versus an appropriate group of healthy matched control participants;

• ESRD participants versus an appropriate group of healthy matched control participants.

If a single set of healthy matched control participants can be used for comparison with all RI and ESRD groups, the following analysis pooled over all populations will be used.

Separately for each pharmacokinetic parameter, individual values of plasma MK-0616 AUC0-inf and Cmax will be natural log-transformed and evaluated with a linear mixed-effects model containing a fixed effect for populations. An unstructured covariance matrix will be used to allow for unequal population variances and to model the correlation between repeated measures (before and after HD) within each ESRD participant via the REPEATED statement in SAS PROC MIXED.

Ninety-five percent (95%) CIs for the least squares means for each population 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 GMs and CIs about the GMs on the original scale.

To compare participants with RI in each of the renal categories (moderate RI, severe RI, ESRD before HD and ESRD after HD) to matching participants with normal renal function, a 2- sided 90% CI for the true difference in means (RI - normal renal function) will be calculated for each PK parameter (AUC0-inf and Cmax) using the mean square error from the model and referencing a t-distribution. For each of the RI populations, these confidence limits will be exponentiated to obtain the 90% CI for the true GMRs (RI/normal renal function) for each PK parameter.

The same approach will be used to address the secondary estimation objective. The extent to which MK-0616 is removed from plasma by HD will be evaluated with the difference in means (ESRD before HD – ESRD after HD), the geometric mean ratio (ESRD before HD/ESRD after HD) and their 90% CIs.

A natural log transformation will be applied to AUC0-inf and Cmax. For each PK parameter, 95% confidence intervals for the least squares means 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 GMs and CIs about the GMs on the original scale. A 2-sided 90% CI for the true difference in means (before HD –after HD) will be calculated for each pharmacokinetic parameter (AUC0-inf and Cmax) using the mean square error from the model and referencing a t-distribution. These confidence limits will be exponentiated to obtain the 90% confidence interval for the true ratio (GMR) of geometric means (before HD/ after HD) for each PK parameter. A scatter plot of AUC0-inf and Cmax by renal function will also be provided.

Urine PK: MK-0616 Ae0-24, Fe, and CLr following a single dose of MK-0616 administered to participants with moderate and severe renal impairment and ESRD, will be estimated and compared to those estimated in healthy matched control participants.

Separately for each urine PK parameter, where possible, individual values of Ae0-24, Fe and CLr will be natural log-transformed and evaluated with a linear fixed-effects model, which is described in the primary analysis. Ninety five percent CIs intervals for the least square means for each population will be constructed. To compare participants with varying degrees of RI (moderate, severe and ESRD) to matching participants with normal renal function, a 2-sided 90% CI for the true ratio of means (RI/normal renal function) will be calculated for each urine PK parameter (Ae0-24, Fe and CLr).

9.5.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of AEs and other relevant parameters, including laboratory test results, vital signs, and ECG measurements.

The overall safety endpoints include the number of participants with at least one AE, drug-related AE, serious AE, serious, drug-related AE, who discontinue from study intervention due to an AE, or with an AE resulting in death.

9.6 Interim Analyses

No formal interim analyses are planned for this study.

9.7 Multiplicity

Not applicable.

9.8 Sample Size and Power Calculations

CCI

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Interventional Clinical Trials

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

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

proactive identification of critical to quality factors utilizing a risk-based approach. Plans are then developed to assess and mitigate risks to those factors as appropriate during the trial. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Trial designs include procedures and systems for the identification, monitoring, and reporting of safety concerns. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

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

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

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

E. Trial Results

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

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

10.1.3 Data Protection

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Publication Policy

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

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

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

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, https://euclinicaltrials.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials Regulation 536/2014 mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials Regulation 536/2014, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.6 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

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

10.1.7 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.8 Source Documents

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

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

10.1.9 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 6 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.
- Because the glucose is part of the standard chemistry laboratory tests and requires fasting, participants should fast (approximately 8 hours) prior to all chemistry laboratory collections. If the individual comes to the screening visit and is not fasting, a recheck may be needed at the discretion of the investigator and the participant may be asked to return at a later time for the safety laboratory collection.

Table 6 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH Reticulocytes		WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Chemistry	BUN	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is above the ULN)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose (fasting)	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Pregnancy Testing	• Highly sensitive serum or urine hCG pregnancy test (as needed for POCBP)			
Other Screening Tests	• FSH (as needed for PONCBP only) • Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines) per site SOP • Serology (HIV antibody, HBsAg, and hepatitis C virus antibody)			

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; HBsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; POCBP=participant of childbearing potential; PONCBP=participant of non-childbearing potential; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; SOP=standard operating procedure; ULN=upper limit of normal; WBC=white blood cell

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

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

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

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

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

10.3.3 Definition of SAE

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

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

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

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

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

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

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

10.3.4 Additional Events Reported

Additional events that require reporting

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

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

10.3.5 Recording AE and SAE

AE and SAE recording

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

Assessment of intensity/toxicity

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

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:
  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).
  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).
  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the study intervention cause the AE?
- The determination of the likelihood that the study intervention caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.
- **The following components are to be used to assess the relationship between the study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**
  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?
  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
  - **Dechallenge:** Was the study intervention discontinued or dose/exposure/frequency reduced?
    - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
    - If no, this is a negative dechallenge.

    (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the study intervention; (3) the study is a single-dose drug study; or (4) study intervention (s) is/are only used 1 time.)
  - **Rechallenge:** Was the participant reexposed to the study intervention in this study?
    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

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

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE STUDY INTERVENTION, OR IF REEXPOSURE TO THE STUDY INTERVENTION POSES ADDITIONAL POTENTIAL SIGNIFICANT

RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

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

Follow-up of AE and SAE

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

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

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

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

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

SAE reporting to the Sponsor via paper CRF

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

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

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Participants of Nonchildbearing Potential (PONCBP)

Participants assigned female sex at birth who are in the following categories are not capable of becoming pregnant and, therefore, are considered PONCBP:

- Premenopausal 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, Müllerian 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
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in participants assigned female sex at birth not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Participants assigned female sex at birth on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Participants of Childbearing Potential (POCBP)

A participant assigned female sex at birth is considered fertile following menarche and capable of becoming pregnant until becoming postmenopausal unless permanently sterile (see below):

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

Participants assigned female sex at birth who are in the following categories are not capable of becoming pregnant and, therefore, not considered POCBP:

- Premenarchal
- Premenopausal 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, Müllerian 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
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in participants assigned female sex at birth who are not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Participants assigned female sex at birth who are 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.

Contraceptives allowed during the study include:
Highly Effective Contraceptive Methods That Have Low User Dependency[a] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only contraceptive implant[b] • IUS[c] • Nonhormonal IUD • Bilateral tubal occlusion (Tubal occlusion includes tubal ligation)
• Azoospermic partner (vasectomized or secondary to medical cause, confirmed by medical history) – All sexual partner(s) of the POCBP must be azoospermic. The participant must provide verbal confirmation of partner azoospermia during Medical History. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.
Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception[b] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[b] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse with a partner capable of producing sperm, during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Methods That Are Not Considered Highly Effective *Failure rate of >1% per year when used consistently and correctly.*
• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action • Penile/external or vaginal/internal condom with or without spermicide[d] • Cervical cap, diaphragm, or sponge with spermicide • A combination of penile/external condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)
[a] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly) [b] If locally required, in accordance with CTFG guidelines, acceptable contraceptives are limited to those which inhibit ovulation [c] IUS is a progestin releasing IUD [d] Vaginal/internal condom used for contraceptive purposes Note: The following are not acceptable methods of contraception: • Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM • Penile/external and vaginal/internal condom should not be used together (due to risk of failure with friction)[d]

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

5. Biorepository Specimen Usage[3, 4]

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

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

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox

(clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens[3, 4]

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

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

8. Data Security[3, 4]

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

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

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

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

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

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

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

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

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

12. Questions

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

13. References

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

10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: Approximate Blood Volume Tables

Panels A, B, and D	Prestudy	Treatment Periods	Poststudy	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Tests	2	1	1	4	10.5	42
Serum hCG (POCBP only)	2	-	1	3	4	12
Serum FSH (postmenopausal PONCBP only)	1	-	-	1	4	4
HIV/Hepatitis Screen (per site SOP)	1	-	-	1	9	9
Chemistry test for Second Creatinine Value (if conducted between Screening Visit 1 and Day 1 Predose)	1	-	-	1	8	8
Blood for MK-0616	-	15	1	16	3	48
Blood for Plasma PCSK9 (free)	-	4	1	5	3	15
Blood for Planned Genetic Analysis	-	1	-	1	8.5	8.5
Approximate Total Blood Volume per Male Participant for Panels A, B, and D[a]						**130.5**
Approximate Total Blood Volume per POCBP for Panels A, B, and D[a]						**142.5**
Approximate Total Blood Volume per PONCBP for Panels A, B, and D[a]						**134.5**

FSH=follicle-stimulating hormone; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; POCBP=participant of childbearing potential; PONCBP=participant of non-childbearing potential; SOP=standard operating procedure

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

Panel C	Prestudy	Treatment Periods	Poststudy	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Tests	2	3	1	6	10.5	63
Serum hCG (POCBP only)	2	1	1	4	4	16
Serum FSH (postmenopausal PONCBP only)	1	-	-	1	4	4
HIV/Hepatitis Screen (per site SOP)	1	-	-	1	9	9
Blood for MK-0616	-	40	1	41	3	123
Blood for Plasma PCSK9 (free)	-	8	1	9	3	27
Blood for Planned Genetic Analysis	-	1	-	1	8.5	8.5
Approximate Total Blood Volume per Male Participant for Panel C[a]						**230.5**
Approximate Total Blood Volume per POCBP for Panel C[a]						**246.5**
Approximate Total Blood Volume per PONCBP for Panel C[a]						**234.5**

FSH=follicle-stimulating hormone; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; POCBP=participant of childbearing potential; PONCBP=participant of non-childbearing potential; SOP=standard operating procedure

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

10.9 Appendix 9: 12-Lead Electrocardiogram Evaluation Criteria

	Screen Failure Criteria	Potentially Significant Postallocation Findings
RHYTHM		
Sinus Tachycardia	>110 bpm	HR >110 bpm and HR increase of ≥25 bpm from baseline
Sinus Bradycardia	<40 bpm	HR <40 bpm and HR decrease of ≥5 bpm from baseline
Sinus Pause/Arrest	>2.0 seconds	>2.0 seconds
Atrial Premature Complex	>1 beat	≥3 beats
Ventricular Premature Complex	All	≥3 beats
Ectopic Atrial Rhythm	None	None
Junctional Rhythm	Junctional Rhythm with HR <40 bpm	Junctional Rhythm with HR <40 bpm
Idioventricular Rhythm	All	All
Atrial Fibrillation	All	All
Atrial Flutter	All	All
Supraventricular Tachycardia	All	All
Ventricular Tachycardia	All	All
AXIS		
Left Axis Deviation	RBBB With LAHB	New Onset LAHB
Right Axis Deviation	RBBB With LPHB	New Onset LPHB
CONDUCTION		
1st Degree AV Block	PR ≥230 ms	PR ≥230 ms + Increase of >15 ms; or PR Increase of >25%
2nd Degree AV Block	Mobitz Type II	Mobitz Type II
3rd Degree AV Block	All	All
LBBB	All	All
RBBB	RBBB With LAHB/LPHB as Defined Above	New Onset RBBB (Not Including Rate-related)
ICRBBB (QRS <120 ms)	No Exclusion	Nothing
Short PR/Preexcitation Syndrome	Delta Wave + PR <120 ms	Delta Wave + PR <120 ms
Other Intraventricular Conduction Delay	QRS ≥130 ms	QRS ≥130 ms + Increase of ≥10 ms
QTc (B or F)		
Male	QTc ≥470 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
Female	QTc ≥480 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
HYPERTROPHY		
Atrial Abnormalities	Definite Evidence of P Mitrale or P Pulmonale	Definite Evidence of P. Mitrale or P. Pulmonale
Ventricular Abnormalities	Voltage Criteria for LVH Plus Strain Pattern	Voltage Criteria for LVH Plus Strain Pattern
MYOCARDIAL INFARCTION		
Acute or Recent	All	All
Old	All	All

	Screen Failure Criteria	**Potentially Significant Postallocation Findings**
ST/T MORPHOLOGY		
ST Elevation Suggestive of Myocardial Injury	In 2 or more contiguous leads	In 2 or more contiguous leads
ST Depression Suggestive of Myocardial Ischemia	In 2 or more contiguous leads	In 2 or more contiguous leads
T-wave Inversions Suggestive of Myocardial Ischemia	In 2 or more contiguous leads	In 2 or more contiguous leads
Nonspecific ST-T Changes (In 2 or More Leads)	No exclusion	In 2 or more contiguous leads
PACEMAKER	**All**	**All**

AV=atrioventricular; bpm=beats per minute; HR=heart rate: ICRBBB=incomplete right bundle branch block; LAHB=left anterior hemiblock; LPHB=left posterior hemiblock; LVH=left ventricular hypertrophy; mm=millimeter; ms=milliseconds, PR=pulse rate; QTcB=QT correction using Bazett's formula; QTcF=QT correction using Fredericia formula; RBBB=right bundle branch block; ST/T=ST-segment/T wave.
Baseline is defined as Predose Day 1.

10.10 Appendix 10: 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 the parameter(s) outlined in the inclusion/exclusion criteria (including repeats 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:
    - The abnormal test may be repeated (refer to items 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.

10.11 Appendix 11: Abbreviations

Abbreviation	Expanded Term
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
Ae	amount excreted
Ae0-24	amount excreted at 0 to 24 hours
Ae_D	amount excreted in dialysate
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
AST	aspartate aminotransferase
AUC	area under the curve
AUC0-inf	area under the curve from 0 to infinity
AUClast	area under the curve last
AV	Atrioventricular/arteriovenous
BMI	body mass index
BP	blood pressure
BSA	body surface area
BT	body temperature
BUN	blood urea nitrogen
CCU	Cardiac care unit
C_D	concentration in dialysate
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	oral clearance
CLr	renal clearance
Cmax	maximum plasma concentration
COVID-19	Coronavirus Disease 2019
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
cr	creatinine
CRF	Case Report Form
CRU	clinical research unit

Abbreviation	Expanded Term
CSR	Clinical Study Report
CTFG	Clinical Trial Facilitation Group
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DPP-4	dipeptidyl peptidase 4
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ESRD	end stage renal disease
FBR	future biomedical research
FDAAA	Food and Drug Administration Amendments Act
Fe	fraction excreted unchanged
FAS	Full Analysis Set
FIH	first in human
FSH	follicle-stimulating hormone
FSR	First Site Ready
GCP	Good Clinical Practice
GI	gastrointestinal
GM	geometric mean
GMR	geometric mean ratio
h	hour
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HD	hemodialysis

Abbreviation	Expanded Term
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ICRBBB	incomplete right bundle branch block
ICU	intensive care unit
ID	identification
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
JRCT	Japan Registry of Clinical Trials
LAHB	left anterior hemiblock
LAM	lactational amenorrhea method
LDL-C	low-density lipoprotein cholesterol
LPHB	left posterior hemiblock
LVH	left ventricular hypertrophy
mAb	monoclonal antibody
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MI	multiple imputation
mm	millimeter
ms	milliseconds
NIMP/AxMP	noninvestigational/auxiliary medicinal product
NSAE	nonserious adverse event

Abbreviation	Expanded Term
NSAID	nonsteroidal anti-inflammatory drugs
OBS	observed GMR
P	primary approach
PCL	Protocol Clarification Letter
PCSK9	Proprotein convertase subtilisin/kexin type 9
PK	pharmacokinetic
POCBP	participant of childbearing potential
PONCBP	participant of non-childbearing potential
PP	per-protocol
PR	pulse rate
QTcB	QT correction using Bazett's formula
QTcF	QT correction using Fredericia formula
RBBB	right bundle branch block
RBC	red blood cell
RI	renal impairment
RNA	ribonucleic acid
RNAi	RNA interference
RR	respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
siRNA	short interfering RNA
SLAB	supplemental laboratory test(s)
SoA	schedule of activities
SOP	Standard Operating Procedures
SSRI	selective serotonin uptake inhibitors
ST/T	segment/T wave
SUSAR	suspected unexpected serious adverse reaction

Abbreviation	Expanded Term
THC	Delta-9-tetrahydrocannabinol
Tmax	time to maximum plasma concentration
t1/2	half life
ULN	upper limit of normal
UTN	Universal Trial Number
VS	vital signs
Vz/F	apparent volume of distribution
WBC	white blood cell
WHO	World Health Organization

11 REFERENCES

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