Official Protocol Title:	An Open-Label, Multiple-Dose Clinical Study to Evaluate the Pharmacokinetics of Enlicitide in Participants With Severe Renal Impairment
NCT Number:	NCT06643377
Document Date:	10-Sep-2024

TITLE PAGE

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Protocol Title: An Open-Label, Multiple-Dose Clinical Study to Evaluate the Pharmacokinetics of Enlicitide in Participants With Severe Renal Impairment

Study Number: 032-00

Compound Code(s): MK-0616

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

Legal Registered Address:

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Approval Date: 10 September 2024

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Original Protocol	10-SEP-2024	Not applicable

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: An Open-Label, Multiple-Dose Clinical Study to Evaluate the Pharmacokinetics of Enlicitide in Participants With Severe Renal Impairment

Short Title: Enlicitide Multiple-Dose Renal Impairment Study

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 severe RI and healthy adults.

Primary Objective	**Primary Endpoint**
To compare the steady-state plasma PK of enlicitide following multiple oral 20-mg doses in participants on a background of statin therapy with severe renal impairment to those of healthy mean age, BMI, and sex matched control participants on a background of statin therapy. Hypothesis: The AUC0-24 of enlicitide following multiple doses administered to participants with severe renal impairment is similar to that of healthy matched control participants (ie, the true ratio of the geometric means [severe renal impairment/healthy control participants] will be contained within [0.50, 2.00]).	Plasma enlicitide AUC0-24, Cmax, Tmax, CL/F, and Vz/F
To evaluate the safety and tolerability of the administration of multiple oral doses of enlicitide in participants on a background of statin therapy with severe renal impairment.	Adverse Events, Discontinuations due to Adverse Events
Secondary Objectives	**Secondary Endpoints**
Not applicable	Not applicable

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Hypercholesterolaemia
Population	Participants with severe renal impairment and healthy participants
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	No Control
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 provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Up to 24 participants will be allocated.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Severe Renal Impairment	MK-0616	20 mg	20 mg	Oral	Panel A: QD for 28 days	Test Product
Healthy Mean-Matched Control	MK-0616	20 mg	20 mg	Oral	Panel B: QD for 28 days	Test Product

Other current or former name(s) or alias(es) for study intervention(s) are as follows: MK-0616, enlicitide decanoate.

Total Number of Intervention Groups/Arms	2
Duration of Participation	Each participant will participate in the study for approximately 10 weeks from the time the participant provides documented informed consent through the final contact. After a screening period of up to 4 weeks, each participant will receive assigned study intervention for approximately 4 weeks. After the end of treatment each participant will be followed for 2 weeks.

Study Governance Committees:

Executive Oversight Committee	No
External 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.

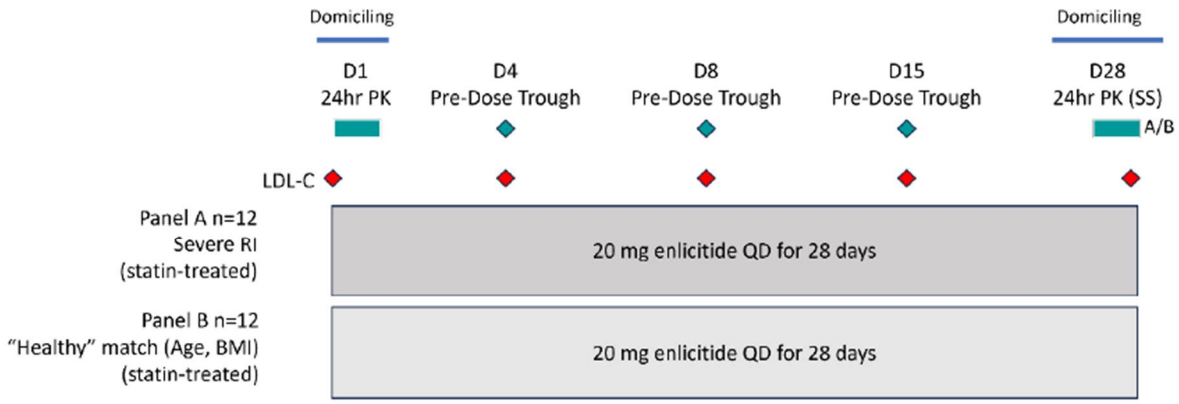
Study Accepts Healthy Participants: Yes

A list of abbreviations is in Appendix 11.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



24hr PK=6 time point collections during the 24hr post dose timeframe; BMI=body mass index; D=Day; LDL-C=low density lipoprotein-cholesterol; PK=pharmacokinetic(s); QD=once a day; RI=renal impairment; SS=steady state

1.3 Schedule of Activities

All Panels																			
Study Period:	**Screening/Rescreening[a]**			**Intervention**														**Post-study[b]**	
Scheduled Day	**Up to D-28**		**D-1**	**D1**							**D2**		**D4**	**D8**	**D15**	**D27**	**D28**	**Post-study**	**Notes**
Hour	**Screening Visit 1**	**Screening Visit 2[c]**	**Check-in**	**Pre-dose**	**0**	**0.5**	**1**	**3**	**4**	**8**	**24**	**30**	**72**	**168**	**336**	**624**	**648**	**~14 days post last dose**	
Administrative/Study Procedures																			
Informed Consent	X																		Sec. 5.1, 8.1.1.1 Includes optional Additional Research Consent Sec. 8.1.1.2
Inclusion/Exclusion Criteria	X	X	X	X															Sec. 5.1, 5.2, 8.1.2
Participant ID Card	X			X															Sec. 8.1.3
Medical History	X			X															Substances: Drugs, alcohol, tobacco, and caffeine; (includes substance usage) 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																Sec. 5.5, 8.1.7

All Panels																			
Study Period:	**Screening/Rescreening[a]**			**Intervention**														**Post-study[b]**	
Scheduled Day	**Up to D-28**		**D-1**	**D1**							**D2**		**D4**	**D8**	**D15**	**D27**	**D28**	**Post-study**	**Notes**
Hour	**Screening Visit 1**	**Screening Visit 2[c]**	**Check-in**	**Pre-dose**	**0**	**0.5**	**1**	**3**	**4**	**8**	**24**	**30**	**72**	**168**	**336**	**624**	**648**	**~14 days post last dose**	
Enlicitide Administration In-Clinic[d]					X						X		X	X	X		X		Sec. 6.4, 8.1.8
Enlicitide Administration at Home[d]																X			Sec. 6.4, 8.1.8
Study Intervention (Enlicitide) Bottle Dispensing for At Home Dosing											X			X	X				Sec. 8.1.8
Participant Visit to CRU	X	X	X										X	X	X	X		X	Sec. 8.1.8
Domiciling[e]			X----------X													X------X			Sec. 8.1.11
Standard Meals[f]						X----------X											X		Sec. 5.3.1
Study Intervention Compliance/Diary Review[g]													X	X	X	X			Sec. 6.4, 8.1.8, 8.1.11
Daily Phone Contact[h]													X----------X						Sec. 6.4
Safety Procedures																			
Full physical examination	X		X[i]								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, RR, BT)	X			X[j]				X			X			X	X		X	X	Sec. 8.3.2, 8.3.2.1

All Panels																			
Study Period:	**Screening/Rescreening[a]**			**Intervention**														**Post-study[b]**	
Scheduled Day	**Up to D-28**		**D-1**	**D1**							**D2**		**D4**	**D8**	**D15**	**D27**	**D28**	**Post-study**	**Notes**
Hour	**Screening Visit 1**	**Screening Visit 2[c]**	**Check-in**	**Pre-dose**	**0**	**0.5**	**1**	**3**	**4**	**8**	**24**	**30**	**72**	**168**	**336**	**624**	**648**	**~14 days post last dose**	
Orthostatic VS (HR, BP)	X			X[j]				X			X							X	Sec. 8.3.2.2
12-lead ECG	X			X[j]				X			X			X	X		X	X	Sec. 8.3.3, Appendix 9
Serum or Urine Pregnancy Test (hCG) - POCBP only	X		X[i]															X	Sec. 5.1, 8.3.5, Appendix 2
Serum FSH – postmenopausal PONCBP only	X																		Appendices 2, 5, 8
HIV, hepatitis B and C screen (per site SOP)	X																		Sec. 5.2, 8.3.4, Appendices 2, 8
Drug screen	X		X[i]																Results to be reviewed prior to dosing. Sec. 5.2, 8.3.4, Appendix 2
Hematology	X		X[i]								X			X	X		X	X	Sec. 8.3.4, Appendices 2, 8
Chemistry	X	X	X[i]								X			X	X		X	X	Sec. 8.3.4, Appendices 2, 8
Urinalysis	X		X[i]								X			X	X		X	X	Sec. 8.3.4, Appendix 2
AE/SAE review	X----------X																		Sec. 8.4, Appendix 3

Confidential

All Panels																			
Study Period:	**Screening/Rescreening[a]**			**Intervention**														**Post-study[b]**	
Scheduled Day	**Up to D-28**		**D-1**	**D1**							**D2**		**D4**	**D8**	**D15**	**D27**	**D28**	**Post-study**	**Notes**
Hour	**Screening Visit 1**	**Screening Visit 2[c]**	**Check-in**	**Pre-dose**	**0**	**0.5**	**1**	**3**	**4**	**8**	**24**	**30**	**72**	**168**	**336**	**624**	**648**	**~14 days post last dose**	
Pharmacokinetics																			
Blood for Plasma Enlicitide Assay[k]				X			X	X		X	X			X	X		X		Sec. 8.6.1, 8.8, 8.10.5, Appendix 8
Pharmacodynamics / Biomarkers																			
Blood for Plasma LDL-C Assay[l]				X										X	X		X		Sec. 8.7, Appendix 8
Blood for Plasma Biomarkers[l]				X										X	X		X		Sec. 8.8, Appendix 8 PCSK9 (free) may be evaluated from this sample
Blood for Genetic Analysis				X															The blood draw should be obtained predose on Day 1 but may be collected at the next scheduled blood draw, if needed from enrolled participants only. Sec. 8.8, Appendix 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; D=day; ECG=electrocardiogram; eGFR=estimated glomerular filtration; FSH=follicle-stimulating hormone; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; HR=heart rate; ID=identification; LDL-C=low density lipoprotein cholesterol; PCSK9=proprotein convertase subtilisin/kexin type 9; PK=pharmacokinetic(s); POCBP=participant of childbearing potential; PONCBP=participant of nonchildbearing potential; QD=once daily; RR=respiratory rate; SAE=serious adverse event; Sec.=section; SOP=standard operating procedure; VS=vital signs.

[a] Rescreening is defined as a separate screening period. All activities conducted during Screening 1 (and 2, if applicable) must be completed as part of Rescreening. See Section 8.10.1.

[b] Poststudy Visit should occur approximately 14 days after the last dose of study intervention. If the visit occurs prior to 14 days, verbal contact should be made to assess for AEs 14 days after the last dose of study intervention.

[c] Screening Visit 2 is optional as baseline eGFR must 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). Data must be available before dosing on Day 1 to confirm eligibility.

[d] QD dosing will occur in the morning at approximately the same time each day. When dosing occurs in the clinic, including when participants are kept domiciled, site staff will witness ingestion of the dispensed study intervention. When participants are not in the CRU (including on Day 27), dosing will occur at home and record the dose in the diary.

[e] All participants will report to the CRU on Day -1, at the time indicated by the CRU (~ 24 hours prior to dosing on Day 1) and all participants will be discharged after completion of the 24-hour postdose procedures on Day 2. All participants will report to the CRU on Day 27, at the time indicated by the CRU (~ 24 hours prior to dosing on Day 28) and all participants will be discharged after completion of the 24-hour postdose procedures.

[f] 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.

[g] Participants should bring the diary when returning to the CRU for study intervention compliance checks. The site may determine if participants should return to the CRU more frequently for compliance checks.

[h] While participants are dosing at home, site staff will contact participants daily to check study intervention administration compliance, review AEs, and remind participants of their next scheduled clinic visit (as applicable).

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

[j] Predose VS and 12-lead ECG to be measured within 3 hours prior to study intervention administration. Semirecumbent Day 1 predose VS (HR and BP) and 12-lead ECG measurements will be done in triplicate. All other scheduled timepoints and measurements, including Screening VS and Screening 12-lead ECG, and Day 1 Predose RR and BT, will be single measurements.

[k] PK samples will be drawn as follows:
Day 1: PK samples will be drawn predose, 1, 3, 8, and 24-hours postdose
Days 8 and 15: PK samples will be drawn predose
Day 28: PK samples will be drawn at predose, 1, 3, 8, and 24-hours postdose

[l] Samples will be collected predose.

2 INTRODUCTION

2.1 Study Rationale

Enlicitide is an oral small molecule cyclic peptide inhibitor of PCSK9 being developed for the treatment of hypercholesterolaemia. Enlicitide is a low clearance drug which is excreted primarily by renal clearance. As such, this study is being conducted to assess the impact of severe RI on the steady-state PK of enlicitide.

2.2 Background

Refer to the IB for detailed background information on enlicitide.

2.2.1 Pharmaceutical and Therapeutic Background

Enlicitide decanoate (historically referred to as MK-0616, and referred to as "enlicitide" throughout this protocol) is a cyclic peptide inhibitor of PCSK9 being developed for reduction of LDL-C. Enlicitide is excreted as unchanged parent predominately through renal clearance.

2.2.2 Ongoing Clinical Studies

MK-0616-028

This study is an open-label, randomized, 2-way crossover, 1-way DDI study to assess the effect of single-dose enlicitide (20-mg tablet) on the single-dose PK of levothyroxine in healthy adult participants. Approximately 28 participants will be enrolled. On Day 1 of each period, a single oral dose of levothyroxine will be administered alone (Treatment A) or with a single oral dose of enlicitide (Treatment B). There will be a washout period of at least 35 days between dosing in each period.

Other Ongoing Studies

Please refer to the IB for information on other ongoing studies.

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 severe RI and healthy adults.

Primary Objectives	**Primary Endpoints**
To compare the steady-state plasma PK of enlicitide following multiple oral 20-mg doses in participants on a background of statin therapy with severe renal impairment to those of healthy mean age, BMI, and sex matched control participants on a background of statin therapy. Hypothesis: The AUC0-24 of enlicitide following multiple doses administered to participants with severe renal impairment is similar to that of healthy matched control participants (ie, the true ratio of the geometric means [severe renal impairment/healthy control participants] will be contained within [0.50, 2.00]).	Plasma enlicitide AUC0-24, Cmax, Tmax, CL/F, and Vz/F
To evaluate the safety and tolerability of the administration of multiple oral doses of enlicitide in participants on a background of statin therapy with severe renal impairment.	Adverse Events, Discontinuations due to Adverse Events
Secondary Objectives	**Secondary Endpoints**
Not applicable	Not applicable
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
[redacted]	


CCI

4 STUDY DESIGN

4.1 Overall Design

This is a non-randomized, parallel-group, multi-site, open-label study of enlicitide in adult male and female participants with severe RI (Panel A) and healthy mean age, BMI, and sex matched control participants (Panel B), all on a background of statin therapy. The study will evaluate safety, PK, and pharmacodynamic effects of multiple QD oral 20 mg doses of enlicitide for a total of 28 days of dosing, consisting of 2 panels (Panels A and B). Both panels will be comprised of 12 participants who will receive multiple doses of enlicitide. Healthy control participants will be matched for mean age (± 15 years) and BMI (± 3.5 kg/m^2) of participants with severe RI. In addition, the ratio of males and females of the healthy participants will be matched to the ratio of males and females of severe RI participants within ± 2. Enrollment into the healthy mean matched control panel (Panel B) will begin once 8 participants with severe RI have been enrolled. Up to an additional 4 healthy participants may be enrolled as needed, to maintain the mean-matching of the healthy participant panel to the severe RI panel.

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

Table 1 Renal Function Group

Panel	**Renal Function Group**	**n**	**eGFR (mL/min)[a,b]**
A	Severe	12	<30 not on dialysis[c]
B	Healthy	12[d]	≥90

BSA=body surface area; CKD-EPI=Chronic Kidney Disease - Epidemiology Collaboration; cr=creatinine; eGFR=estimated glomerular filtration rate; RI=renal impairment

[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 the 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 the participant BSA.

[c] Reasonable efforts will be made to enroll at least 2 to 3 participants in the severe RI group who have eGFR values of 10 to 20 mL/min.

[d] May need to enroll more than 12 to enable mean matching of the healthy mean match control participants to the participants with severe RI.

All participants will receive multiple QD oral 20-mg doses of enlicitide for a total of 28 days of dosing. All doses of enlicitide 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 doses). Participants will self-administer enlicitide at home, when not in the CRU.

All participants will be admitted to the CRU on Day -1. Starting on Day 1, participants will have a predose PK sample drawn and will then begin receiving multiple QD oral 20-mg doses of enlicitide for a total of 28 days of dosing. On Study Day 1, PK samples will be drawn at multiple timepoints postdose and participants will remain in the clinic until 24 hours postdose for PK sampling. There will be additional outpatient visits through 28 days for PK and safety assessments. On Study Day 27, participants will be admitted to the CRU at the time indicated by the CRU, in preparation for predose procedures and dosing on Day 28. On Study Day 28, PK samples will be drawn predose and at multiple timepoints through 24 hours postdose in the clinic. There will be a follow up visit approximately 14 days after the last dose of enlicitide. Safety will be monitored throughout the study by repeated clinical and laboratory evaluations.

Because this is a Phase 1 assessment of enlicitide 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 8.10.6 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

A single dose PK study (Protocol 020) was performed in statin-treated participants with moderate RI, severe RI, ESRD on hemodialysis and mean matched control participants who were also taking statins to control cholesterol. In that study, preliminary PK results indicated that single dose exposure of enlicitide CCI [redacted] CCI [redacted] The single dose exposure in severe RI CCI [redacted] This study is being conducted to assess the impact of severe RI on the steady-state PK of enlicitide.

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

PK parameters selected for evaluation in this study will effectively inform the PK profile of enlicitide and include the following: AUC0-24, Cmax, Tmax, CL/F, and Vz/F.

4.2.1.4 CCI

CCI

4.2.1.5 CCI

CCI

4.2.1.6 Additional Research Rationale

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

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 these purposes is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time.

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 severe RI 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 enlicitide is 20 mg taken once daily. Once daily doses of enlicitide, administered for 4 weeks, will be sufficient to assess the effect of severe RI on the steady-state PK of enlicitide. In healthy participants, the steady-state AUC0-24 is anticipated [redacted] Preliminary data from a Phase 1 study that included participants with moderate, severe RI, and ESRD on HD (MK-0616-020) suggests that enlicitide exposure after a single dose [redacted] The plasma exposure of enlicitide in [redacted] Based on the population PK model that was developed using available Phase 1 and Phase 2 data, the steady-state AUC0-24 (AUCss) for participants with eGFR = 20 ml/min/1.73 m^2 is projected to [redacted] As such, the maximum steady-state Cmax and AUC0-24 in this study are anticipated to be [redacted] In the Phase 2b study, participants in [redacted]

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 enlicitide. In P008 (Phase 2b study), at the 18 mg dose, [redacted]

CCI [redacted] Therefore, we do not plan to limit or restrict participants to a particular dose level (ie, high/medium/low intensity statin), beyond the requirement to remain on a stable dose of 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.

As this is a Phase 1 assessment of enlicitide 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 8.10.6.

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), or the last participant on active treatment is consented in the extension study. 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, 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 hypercholesterolemia **for participants in Panels A and B, and RI for participants in Panel A**. Participants that have stable, chronic medical or psychiatric conditions, including but not limited to hypertension, 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 B)**.
2. Be in good health based on laboratory safety tests obtained at the screening visit and before administration of the initial dose of study intervention, with the exception of hypercholesterolemia **for participants in Panels A and B, and RI for participants in Panel A**. 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 between 18 and 40 kg/m^2, inclusive. See Section 8.3.1 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height $(m)^2$.
   Healthy Participants (Panel B): BMI must be ± 3.5 kg/m^2 of the mean BMI of participants within the severe RI panel.
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 severe RI (Panel A): <30 mL/min (but not on dialysis);

   For healthy participants (Panel B): ≥90 mL/min;

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

   $$eGFR_{cr} = 142 \times \min(S_{cr}/K,1)^{\alpha} \times \max(S_{cr}/K, 1)^{-1.200} \times 0.994^{Age} \times 1.012 \text{ [if female]}$$

   where S_{cr} 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 S_{cr}/k or 1, max indicates the maximum of S_{cr}/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 (ie, on Day -1) 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.

Demographics

6. Is an individual of any sex/gender, from 18 years to 85 years of age inclusive, at the time of providing the informed consent. Follow local regulatory requirements if the legal age of consent for participation is >18 years of age.

   Healthy Participants (Panel B): Age must be within ± 15 years of the mean age of participants within the severe RI panel.

Assigned Female Sex at Birth

7. Participants assigned female sex at birth are eligible to participate if:
   - they are a PONCBP, as defined in Appendix 5.

8. A participant assigned female sex at birth is eligible to participate if not breastfeeding during the study intervention period and for at least 8 weeks after the last dose of study intervention enlicitide.
9. A POCBP is eligible to participate if not pregnant and if a negative highly sensitive pregnancy test (urine or serum), as required by local regulations, has been obtained 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. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.5.

10. A POCBP is eligible to participate if they use an acceptable contraceptive method or if they adhere to penile-vaginal intercourse abstinence 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.

Note: The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recent initiation) 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 local contraception requirements for any of the study interventions are more stringent than the requirements above, the local requirements are to be followed. Medical history, menstrual history, and recent sexual activity should be reviewed by the investigator to decrease the risk for inclusion of a POCBP with an early undetected pregnancy.

Informed Consent

11. The participant has provided documented informed consent.

Additional Categories

12. 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. 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 GI 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. **Participants with RI (Panel A):** History of any illness, other than hypercholesterolemia and 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. **Healthy Participants (Panel B):** History of clinically significant endocrine, GI, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or diseases, other than hypercholesterolemia. Participants with a remote history of uncomplicated medical events may be enrolled in the study at the discretion of the investigator.

7. 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.
8. History of cancer (malignancy). Participants with definitively treated disease who, in the opinion of the study investigator, are highly unlikely to have a recurrence for the duration of the study may be enrolled at the discretion of the investigator.
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 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 positive hepatitis C antibodies due to resolved disease may be enrolled at the discretion of the investigator, only if a confirmatory negative hepatitis C RNA test is obtained, and there is no clinical evidence of infection or possible recent exposure.
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. **Participants with RI (Panel A):** 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. 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 for allowed medical conditions, and Section 6.5. for allowed medications.
15. **Healthy Participants (Panel B):** Unable to refrain from or anticipates the use of any medication (other than statins), including prescription and nonprescription drugs or herbal remedies beginning approximately 2 weeks (or 5 half-lives) prior to administration of the initial dose of study intervention, throughout the study, until the poststudy visit. There may be certain medications that are permitted (see Section 6.5).

Prior/Concurrent Clinical Study Experience

16. 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

17. **Participants with RI (Panel A):** The participant meets the following criteria for ECG:
    - Heart rate <40 or >110 bpm
    - QTc interval >500 msec
    - Any significant arrythmia or conduction abnormality, including but not specific to atrioventricular block [second 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).
18. **Healthy Participants (Panel B):** QTc interval ≥470 msec (for males) or ≥480 msec (for females).

Other Exclusions

19. Under the age of legal consent.
20. **Participants with RI (Panel A):** Does not agree to follow the smoking restrictions as defined by the CRU.
21. **Healthy Participants (Panel B):** 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.
22. Consumes greater than 3 servings of alcoholic beverages (1 serving is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day. Participants who consume 4 servings of alcoholic beverages per day may be enrolled at the discretion of the investigator.
23. Consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.
24. **Participants with RI (Panel A):** 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.
25. **Healthy Participants (Panel B):** 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.

26. Is unwilling to comply with the study restrictions (see Section 5.3 for a complete summary of study restrictions).
27. 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.

28. 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

On f**ull PK sampling days (ie, Days 1 and 28)**, all participants (Panels A and B) 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 investigator 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 of meals will be the same on each full PK sampling day in each panel, 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 required. Water will be restricted 1 hour before and 30 minutes after study intervention administration.

After at least 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.

On **intermediate days (ie, Days 2 to 27)**, all participants (Panels A and B) will fast from all food and drinks, except water, for at least 8 hours before study intervention administration.

Participants will remain fasted until at least 30 minutes postdose. Meals and snacks will be unrestricted in caloric content, composition, and timing.

Each study intervention administration will need to be taken with approximately 240 mL of water. Additional water may be provided in 50-mL increments if required. Water will be restricted 1 hour before and 30 minutes after study intervention administration.

Instructions on whether to take enlicitide 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 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 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 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 on **full PK sampling days (ie, Days 1 and 28)**.
- 12 hours before poststudy visit.

On **intermediate days (Days 2 to 27)**, and 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 Screening Visit 1. A recheck may be needed if participants did not refrain from consuming alcohol 24 hours prior to Screening Visit 1.

Participants will refrain from consumption of alcohol from:

- 24 hours before the Screening 2 Visit.
- 24 hours before and after study intervention administration **on full PK sampling days (ie, Days 1 and 28)**.
- 24 hours before poststudy visit.

On **intermediate days (Days 2 to 27)** and 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

Participants with RI (Panel A): Participants will follow the smoking restrictions (and if applicable, the use of nicotine/nicotine-containing products) defined by the CRU.

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

5.3.3 Activity Restrictions

Participants 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, 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 allocated 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.

Participants may be rescreened as appropriate, per Section 8.10.1.

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 assignment of 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.

Global clinical supply complaints and/or temperature excursions are to be reported to the Clinical Complaints Intake mailbox, via email to clinical.complaints.intake@MSD.com.

6.1 Study Intervention(s) Administered

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

Country-specific requirements are noted in Appendix 7.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	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
Severe Renal Impairment	Experimental	MK-0616	Drug	Tablet	20 mg	20 mg	Oral	Panel A: QD for 28 days	Test Product	IMP	Provided centrally by Sponsor
Healthy Mean-Matched Control	Experimental	MK-0616	Drug	Tablet	20 mg	20 mg	Oral	Panel B: QD for 28 days	Test Product	IMP	Provided centrally by Sponsor

EEA=European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product; QD=once daily.
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 will be allocated by nonrandom assignment according to a computer-generated allocation schedule.

A sample allocation table is provided below in Table 3.

Table 3 Allocation of Participants to Treatment

Number of Participants	Treatment
Panel A: Severe RI	
n=12	20 mg enlicitide QD for 28 days
Panel B: Healthy Mean-Match	
n=12	20 mg enlicitide QD for 28 days
QD=once daily; RI=renal impairment.	

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.

In-Clinic Dosing:

When dosing occurs in-clinic (for selected in-clinic days, including when participants are kept domiciled overnight), site staff will administer study intervention and study-site personnel will examine each participant's mouth to ensure that the study intervention was ingested. The date and time of each dose administered in the clinic will be recorded in the diary/source documents and recorded in the CRF.

At-home Dosing:

- When participants self-administer study intervention at home, compliance with study intervention will be assessed at each return visit. Compliance will be assessed by direct questioning, counting returned tablets, daily phone contact while participants are dosing at home, site review of the completed diary, and documented in the source documents and CRF. The site may determine if participants should return to the CRU more frequently for compliance checks. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.
- A record of the number of enlicitide tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates will also be recorded in the CRF.

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 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.

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 (Panel A):

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.

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. 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

6.6.1.1 Study 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), an amendment will be submitted for approval.

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

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 a PCL (only applicable if not all procedures should be done per Section 1.3).

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 2 or more cumulative missed doses.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- The participant has a positive drug screen at any time during the course of the study (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.

Discontinuation from study intervention is "permanent." Once a participant is discontinued from study intervention, they shall not be allowed to restart study intervention.

7.2 Participant Withdrawal From the Study

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

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

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

7.3 Lost to Follow-up

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before 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. If there are changes to the participant's status during the study (eg, age of majority requirements or health), the investigator or medically qualified designee must ensure the appropriate documented informed consent from the participant (or their legally acceptable representative) 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 Additional Research

The investigator or medically qualified designee will explain the optional Additional Research to the participant, or the participant's legally acceptable representative, answer all their questions, and obtain documented informed consent before performing any procedure related to Additional Research. A copy of the informed consent will be given to the participant before performing any procedure related to this research.

The original full consent including Additional Research, any subsequent revised version, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. If new information becomes available, which may be relevant to the participant's willingness to continue participation in this research, the participant or their legally acceptable representative should be informed in a timely manner.

If the IRB/IEC does not provide approval, the study may proceed without Additional Research and participants will not be consented for this research.

If the Additional Research consent is under review or unavailable, then the FBR consent is to be used.

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 prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 14 days before the 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 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 8.10.1. 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

The first dose of study intervention will be administered at the study site on Study Day 1. Subsequent dosing will be performed once daily, in-clinic (for selected in-clinic days, including when participants are kept domiciled overnight) or at home, at approximately the same time each day as described in Section 1.3.

Participants will receive a bottle of study intervention at the visits described in Section 1.3 for at home dosing. When participants return to the CRU, the study intervention bottle will be collected.

Each bottle dispensed will contain enlicitide. Participants will be instructed on how to administer study intervention by the site staff, and participants will be instructed to record dosing and fasting information in the diary.

8.1.8.1 Timing of Dose Administration

All doses of enlicitide will be given in the morning at approximately the same time each day.

The study intervention will be administered with approximately 240 mL of water following at least an 8-hour overnight 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.

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 8.10.4 to have the applicable procedures conducted. However, the investigator may decide to perform the poststudy procedures at the time of discontinuation or as soon as possible after discontinuation. If the poststudy visit occurs prior to the safety follow-up time frame as specified in Section 8.4.1, 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 Additional Research

Participants may withdraw from Additional Research. 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 this research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed 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

Panels A and B:

Participants will report to the CRU on Day −1 before the scheduled day of study intervention (enlicitide) administration on Day 1 and remain in the unit until 24 hours postdose on Day 2. On Day 27, participants will report to the CRU and remain in the unit through completion of Day 28 procedures (ie, through 24 hour postdose PK sample draw).

At the discretion of the investigator, participants may be requested to remain in the CRU longer.

Participants may be permitted to leave the unit, for emergency situations only, during the domiciling period at the discretion of the investigator after discussion with the Sponsor. The decision how to monitor the participant will be at the discretion of the investigator after discussion with the Sponsor.

Study staff will witness dosing and diary completion when the participants are in the CRU. When dosing occurs in the clinic, including when participants are kept domiciled, site staff will administer study intervention, and site staff will witness ingestion of the dispensed study intervention.

8.1.12 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably

calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy Assessments

There are no direct efficacy assessments in this study.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood to be drawn/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 the 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 enlicitide. 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 procedures.

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 B), 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. Participants may need to remove interfering garments.

Participants should be resting in the semirecumbent 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 may be marked on the skin of each participant with an ECG skin-marker pen to ensure reproducible electrode placement.

Day 1 predose ECGs will be obtained in triplicate at least 1 minute apart within 3 hours before dosing enlicitide. 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 study, 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.

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.

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

Type of Event	**Reporting Period: Consent to Randomization/ Allocation**	**Reporting Period: Randomization/ 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

Type of Event	**Reporting Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ 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
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 (unless an SAE)
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 (unless an SAE)

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. 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). The investigator will also make every attempt to follow 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:

- An overdose of Sponsor’s product, as defined in Section 8.5.

- 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 study intervention administered that exceeds the dose prescribed by the protocol.

It is up to the investigator or the reporting physician to decide whether a non-study intervention dose (eg, rescue or concomitant medication) is to be considered an overdose, with notification of the Sponsor.

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

8.6 Pharmacokinetics

The decision as to which plasma samples collected will be measured for evaluation of PK/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. See Section 8.8.

8.6.1 Blood Collection for Plasma Enlicitide Assay

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

8.7 Pharmacodynamics

Sample collection, storage, and shipment instructions for pharmacodynamic samples (LDL-C) will be in the Study Operations Manual.

Exploratory PD Parameters may be assessed in samples described in Section 8.8.

8.8 Biomarkers

To identify novel biomarkers, CCI [redacted] as specified in the SoA (Sec. 1.3):

- Blood for genetic analysis
- Blood for Plasma Biomarkers (eg, plasma for the PCSK9 (free) Assay will be stored and analysis may be performed based upon PK results)
- Leftover PK for Exploratory Biomarkers

Sample collection, storage and shipment instructions for the exploratory biomarker specimens will be provided in the Study Operations Manual.

8.8.1 Genetic Analysis Specimen Collection

The genetic analysis specimen should be collected CCI [redacted] This specimen will not be collected at the site if the IRB/IEC does not approve the collection based on a local law or regulation. If the specimen is collected, leftover extracted DNA will be stored for Additional Research if the participant provides documented informed consent for this research. If genetic analysis is not approved as part of the study, this specimen will be collected under a separate optional informed consent.

The genetic analysis specimen should be obtained pre-dose on Day 1 but may be collected at the next scheduled visit, if needed. Specimen collection, storage, and shipment instructions for genetic analysis specimens will be in the Study Operations Manual.

8.9 Additional Research

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

If the participant has provided documented informed consent for Additional Research, the following leftover specimens will be included for Additional Research:

- Leftover specimens listed in Section 8.8

8.10 Visit Requirements

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

8.10.1 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.

Rescreening is defined as a separate screening period and can be initiated as appropriate, including for screen failures (Section 5.4). Rescreening is to include all screening procedures listed in the SoA (Section 1.3), including consent review. Rescreen procedures cannot be conducted the day prior to intervention allocation if there are Day −1 procedures planned per protocol.

8.10.2 Treatment Period Visit

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

8.10.3 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 a PCL.

8.10.4 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.

8.10.5 Critical Procedures Based on Study Objectives: Timing of Procedure

For this study, the blood sample for the enlicitide assay is the critical procedure.

At any postdose time point, the blood sample for the enlicitide assay 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. The order of procedures should occur as follows: Vitals>ECG>PK sampling>Safety Labs>UA.

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) Collection Windows (Panels A and B)

Study Day	PK Collection	PK Collection Window
Day 1	Predose	≤3 hours
	1 to <24 hours	±15 minutes
	24 hours	±1 hour
Days 8 and 15	Predose	≤3 hours
Day 28	Predose	≤3 hours
	1 to <24 hours	±15 minutes
	24 hours	±1 hour
PK=pharmacokinetic		

Predose and Postdose Procedures

- Predose standard safety evaluations (Days 1, 2, 8, 15, and 28): 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
  - Prior to 24-hours postdose may be obtained within 15 minutes of the theoretical sampling time
  - At 24-hours postdose may be obtained within 1 hour of the theoretical sampling time
  - Poststudy evaluation must be obtained within 48 hours of the theoretical sampling time
- Note: Visit windows defined by ±X day(s) refers to calendar days.

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

This is a Phase 1 assessment of enlicitide 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.

- Repeat of or decrease in the dose of the study intervention administered in any given panel
- Entire panel(s) may be omitted
- Decrease in the duration of study intervention administration (eg, number of days)
- Adjustment of the dosing interval (eg, divided doses [BID to QD, QD to BID, TID, or vice versa])
- Addition of PK pause
- Instructions to take study intervention with or without food or drink may also be modified based on newly available data
- Modification of the PK/pharmacodynamic sample processing and shipping details based on newly available data

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

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

The timing of procedures for assessment of safety procedures (eg, VS, 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 their 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 details the principal statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to the statistical analysis plan stated below, then these deviations to the plan will be listed, along with an explanation as to why they occurred, in the Clinical Study Report.

9.1 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 Medicine Department of the Sponsor.

9.2 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

Primary:

Hypothesis: The AUC0-24 of enlicitide following multiple doses administered to participants with severe renal impairment is similar to that of healthy matched control participants (i.e., the true ratio of the geometric means [severe renal impairment/healthy control participants] will be contained within [0.50, 2.00]).

Exploratory:

Estimation: Percent reduction from baseline in plasma LDL-C for each population and treatment will be provided at Days 8, 15, and 28. Baseline will be defined as LDL-C collected pre-dose on Day 1.

Estimation: Percent change from baseline in plasma free PCSK9 for each population and treatment will be provided at Days 8, 15, and 28. Baseline will be defined as PCSK9 collected pre-dose on Day 1.

9.3 Analysis Endpoints

Safety and pharmacokinetics/pharmacodynamics endpoints that will be evaluated are listed below.

9.3.1 Primary Endpoints

Pharmacokinetics: Plasma enlicitide AUC0-24, Cmax, Tmax, CL/F, and Vz/F, collected at Day 28.

Safety: Adverse events, discontinuations due to adverse events.

9.3.2 Secondary Endpoints

Not applicable.

9.3.3 CCI

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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 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 participants or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR. At the end of the study, all participants who are compliant with the study procedure as aforementioned and have available data from at least one treatment will be included in the Per-Protocol dataset. This population will be used for the pharmacokinetics and pharmacodynamics analyses.

9.5 Statistical Methods

9.5.1 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.

The safety evaluation will include a summary by population and treatment of the number and percentage of participants with each type of AE.

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

9.5.2 Statistical Methods for Pharmacokinetic Analyses

Model-Based PK Summary

Plasma PK parameters of AUC0-24 and Cmax at Day 28 will be natural log transformed and evaluated with separate linear fixed effects models containing population (healthy, severe) and a heterogeneous covariance structure for population. Ninety-five percent confidence intervals for the least squares means by population will be constructed on the natural log scale and will reference the t-distribution. Exponentiating the least-squares means and lower and upper limits of these confidence intervals will yield estimates for the population geometric means and confidence intervals about the geometric means on the original scale for each population. Sample code is as follows:

```
proc mixed data=adpp ;
    class population (ref="healthy") subjid ;
    model lnpk=population / s cl=0.10 ddfm=kr ;
    repeated / group=population type=un ;
    lsmeans population / alpha=0.05 cl ;
run ;
```

To address the primary hypothesis for AUC0-24, the least squares mean differences (severe - healthy) and 90% confidence interval from this model will be back-transformed to obtain the geometric mean ratio and 90% confidence interval. If this confidence interval falls within (0.50, 2.00), then the hypothesis of similarity between the severe renal impairment population and the healthy population will be supported.

Descriptive Statistics

Individual values will be listed for each PK parameter by population (healthy, severe) and Day, and the following (nonmodel-based) descriptive statistics will be provided: N (number of participants with nonmissing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 × standard deviation/arithmetic mean), median, minimum, maximum, GM, and geometric percent CV (calculated as 100 × sqrt(exp(s2) - 1), where s2 is the observed variance on the natural log-scale).

9.5.3 Statistical Methods for Pharmacodynamic Analyses

Individual values will be listed for each available PD parameter by population (healthy, severe) and Day, and the following (nonmodel-based) descriptive statistics will be provided: N (number of participants with nonmissing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 × standard deviation/arithmetic mean), median,

minimum, maximum, GM, and geometric percent CV (calculated as 100 × sqrt(exp(s2) - 1), where s2 is the observed variance on the natural log-scale).

9.6 Interim Analyses

Not applicable.

9.7 Multiplicity

Not applicable.

9.8 Sample Size and Power Calculations

The 20mg dose panel (Panel A) from healthy subjects in the multiple dose study MK-0616-003 was used to estimate a log-scale steady-state between subject standard deviation of 0.271 for AUC0-24 on Day 14 of once daily administration of enlicitide. CCI

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If the true steady-state AUC0-24 adjusted geometric mean ratio following administration of once daily 20 mg oral doses of enlicitide for the patients with severe renal impairment is 1.20 times that of the matched healthy control group (GMR=1.20), then a sample size of n=12 treated severe patients and n=12 subjects in the matched healthy control group provide this study with 98.3% probability of observing the 90% CI for the geometric mean ratio (GMR) to be contained within 0.50 to 2.00.

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), Regulation (EU) 536/2014, the 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 their 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 their 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 their 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.

The Sponsor has EU-approved Binding Corporate Rules since 2017, covering all aspects of its Global Privacy Program (Corporate Policy 20), and is self-certified pursuant to the EU-US Data Privacy Framework.

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 (eg, EU CTR: 25 years after the end of the study). 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.
- Laboratory safety tests (hematology and chemistry) will be performed after an approximately 8-hour fast. 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	
Lipid Panel	Total Cholesterol	HDL-C	LDL-C	Triglycerides
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 in 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; HDL-C=high density lipoprotein-cholesterol; HIV=human immunodeficiency virus; LDL-C=low density lipoprotein-cholesterol; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; POCBP=participant of childbearing potential; PONCBP=participant of nonchildbearing potential; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WBC=white blood cell

Notes: Laboratory safety tests will be performed after an approximately 8-hour fast for hematology, chemistry, and lipid panel labs only.

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

- 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.

10.5.2 Contraceptive Requirements for Study Participants Who Are Able to Become Pregnant

Contraceptives allowed during the study include:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only contraceptive implant • IUS [a] • 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 *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception - 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 [c] • 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] IUS is a progestin releasing IUD [b] 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) [c]

10.6 Appendix 6: Exploratory Biomarkers

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.

Confidential Participant Information for Biomarker Research [1]

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

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

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

Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses using biomarker 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 the protocol and consent. Biomarker specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

Retention of Specimens

Biomarker and other specimens will be stored in the biorepository for potential analysis for up to 15 years from the end of the study. If there are regulatory or governmental authority questions that are being answered, specimens may be stored for longer. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

The specimens will be stored in a limited access facility that operates to assure the integrity of the specimens and under strict supervision. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

Data Security

Databases containing specimen information and research 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.

Reporting of Exploratory Research Data to Participants

Results obtained from genetic and biomarker research will not be given to study participants or the trial doctor.

If important research findings are discovered, the Sponsor may share this information by:

- publishing the results in peer-reviewed journals
- presenting the results at national meetings
- providing the results on a publicly accessible website that would be available 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.

Questions

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

References

[1] 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

10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: Approximate Blood Volume Table

Panels A and B	Prestudy	Treatment Periods	Poststudy	Total Collections	mL Per Collection	Total mL/Test
Laboratory Safety Tests	1	5	1	7	10.5	73.5
Chemistry test for second creatinine value (if conducted between Screening Visit 1 and Day 1 Predose)	1	-	-	1	8	8
Serum hCG (POCBP only)	1	1	1	3	4	12
Serum FSH (postmenopausal PONCBP only)	1	-	-	1	4	4
HIV/Hepatitis Screen (per site SOP)	1	-	-	1	9	9
Blood for enlicitide	-	12	-	12	3	36
Blood for Plasma for Lipid Panel (including LDL-C)	-	4	-	4	6	24
Blood for Plasma Biomarkers	-	4	-	4	3	12
Blood for Genetic Analysis	-	1	-	1	8.5	8.5
Approximate Total Blood Volume per Male Participant[a]						**171 mL**
Approximate Total Blood Volume per POCBP[a]						**183 mL**
Approximate Total Blood Volume per Female PONCBP[a]						**175 mL**

FSH=follicle-stimulating hormone; hCG=human chorionic gonadotropin; HIV-human immunodeficiency virus; LDL-C=low density lipoprotein-cholesterol; PK=pharmacokinetic; POCBP=participant of childbearing potential; PONCBP=participant on nonchildbearing potential; SOP=standard operating procedure

[a] If additional PK/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	All	All
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; 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 participant may be excluded from the study.
    - The participant may be included in the study if the abnormal value(s) is NCS (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document).
    - The participant may be included in the study if the abnormality is consistent with a pre-existing medical condition which is not excluded per protocol (eg, elevated eosinophil count in a participant with asthma or seasonal allergies), the medical condition should be annotated on the laboratory report.
    - 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
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUCss	area under the curve at steady state
AUC0-24	area under the curve from 0 to 24 hours postdose
BID	twice daily
BMI	body mass index
BP	blood pressure
BSA	body surface area
CCU	cardiac care unit
CKD-EPI	Chronic Kidney Disease - Epidemiology Collaboration
CL/F	oral clearance
Cmax	maximum plasma concentration
COVID-19	coronavirus disease 2019
cr	creatinine
CRF	Case Report Form
CRU	clinical research unit
CSR	Clinical Study Report
CV	coefficient of variation
DDI	drug-drug interaction
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

Abbreviation	Expanded Term
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ESRD	end-stage renal disease
FDAAA	Food and Drug Administration Amendments Act
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
HD	hemodialysis
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
ICU	intensive care unit
ID	identification
IEC	Independent Ethics Committee
IL-10	interleukin 10
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board

Abbreviation	Expanded Term
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
JRCT	Japan Registry of Clinical Trials
LAM	lactational amenorrhea method
LDL-C	low density lipoprotein-cholesterol
mAb	monoclonal antibody
mRNA	messenger RNA
NCS	not clinically significant
P	protocol (number)
PCL	Protocol Clarification Letter
PCSK9	proprotein convertase subtilisin/kexin type 9
PK	pharmacokinetic
POCBP	participant/participants of childbearing potential
PONCBP	participant/participants of nonchildbearing potential
PP	per-protocol
PR	pulse rate
RI	renal impairment
RNA	ribonucleic acid
RNAi	RNA interference
RR	respiratory rate
SAE	serious adverse event
SD	standard deviation
siRNA	short interfering RNA
SLAB	supplemental laboratory test(s)
SNP	single nucleotide polymorphism
SoA	schedule of activities
SOP	Standard Operating Procedures
SSRI	selective serotonin uptake inhibitors
SUSAR	suspected unexpected serious adverse reaction
THC	delta-9-tetrahydrocannabinol

Abbreviation	Expanded Term
TID	three times daily
Tmax	time to maximum plasma concentration
UA	urinalysis
ULN	upper limit of normal
UTN	Universal Trial Number
VS	vital sign(s)
Vz/F	apparent volume of distribution
WHO	World Health Organization

11 REFERENCES

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