Official Protocol Title:	An Open-Label, Single-Dose Clinical Study to Evaluate the Pharmacokinetics of Enlicitide in Participants with Hepatic Impairment
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Clinical Protocol

An Open-Label, Single-Dose Clinical Study to Evaluate the Pharmacokinetics of Enlicitide in Participants with Hepatic Impairment

Celerion Project No.: CA43214

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US FDA IND No.: 152853

Study Phase: Phase 1

Final Protocol Date: 30 July 2024

Good Clinical Practices (GCP) Statement

This study is to be performed in full compliance with the protocol, GCP, and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement

PROTOCOL REVISION HISTORY

Date/Name	Description
30Jul2024 by PPD	Final Protocol

PRINCIPAL INVESTIGATOR – SIGNATORY

An Open-Label, Single-Dose Clinical Study to Evaluate the Pharmacokinetics of Enlicitide in Participants with Hepatic Impairment

If the protocol is executed using the Veeva platform, the e-signature page will be found at the end of the PDF document.

Signature: Date: _____

Printed name:

Title:

Address:

SPONSOR AND SPONSOR'S REPRESENTATIVE – SIGNATORY

An Open-Label, Single-Dose Clinical Study to Evaluate the Pharmacokinetics of Enlicitide in Participants with Hepatic Impairment

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Signature: _____ Date: _____

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ABBREVIATIONS

Pharmacokinetic parameter abbreviations and definitions are found in Section 8.4.2.
International units of measurement are not included in this list.

AE	Adverse event
ALT	Alanine aminotransferase
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
BMI	Body mass index
BSA	Body surface area
CFR	Code of Federal Regulations
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	Coronavirus disease-2019
CrCl	Creatinine clearance
CRF	Case report form
CRU	Clinical research unit
DMP	Data management plan
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECI	Event of clinical interest
EFSA	European Food Safety Authority
eGFR	Estimated glomerular filtration rate
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FMF	Final market formulation
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GMR	Geometric mean ratio
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HI	Hepatic impairment/impaired

HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IUD	Intrauterine device
LDL	Low density lipoprotein
LDL-C	Low density lipoprotein cholesterol
LLN	Lower limit of normal
LSM	Least-squares mean
MELD	Model for End-Stage Liver Disease
No.	Number
PCSK9	Protein convertase subtilisin/kexin type 9
PD	Pharmacodynamic(s)
PI	Principal Investigator
PK	Pharmacokinetic(s)
PMP	Postmenopausal
popPK	Population pharmacokinetic(s)
QA	Quality assurance
QD	Once daily
QTcF	Corrected value of the interval between the Q and T waves on the electrocardiogram tracing, corrected using Fridericia formula
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
USA	United States of America

1 PROTOCOL SUMMARY

1.1 Protocol Synopsis

<table>
<tr><td>Protocol Title:</td><td colspan="2">An Open-Label, Single-Dose Clinical Study to Evaluate the Pharmacokinetics of Enlicitide in Participants with Hepatic Impairment</td></tr>
<tr><td>Short Title:</td><td colspan="2">Enlicitide Hepatic Impairment Study</td></tr>
<tr><td>Compound:</td><td colspan="2">Enlicitide (enlicitide decanoate; MK-0616)</td></tr>
<tr><td>Study Phase:</td><td colspan="2">Phase 1</td></tr>
<tr><td rowspan="3">Study Objectives and Endpoints:</td><td>Objectives</td><td>Endpoints</td></tr>
<tr><td colspan="2">Primary</td></tr>
<tr><td>Part 1
• To evaluate the plasma pharmacokinetics (PK) of single-dose enlicitide in participants with moderate hepatic impairment (HI) compared to healthy matched control participants.
Hypothesis: The AUC0-inf of enlicitide after administration of a single 20 mg dose in participants with moderate HI and healthy matched control participants will be similar (i.e., the ratio of the geometric means [moderate HI/healthy control participants] will be contained within [0.50, 2.00]).</td><td>• AUC0-inf and Cmax for enlicitide in plasma.</td></tr>
</table>

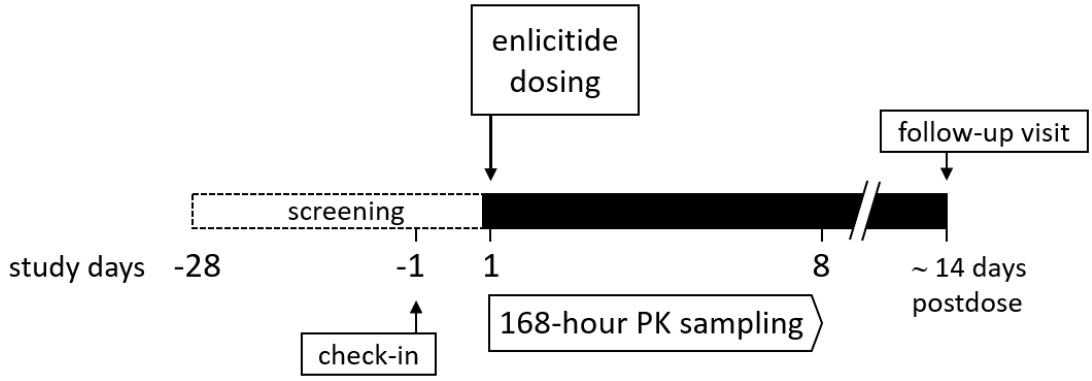
	Part 2 (optional) • To evaluate the plasma PK of single-dose enlicitide in participants with mild HI compared to healthy matched control participants. **Hypothesis:** The AUC0-inf of enlicitide after administration of a single 20 mg dose in participants with mild HI and healthy matched control participants will be similar (i.e., the ratio of the geometric means [mild HI/healthy control participants] will be contained within [0.50, 2.00]).	• AUC0-inf and Cmax for enlicitide in plasma.
	Secondary	
	Part 1 • To evaluate other plasma PK parameters of single-dose enlicitide in participants with moderate HI compared to healthy matched control participants.	• AUC0-24, AUC0-last, Tmax, t½, CL/F, Vz/F for enlicitide in plasma.
	• To evaluate the safety and tolerability of a single dose of enlicitide in participants with moderate HI.	• Treatment-emergent adverse events (TEAEs), clinical laboratory tests, standard and orthostatic vital signs, 12-lead electrocardiograms (ECGs), and discontinuations from study due to adverse event(s) (AE[s]).

	Part 2 (optional) • To evaluate other plasma PK parameters of single-dose enlicitide in participants with mild HI compared to healthy matched control participants. • To evaluate the safety and tolerability of a single dose of enlicitide in participants with mild HI.	• AUC0-24, AUC0-last, Tmax, t½, CL/F, Vz/F for enlicitide in plasma. • TEAEs, clinical laboratory tests, standard and orthostatic vital signs, 12-lead ECGs, and discontinuations from study due to AE(s).
Study Design:	This is an open-label, single-dose study to evaluate the effect of moderate HI (Child-Pugh B, Part 1) and mild HI (Child-Pugh A, Part 2, optional) on the PK, safety, and tolerability of enlicitide. Part 1 of the study will be initiated first, with participants with moderate HI (Group 1) enrolled prior to their healthy matched control participants (Group 2). Following data review, the study may proceed to Part 2, with participants with mild HI (Group 3), if it is deemed necessary. Additional healthy matched control participants (up to an additional 10 participants) may be additionally enrolled in Part 2, as appropriate. Impaired hepatic function will be classified by the numerical Child-Pugh score of hepatic function. All participants will receive a single oral dose of enlicitide on Day 1. PK blood samples will be collected predose and up to 168 hours postdose. Throughout the study, safety will be monitored by repeated clinical and laboratory evaluations. All participants who received the study drug (including participants who terminate the study early) will return to the clinical research unit (CRU) approximately 14 days after dosing for follow-up procedures, and to determine if any AE has occurred since the last study visit.	
Study Duration:	The total planned study duration (from screening to follow-up) for each participant is approximately 6 weeks.	

Number of Participants:	Up to 40 adult male and female participants will be enrolled, with 10 participants with moderate HI (Group 1), up to 20 healthy matched control (Group 2) participants, and 10 participants with mild HI (Group 3). In each of Group 1 and Group 3, there should be approximately a 1:1 ratio of males to females (±1 of each sex). In Part 1, healthy control participants will be enrolled after all moderate HI participants have been dosed and will be matched to participants with moderate HI by the mean age (± 10 years), mean body mass index (BMI; ± 20%), and total sex (± 1, and not more than 60% male or female). If Part 2 is conducted, data from the healthy control participants in Part 1 who satisfy the mean age (± 10 years), mean BMI (± 20%), and total sex (± 1) matching criteria of participants with mild HI (Group 3) enrolled in Part 2 will be used; however up to 10 additional healthy participants may be additionally enrolled in Part 2 if the matching criteria are not met.
Dosage, Dosage Form, Route, and Dose Regimen:	All participants will receive a single oral dose of 20 mg enlicitide/CCI [redacted] (1 x 20 mg enlicitide/CCI [redacted]) on Day 1.

1.2 Study Schema

Figure 1: Schematic of Study Design for Each Group



Abbreviation: PK = Pharmacokinetic(s).

1.3 Schedule of Activities

Study Procedures [a]	Screening [b]	Study Days																Follow-up [c]
Days →		-1	1									2		3	4	6	8	
Hours →		C-I [d]	0	0.5	1	1.5	2	3	5	8	12	24	36	48	72	120	168	
Administrative Procedures																		
Informed Consent	X																	
Informed Consent for FBR (optional)	X																	
Inclusion/Exclusion Criteria	X	X	X [e]															
Medical History	X																	
Participant ID Card																	X [f]	
Safety Evaluations																		
Full Physical Examination	X	X										X						X
Height	X																	
Weight	X	X																X
Standard Triplicate HR and BP			X [g]															
Orthostatic HR and BP	X		X [g]		X		X					X					X [f]	X
Standard Single RR and T	X		X [g]		X							X					X [f]	X
Triplicate 12-Lead ECG			X [g]															
Single 12-Lead ECG	X				X							X						X
Hem, Serum Chem [h], and UA	X	X															X [f]	X
Coagulation	X	X															X [f]	X
Pregnancy Test (Females Only) [i]	X	X																
Serum FSH (PMP Females Only)	X																	
Urine/Saliva Drug Screen	X	X																
Urine/Breath Alcohol Screen	X	X																
HIV/Hepatitis Screen	X																	
COVID-19 Screen		X																
Hepatic Function Assessment	X [j]																	
AE Monitoring	X	X																X
Concomitant Medication Monitoring	X	X																X
Study Drug Dosing / PK / PD / Biomarkers																		
Participant Assignment			X															
Enlicitide Dosing			X															
Blood for Enlicitide PK			X [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood for Plasma PD Markers (Free PCSK9)			X [e]									X		X	X			X
Blood for Genetic Analysis			X [k]															
Other Procedures																		
Confinement in the CRU		X																
Visit and Return Visit	X																	X

a For details on procedures, refer to Section 8.

b Within 28 days prior to dosing.

c All participants who received the study drug (including participants who terminate the study early) will return to the CRU approximately 14 days after dosing for follow-up procedures, and to determine if any AE has occurred since the last study visit.

d Participants will be admitted to the CRU on Day -1, at the time indicated by the CRU.

e To be performed prior to dosing.

f To be performed on Day 8 or prior to early termination from the study.

g To be performed within 3 hours prior to dosing.

h Samples for serum chemistry will be obtained after a fast of at least 12 hours, however, in case of dropouts or rechecks, participants may not have fasted for 12 hours prior to when the serum chemistry sample is taken.

i Serum pregnancy test(s) will be performed at screening. Serum or urine pregnancy tests will be performed at all other scheduled time points.

j Child-Pugh scores will be assigned to participants with HI only. A baseline Child-Pugh score will be obtained by taking the mean of the Child-Pugh score obtained from the screening visit and from historical values within a 6-month period prior to the screening visit. If no historical measurement is available, a second baseline Child-Pugh score will be taken during the screening period (> 72 hours apart) and the mean of the 2 values will be used for HI group assignment; the second Child-Pugh score may be obtained at the time of check-in (Day -1). In Group 1 (moderate HI), at least 4 participants must have a score of 2 or higher on at least 1 of the laboratory parameters (i.e., albumin, INR, and bilirubin) on the Child-Pugh scale.

k To be obtained predose, but may be collected at the next scheduled blood draw, if needed.

Abbreviations: AE = Adverse event(s), BP = Blood pressure, C-I = Check-in, Chem = Chemistry, COVID-19 = Coronavirus disease 2019, CRU = Clinical research unit, ECG = Electrocardiogram, EOT/ET = End-of-Treatment or early termination, FBR = Future biomedical research, FSH = Follicle-stimulating hormone, F/U = Follow-up, Hem = Hematology, HI = Hepatic impairment, HIV = Human immunodeficiency virus, HR = Heart rate, ID = Identification, INR = International normalized ratio, PD = Pharmacodynamic(s), PI = Principal Investigator, PK = Pharmacokinetics, PMP = Postmenopausal, PCSK9 = Protein convertase subtilisin/kexin type 9, RR = Respiratory rate, T = Temperature, UA = Urinalysis.

2 INTRODUCTION

2.1 Enlicitide (MK-0616)

Enlicitide decanoate (previously referred to as MK-0616) will be referred to as enlicitide throughout this protocol.

Cardiovascular disease, principally atherosclerotic cardiovascular disease (ASCVD), is the leading cause of global mortality and a major contributor to disability. Epidemiologic, genetic, and clinical intervention studies have shown that low density lipoprotein cholesterol (LDL-C) is causally associated with ASCVD, and that lifestyle and pharmacologic reductions in LDL-C lower the risk of myocardial infarction, stroke, and death from cardiovascular disease. Despite the availability of several proven LDL-C-lowering therapies (e.g., statins, ezetimibe, bile acid sequestrants, protein convertase subtilisin/kexin type 9 [PCSK9] inhibitors), a substantial proportion of patients with hypercholesterolemia are not at guideline-recommended LDL-C targets (Fox et al. 2018). This information supports the need for additional LDL-C-lowering therapies for the treatment of hypercholesterolemia.

PCSK9 is a well-validated target for lowering LDL-C and reducing ASCVD risk, with strong human genetics implicating an important role for PCSK9 in regulating LDL-C. Circulating PCSK9 molecules bind to cell surface low density lipoprotein (LDL) receptors and direct the receptors to intracellular lysosomes for degradation instead of back to the surface, resulting in reduced clearance of LDL-C from the circulation. Thus, blockade of the PCSK9-LDL receptor interaction increases steady-state levels of cell surface hepatic LDL receptors, which enhances LDL-C clearance and lowers circulating levels of LDL-C.

Several injectable PCSK9 inhibitors have received regulatory approval for the treatment of hypercholesterolemia. Unlike these injectable therapies, enlicitide is an orally administered PCSK9 inhibitor for the treatment of hypercholesterolemia. An oral PCSK9 inhibitor, that can achieve equivalent LDL-C-lowering to the injectable PCSK9 inhibitors, offers potential advantages in simplicity of dosing, patient preference, and access.

Refer to the Investigator's Brochure (IB) for detailed background information on enlicitide.

2.2 Rationale

2.2.1 Rationale for this Study and Study Design

The liver is involved in drug clearance through a variety of oxidative and conjugative metabolic pathways and/or through biliary excretion of the unchanged drug or drug metabolites. Hepatic insufficiency from acute or chronic liver disease may affect metabolism and/or excretion, leading to drug and/or metabolite accumulation and/or failure to form a drug metabolite. In addition, alterations in drug solubility, absorption and disposition may occur. Hepatic disease can therefore alter drug levels, potentially leading to an effect on efficacy and/or safety (FDA 2003).

Preclinical studies, in rats and monkeys, demonstrated that enlicitide is metabolically stable systemically and within the gastrointestinal tract and is excreted as unchanged parent peptide in rat and cynomolgus monkeys predominately by renal clearance. No circulating or excreted metabolites have been observed in either species. Clinically, enlicitide eliminated primarily through renal excretion. Preliminary data, from a human ADME study (MK-0616-016), indicate that the parent, enlicitide, is the major radioactive component in plasma, accounting for 96.6% of the total radioactivity, with no reportable metabolites identified in urine, feces, or plasma.

PCSK9 is ubiquitously expressed in many tissues and cell types with the highest levels of expression in liver, intestine, lung, cerebellum, and pancreatic tissues, and circulating PCSK9 is derived primarily from synthesis and secretion from the liver. The totality of the preclinical and clinical data indicates hepatic elimination is not the major route of elimination for enlicitide. Given this, it is not anticipated that hepatic functional impairment will significantly alter the PK of enlicitide. The marketed anti-PCSK9 monoclonal antibodies evolocumab and alirocumab were both evaluated in HI PK studies (evaluating PK in moderate HI participants versus healthy controls), and do not recommend dose adjustment in HI populations (Praluent® 2021, Repatha® 2021).

This Phase 1 study will evaluate the general PK, safety, and tolerability of a single dose of enlicitide in participants with moderate HI, compared to participants in good health.

The open-label, single-dose study design has been selected to evaluate the effect of HI on the PK of enlicitide. The current study design is in accordance with regulatory guidance of the FDA (FDA 2003) and the European Medicines Agency (EMA; [EMA 2005]).

In the current study, participants with chronic, stable hepatic insufficiency meeting a Child-Pugh score of 7-9 corresponding to moderate HI will be eligible for enrollment. In addition, as the laboratory parameters specified in the Child-Pugh scale (e.g., reduced serum albumin, increased serum bilirubin, and increased international normalized ratio [INR]) may be better associated with the capacity of the liver to eliminate drugs, in comparison to ascites and encephalopathy (EMA 2005), at least 4 participants with moderate HI will be required to have a score of at least 2 on one of the laboratory parameters (i.e., bilirubin, albumin, or prothrombin time / INR) on the Child-Pugh scale.

Since intra-participant PK assessment is not feasible in a HI study, participants in good health without HI will serve as a control group and be matched to the demographic parameters (mean age, mean BMI, and sex) of the moderate HI group.

After reviewing data collected from participants with moderate HI (Part 1), if deemed necessary, Part 2 will be initiated and participants with mild HI (Child-Pugh Class A) and additional healthy control participants (if required) matching the mean age, mean BMI, and sex of the mild HI group will be enrolled.

2.2.2 Rationale for the Dose Selection

The 20 mg dose of enlicitide is the clinical dose being utilized in ongoing Phase 3 clinical studies. This dose is based on the population PK (popPK) analysis of data from Phase 1 and 2 studies, exposure-response and dose-response analyses of data from the Phase 2 study, and results from a relative bioavailability study of the final market formulation (FMF) tablet versus fit-for-purpose capsule formulation used in Phase 1 and 2 studies. This dose is expected to maximize the efficacy of enlicitide, with a predicted LDL-C reduction of > 50% in the overall population. Furthermore, based on popPK modeling, the steady state Cmax and AUC0-24 for this dose are predicted to be 9.0 and 2.3-fold lower, respectively, than the corresponding exposures seen in the highest well-tolerated dose exposures (300 mg single dose) in healthy adults, and both parameters will be 1.3-fold lower than the highest dose studied in Phase 2b (30 mg) which was also well tolerated. As such, this dose provides adequate exposure margins for safety. See IB for additional details, including preclinical study data.

Enlicitide has been generally well tolerated in healthy participants in completed and ongoing Phase 1 studies to date at single doses up to 300 mg, and multiple doses up to 120 mg (once daily for 3 weeks, following an escalation from 60 mg once daily for 1 week in statin-treated participants). Enlicitide was also generally well tolerated in patients with hypercholesterolemia studied in a recently completed Phase 2b study, which included a top dose of 30 mg, administered once daily for 8 weeks.

2.2.3 Rationale for the Use of Child-Pugh Classification to Assess Impaired Hepatic Function

The Child-Pugh classification will be used to categorize hepatic insufficiency due to its widespread use and acceptance by regulatory agencies (including the US FDA [FDA 2003] and the European Medicines Agency [EMA; EMA 2005]). It is the most established approach for categorization of liver impairment, and has been shown to correlate with hepatic (i.e., metabolic) clearance for several compounds (FDA 2003).

In the current study, participants with chronic, stable hepatic insufficiency with features of cirrhosis due to any etiology will be enrolled, and the Child-Pugh scale will be used to classify the severity of liver disease. The scale employs 5 clinical measures of liver disease listed in Table 1. Each clinical measure is scored 1 to 3, with 3 indicating most severe derangement. The bilirubin score in the table is dependent upon the type of cirrhosis (primary biliary cirrhosis versus all other causes). Participants' scores of 5 to 6, 7 to 9, and 10 to 15, inclusive, on this scale will be classified as having mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic failure, respectively.

Table 1: Child-Pugh Classification Criteria

Finding	Points scored for each observed finding		
	1	**2**	**3**
Encephalopathy [1]	None	Grade 1 or 2 (or suppressed with medication)	Grade 3 or 4 (or refractory)
Ascites [2]	Absent	Slight or participant on 1 medication to control ascites	Moderate or severe, or participant on 2 or more medications to control ascites or requires paracentesis (if the combination of 2 medications are used primarily to minimize)
Bilirubin (mg/dL)	< 2	2 to 3	> 3
Albumin (g/dL)	> 3.5	2.8 to 3.5	< 2.8
INR	< 1.7	1.7 to 2.3	> 2.3
or prothrombin time (second[s] prolonged)	< 4	4 to 6	> 6

Adapted from FDA Guidance for Industry. Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (FDA 2003).

1 Encephalopathy is graded according to the following criteria:
Grade 0: normal consciousness, personality, neurological examination, and electroencephalogram.
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles/sec waves.
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves.
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.
Grade 4: unarousable coma, no personality/behavior, decerebrate, slow 2 to 3 cycles/sec delta activity.

2 Ascites is graded according to the following criteria:
Absent: No ascites detectable by manual investigation.
Slight: ascites palpation doubtful.
Moderate: ascites detectable by palpation.
Severe: necessity of paracentesis, does not respond to medicinal treatment.

2.3 Risks and/or Benefits to Participants

The dose of enlicitide to be administered in this study is not expected to induce any potential risk to the healthy participants enrolled in this study, as it is less than the safe doses assessed previously and provides an adequate safety margin based on clinical exposures from previous studies. The tablet formulation used in this study is a compressed tablet, containing 20 mg of enlicitide and CCI as the key components.

Sodium caprate is a medium chain fatty acid that is a FDA-approved food additive, as per FDA Title 21 Code of Federal Regulations (CFR) 172.860 (FDA 2023) and is considered safe for use per the European Food Safety Authority (EFSA 2017). Sodium caprate was well tolerated in nonclinical studies without adverse systemic effects. For chronic oral

administration, the no observed adverse effect level for caprate in monkeys and rats corresponded to body surface area (BSA) multiples of CCI [redacted].

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

The safety monitoring practices employed by this protocol (i.e., AEs, clinical laboratory tests, standard and orthostatic vital signs, 12-lead ECGs, and physical examinations) are adequate to protect the participants' safety and should detect all expected TEAEs. The risk to participants in this study is minimized by compliance with the eligibility criteria, safety monitoring, and confinement at the CRU for the duration of the study.

There will be no direct therapeutic benefit for study participants from receipt of study drugs, as clinical studies are designed to provide information about the safety and properties of an investigational medicine. An indirect health benefit to the healthy participants enrolled in this study is the free medical tests received at screening and during the study.

3 STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
Part 1 • To evaluate the plasma PK of single-dose enlicitide in participants with moderate HI compared to healthy matched control participants. **Hypothesis:** The AUC0-inf of enlicitide after administration of a single 20 mg dose in participants with moderate HI and healthy matched control participants will be similar (i.e., the ratio of the geometric means [moderate HI/healthy control participants] will be contained within [0.50, 2.00]).	• AUC0-inf and Cmax for enlicitide in plasma.
Part 2 (optional) • To evaluate the plasma PK of single-dose enlicitide in participants with mild HI compared to healthy matched control participants. **Hypothesis:** The AUC0-inf of enlicitide after administration of a single 20 mg dose in participants with mild HI and healthy matched control participants will be similar (i.e., the ratio of the geometric means [mild HI/healthy control participants] will be contained within [0.50, 2.00]).	• AUC0-inf and Cmax for enlicitide in plasma.

Secondary	
Part 1 • To evaluate other plasma PK parameters of single-dose enlicitide in participants with moderate HI compared to healthy matched control participants.	• AUC0-24, AUC0-last, Tmax, t½, CL/F, Vz/F for enlicitide in plasma.
• To evaluate the safety and tolerability of a single dose of enlicitide in participants with moderate HI.	• TEAEs, clinical laboratory tests, standard and orthostatic vital signs, 12-lead ECGs, and discontinuations from study due to AE(s).
Part 2 (optional) • To evaluate other plasma PK parameters of single-dose enlicitide in participants with mild HI compared to healthy matched control participants.	• AUC0-24, AUC0-last, Tmax, t½, CL/F, Vz/F for enlicitide in plasma.
• To evaluate the safety and tolerability of a single dose of enlicitide in participants with mild HI.	• TEAEs, clinical laboratory tests, standard and orthostatic vital signs, 12-lead ECGs, and discontinuations from study due to AE(s).
Exploratory	
Part 1 and Part 2 • To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in the study.	• Germline genetic variation and association to clinical data collected in this study.
• To explore the % change in plasma free PCSK9 from baseline in participants with HI compared to healthy matched control participants.	• Percent (%) reduction in free PCSK9 from baseline.

4 STUDY DESIGN

4.1 Description of Study Design

This is an open-label, single-dose study to evaluate the effect of moderate HI (Child-Pugh B, Part 1) and mild HI (Child-Pugh A, Part 2, optional) on the PK, safety, and tolerability of enlicitide.

Part 1 of the study will be initiated first, with participants with moderate HI (Group 1) enrolled prior to their healthy matched control participants (Group 2). Following data review, the study may proceed to Part 2, with participants with mild HI (Group 3), if it is deemed necessary. Additional healthy matched control participants (up to an additional 10 participants) may be additionally enrolled in Part 2, as appropriate.

Impaired hepatic function will be classified by the numerical Child-Pugh score of hepatic function (Section 2.2.3).

Up to 40 adult male and female participants will be enrolled, with 10 participants with moderate HI (Group 1), up to 20 healthy matched control (Group 2) participants, and 10 participants with mild HI (Group 3).

In Part 1, healthy control participants will be enrolled after all moderate HI participants have been dosed and will be matched to participants with moderate HI by the mean age (± 10 years), mean BMI (± 20%), and total sex (± 1, and not more than 60% male or female). If Part 2 is conducted, data from the healthy control participants in Part 1 who satisfy the mean age (± 10 years), mean BMI (± 20%), and total sex (± 1) matching criteria of participants with mild HI (Group 3) enrolled in Part 2 will be used; however up to 10 additional healthy participants may be additionally enrolled in Part 2 if the matching criteria are not met.

Screening of participants will occur within 28 days prior to dosing.

All participants will receive a single oral dose of enlicitide on Day 1. PK blood samples will be collected predose and up to 168 hours postdose.

Throughout the study, safety will be monitored by repeated clinical and laboratory evaluations.

Discontinued participants may be replaced at the discretion of the Sponsor.

4.1.1 Confinement and Follow-Up

Participants will be housed on Day -1, at the time indicated by the CRU, until completion of study procedures on Day 8. At all times, a participant may be required to remain at the CRU for longer at the discretion of the Principal Investigator (PI) or designee.

All participants who received the study drug (including participants who terminate the study early) will return to the CRU approximately 14 days after dosing for follow-up procedures, and to determine if any AE has occurred since the last study visit.

For participants who terminate the study early and agree to complete follow-up procedures, phone call(s) may replace the return visit if the participant cannot or is unwilling to return for the visit.

4.1.2 Study Duration

The total planned study duration (from screening to follow-up) for each participant is approximately 6 weeks.

4.2 Beginning and End of Study

The overall study begins when the first participant 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. If there is an unresolved AE, end date of concomitant medication, or an assessment date that is after the end of study, the date of study completion will be inclusive of that resolution/assessment date.

A participant is considered to have completed the study if the participant completed dosing, did not terminate the study early, and has completed the last scheduled procedure i.e., the follow-up visit shown in the Schedule of Activities (Section 1.3).

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

4.2.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

4.3 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameter

This is a Phase 1 assessment of enlicitide in humans, and the PK, PD, 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 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 design may be permitted based on newly available data:

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

The total blood volume withdrawn from any single participant will not exceed the maximum allowable volume during their participation in the entire study (Table 4).

The timing of procedures for assessment of safety procedures (e.g., standard and orthostatic vital signs, ECGs, safety laboratory tests) 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 PI for retention. The letter may be forwarded to the IRB at the discretion of the PI.

If necessary, a participant must be discontinued for the reasons described in Section 7.

5 STUDY POPULATION

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

5.1 Inclusion Criteria

Participants must fulfill all of the following inclusion criteria to be eligible for participation in the study:

All Participants:

1. Adult, male or female, 18 to 75 years of age, inclusive, at the screening visit.

   A participant is considered female if assigned female sex at birth.

2. Must follow protocol-specified contraception guidance as described in Section 5.3.4.

3. Is a continuous non-smoker or moderate smoker (≤ 10 cigarettes per day or equivalent) for at least 3 months prior to dosing based on participant self-reporting. Participant must agree to maintain the same smoking status (i.e., smoker or non-smoker) from screening and until after the last PK sample collection. Smokers must agree to smoke no more than 10 cigarettes (or equivalent) per day from check-in until after the last PK sample collection and must agree to refrain from smoking and/or using any tobacco products for 2 hours prior to dosing until 4 hours postdose.

4. Has body mass index (BMI) ≥ 18.0 and ≤ 40.0 kg/m^2 at the screening visit.

5. Understands the study procedures in the informed consent form (ICF), and is willing and able to comply with the protocol.

6. Has provided documented informed consent for the study.

Participants with Moderate HI (Group 1) or Mild HI (Group 3):

7. Has a diagnosis of chronic (> 6 months), stable (no acute episodes of illness within the previous 2 months due to deterioration in hepatic function) hepatic insufficiency at the screening visit with features of cirrhosis due to any etiology.

8. Is classified as having moderate HI (Class B, score of 7 to 9, inclusive; Group 1 only) or mild HI (Class A, score of 5 to 6, inclusive; Group 3 only) by the Child-Pugh classification system. In Group 1 (moderate HI), at least 4 participants must have a score of 2 or higher on at least 1 of the laboratory parameters (i.e., albumin, INR, and bilirubin) on the Child-Pugh scale (Table 1).

   Note: Baseline Child-Pugh scores will be obtained by taking the mean of the Child-Pugh score obtained from the screening visit and from historical values within a 6-month period prior to the screening visit. If no historical measurement is available, a second

baseline Child-Pugh score will be taken during the screening period (>72 hours apart) and the mean of the 2 values will be used for group assignment; the second Child-Pugh score may be obtained at the time of check-in (Day -1).

9. With the exception of HI, is in generally good health based on medical history, physical examination, vital signs measurements and ECGs performed at the screening visit and prior to dosing. Participants with stable, chronic medical or psychiatric conditions may be included at the discretion of the PI and Sponsor. See Appendix 2 for clinically notable ECG findings.

10. With the exception of HI, is sufficiently healthy for study participation based on clinical laboratory profiles (see Appendix 3 for algorithm to assess out of range laboratory values) at the screening visit and check-in, including the following:

    - Platelets > 75 000/µL at the screening visit.
    - Hemoglobin > 10 g/dL at the screening visit.
    - Estimated glomerular filtration rate (eGFR) of > 60 mL/min based on the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine Equation, adjusted for the participant's BSA, at the screening visit.

      The 2021 CKD-EPI Creatinine equation is defined as follows:

      $eGFR = 142 \times \min(SCr/k,1)^{\alpha} \times \max(SCr/k,1)^{-1.200} \times 0.994^{Age}$ [× 1.012 (if female)]

      By this equation, SCr is serum creatinine, k is 0.9 (if male) and 0.7 (if female), α is -0.302 (if male) and -0.241 (if female), min indicates the minimum of SCr/k or 1, and max indicates the maximum of SCr/k or 1.

      Calculated 2021 CKD-EPI eGFR (mL/min/1.73 m^2) will then be multiplied by the participant's BSA calculated using an appropriate formula and divided by 1.73 to give a de-indexed eGFR (mL/min):

      De-indexed eGFR (mL/min) = $eGFR \left(\frac{\frac{mL}{min}}{1.73m^2} \right) x \frac{BSA\ (m^2)}{1.73}$

      At the discretion of the PI or designee a measured creatinine clearance (CrCl), as determined by a 24-hour urine collection, may be used in place of, or in conjunction with, the eGFR.

      Participants who have an eGFR or measured CrCl of up to 10% below either 60 mL/min (for CrCl or eGFR) may be enrolled in the study at the discretion of the PI or designee.

<u>Healthy Control Participants (Group 2):</u>

11. Must match the mean age (± 10 years) of participants with moderate HI (Group 1) and/or mild HI (Group 3).

12. Must match the mean BMI (± 20%) of participants with moderate HI (Group 1) and/or mild HI (Group 3).

13. Must match the sex ratio (± 1) of participants with moderate HI (Group 1) and/or mild HI (Group 3).

14. Is medically healthy with no clinically significant medical history, physical examination, clinical laboratory profiles (see Appendix 3 for algorithm to assess out of range laboratory values), vital signs, and ECGs (see Appendix 2 for clinically notable ECG findings), as deemed by the PI or designee, including the following:

    - Leukocyte count, platelet count, hemoglobin, INR, and activated partial thromboplastin time are ≥ lower limit of normal (LLN) and ≤ upper limit of normal (ULN) at the screening visit.
    - Total bilirubin is ≤ ULN, or direct bilirubin ≤ ULN for participants with total bilirubin levels > ULN at the screening visit.
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are ≤ ULN at the screening visit.
    - Semi-recumbent blood pressure is ≥ 90/40 mmHg and ≤ 150/95 mmHg at the screening visit.
    - Semi-recumbent heart rate is ≥ 40 bpm and ≤ 99 bpm at the screening visit.
    - Orthostatic vital sign results with a decrease in systolic blood pressure ≤ 20 mmHg and decrease in diastolic blood pressure ≤ 10 mmHg at the screening visit.
    - QTcF interval is < 470 msec (males) and < 480 msec (females) and has ECG findings considered normal or not clinically significant by the PI or designee at the screening visit.
    - eGFR of > 60 mL/min based on the 2021 CKD-EPI Creatinine Equation, adjusted for the participant's BSA, at the screening visit.

      The 2021 CKD-EPI Creatinine equation is defined as follows:

      $eGFR = 142 \times \min(SCr/k,1)^{\alpha} \times \max(SCr/k,1)^{-1.200} \times 0.994^{Age}$ [× 1.012 (if female)]

      By this equation, SCr is serum creatinine, k is 0.9 (if male) and 0.7 (if female), α is -0.302 (if male) and -0.241 (if female), min indicates the minimum of SCr/k or 1, and max indicates the maximum of SCr/k or 1.

      Calculated 2021 CKD-EPI eGFR (mL/min/1.73 m^2) will then be multiplied by the participant's BSA calculated using an appropriate formula and divided by 1.73 to give a de-indexed eGFR (mL/min):

      De-indexed eGFR (mL/min) = $eGFR \left(\frac{\frac{mL}{min}}{1.73m^2}\right) x \frac{BSA\ (m^2)}{1.73}$

At the discretion of the PI or designee a measured CrCl, as determined by a 24-hour urine collection, may be used in place of, or in conjunction with, the eGFR.

Participants who have an eGFR or measured CrCl of up to 10% below either 60 mL/min (for CrCl or eGFR) may be enrolled in the study at the discretion of the PI or designee.

5.2 Exclusion Criteria

Participants must not be enrolled in the study if they meet any of the following criteria:

All Participants:

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study. Participants who have had situational depression may enroll in the study at the discretion of the PI (e.g., if deemed well controlled and stable in the opinion of the PI).

2. Has a history or presence of alcohol or drug abuse (except for cannabis products) within the past 2 years prior to dosing.

3. Has a history or presence of hypersensitivity or idiosyncratic reaction to the study drug or related compounds.

4. History of gastrointestinal disease which may affect food and drug absorption, as determined by the PI or designee, or has had a 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.

5. Has a history of cancer (malignancy). Participants with adequately treated disease deemed as "cured," or who, in the opinion of the PI or designee, are highly unlikely to sustain a recurrence for the duration of the study may be enrolled at the discretion of the PI or designee.

6. Female participant with a positive pregnancy test at the screening visit or at check-in or who is lactating.

7. Has a positive drug result at screening or check-in, unless the positive drug screen is due to prescription drug use that is approved by the PI or designee and Sponsor.

8. Has a positive alcohol result at screening or check-in.

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

10. 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.

11. Is unable to refrain from or anticipates the use of any drugs (except for permitted medication as detailed in Section 6.7), including prescription and non-prescription medications, herbal remedies, or vitamin supplements, as indicated in Section 6.7.

12. Has received an anti-PCSK9 monoclonal antibody or small interfering ribonucleic acid (RNA) or RNA interference for PCSK9 within 12 months prior to the screening visit. The window will be derived from the date of the last dose in the previous study.

13. Is on statin background therapy.

14. Has a positive result for human immunodeficiency virus (HIV) at the screening visit.

15. Has a positive coronavirus disease 2019 (COVID-19) result at check-in.

16. Has been on a diet incompatible with the on-study diet, in the opinion of the PI or designee, within the 30 days prior to dosing.

17. Has had major surgery and/or donated or lost significant volume of blood within 56 days prior to dosing.

18. Plasma donation within 7 days prior to dosing.

19. Participation in another clinical study within 30 days or within 5 half-lives (if known), prior to dosing, whichever is longer. The 30-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of the current study.

20. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling, or child) who is CRU or Sponsor staff directly involved with this study.

Participants with Moderate HI (Group 1) or Mild HI (Group 3):

21. With the exception of HI, has a history or presence of clinically significant medical or psychiatric condition or disease, any illness that, in the opinion of the PI or designee, might confound the results of the study or poses an additional risk to the participant by their participation in the study.

22. Severe complications of liver disease within the preceding 3 months of the screening visit.

23. Primary biliary cholangitis or biliary obstruction.

24. Has a history of a recent (within 3 months prior to the screening visit) variceal bleeds.

25. Has evidence of hepatorenal syndrome.

26. Has fluctuating or rapidly deteriorating hepatic function from the screening visit until prior to dosing, in the opinion of the PI.

27. Is not in sufficient health, with regard to stability of HI, to undergo participation in the study with anticipated survival of < 3 months, in keeping with a Model for End-Stage Liver Disease (MELD) score of ≥ 25.

28. Has a history of liver or other solid organ transplantation.

29. Has an active infection requiring systemic therapy.

30. Requires paracentesis more often than 2 times per month.

31. Has transjugular intrahepatic portosystemic shunt and/or has undergone portacaval shunting.

32. Has encephalopathy Grade 3 or worse within 28 days prior to dosing.

33. Has received antiviral and/or immune modulating therapy for hepatitis B virus (HBV) or hepatitis C virus (HCV) within 90 days prior to dosing.

34. Is using HIV protease inhibitors.

35. Is positive for HBV with a HBV deoxyribonucleic acid (DNA) level in serum or plasma of > 1000 IU/mL at the screening visit.

36. Is positive for HCV and has a detectable HCV viral load at the screening visit. Note: Participants with a documented cure and/or a positive serologic test for HCV with a negative HCV viral load may be included upon consultation with the Sponsor.

Healthy Control Participants (Group 2):

37. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the PI or designee.

38. History of any illness that, in the opinion of the PI or designee, might confound the results of the study or poses an additional risk to the participant by their participation in the study.

39. Has a positive result for hepatitis B surface antigen (HBsAg) or HCV at the screening visit.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

5.3.1.1 Meals

Water (except water provided with dosing) will be restricted 1 hour prior to and 1 hour after dosing, but will be allowed ad libitum at all other times. Other fluids may be given as part of meals and snacks but will be restricted at all other times throughout the confinement period.

Participants will be required to fast overnight for at least 10 hours prior to dosing and will continue to fast for at least 4 hours postdose.

After dosing, if a participant exhibits symptoms of hypoglycemia, a light snack (e.g., toast, juice) may be provided at the discretion of the PI and will be documented

Each meal and/or snack served at the CRU will be standardized and of similar caloric content and composition and will be taken at approximately the same time in each period.

When confined, standard meals and snacks will be provided at appropriate times, except when participants are required to fast. When confined in the CRU, participants will be required to fast from all food and drink except water between meals and snacks.

5.3.1.2 Dietary Restrictions

The consumption of foods and beverages containing the following substances will be prohibited as indicated:

- Grapefruit juice, grapefruits, grapefruit products, Seville orange, and poppy seeds: 14 days prior to dosing and until the last PK sample collection.
- Other fruit juices: 24 hours prior to and after dosing. On all other days during the study, consumption of fruits and fruit juices (except for grapefruit, grapefruit juices, grapefruit products, and Seville orange) is allowed.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

Participants will refrain to use the following:

- Xanthines/Caffeine-containing foods or beverages: 24 hours prior to dosing and until the last PK sample collection (small amounts of caffeine derived from normal foodstuffs e.g., 250 mL/8 oz/1 cup decaffeinated coffee or other decaffeinated beverage, per day, with the exception of espresso; 45 g/1.5 oz chocolate bar, per day, would not be considered a deviation to this restriction).
- Alcohol-containing foods or beverages: 48 hours prior to dosing and until the last PK sample collection.
- Tobacco/nicotine containing products: participant must agree to maintain the same smoking status (i.e., smoker or non-smoker) from screening and until after the last PK

sample collection. Depending on the CRU rules and regulations, participants may be prohibited from smoking during their confinement or during portions of their confinement.

- Cannabis containing products: check-in until the last PK sample collection.

5.3.3 Activity Restrictions

Participants will remain ambulatory or seated upright for the first 4 hours postdose, except when they are supine or semi-reclined for study procedures.

Should AEs occur at any time, participants may be placed in an appropriate position or will be permitted to lie down on their right side.

Participants will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from the screening visit until the last blood sample collection.

Participants will be cautioned against activities requiring mental alertness, judgment and physical coordination such as driving, operating machinery, or power equipment for a period of 24 hours postdose.

5.3.4 Contraception Requirements

5.3.4.1 Definitions

The definitions below apply to both female participants and female non-participants (i.e., female partner of male participant).

Females of childbearing potential are defined as all females physiologically capable of becoming pregnant.

Females of non-childbearing potential are defined as follows:

- Females who have undergone one of the following sterilization procedures at least 6 months prior to dosing/dosing administered to the male partner:
  - Hysteroscopic sterilization.
  - Bilateral tubal ligation or bilateral salpingectomy.
  - Hysterectomy.
  - Bilateral oophorectomy.

  or
- Females who are postmenopausal (PMP) with amenorrhea for at least 1 year prior to dosing/dosing administered to the male partner and, for female participants only, have follicle-stimulating hormone (FSH) serum levels consistent with PMP status at the screening visit.

5.3.4.2 Guidance for Female Participants

Female participants of non-childbearing potential are not required to use any contraception methods.

Female participants of childbearing potential must agree to one of the following methods of contraception:

- Sexually inactive for at least 28 days prior to dosing.
- Non-hormonal releasing intrauterine device (IUD) or hormonal contraceptives (e.g., oral, IUD, vaginal ring, transdermal patch, depot, implantable, etc.) for at least 3 months prior to dosing.
- Surgical sterilization of the partner (vasectomy for 4 months minimum prior to dosing).
- Physical barrier method (e.g., condom, diaphragm) with spermicide for at least 14 days prior to dosing.

A female participant who claims to be sexually inactive, but becomes sexually active during the course of the study must agree to use a physical barrier method (e.g., condom, diaphragm) with spermicide from the time of the start of sexual activity and throughout the study.

In addition, female participants of childbearing potential will be advised to remain sexually inactive or to keep the same birth control method for at least 28 days after dosing.

Female participant must agree not to donate ova from the first dosing until at least 28 days after dosing.

5.3.4.3 Guidance for Male Participants

If capable of producing sperm, the male participant must agree to the following from the first dosing until at least 90 days after the dose of study drug:

- Refrains from donating sperm

  PLUS either:

- Abstains from penile-vaginal intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agrees to remain abstinent

  OR

- Uses contraception as detailed below unless confirmed to be azoospermic (vasectomized for at least 4 months prior to the first dosing or secondary to medical cause, documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview) as detailed below:

- Uses a penile/external condom when having penile-vaginal intercourse with a female partner of childbearing potential who is not currently pregnant PLUS partner use of an additional contraceptive method, as a condom may break or leak.

  Note: Participants capable of producing ejaculate whose partner is pregnant or breastfeeding must agree to use a penile/external condom during each episode of sexual activity in which the partner is at risk of drug exposure via ejaculate.

- Contraceptive use by participants capable of producing sperm should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study drugs are more stringent than the requirements above, the local label requirements are to be followed.

6 STUDY TREATMENTS AND CONCOMITANT THERAPY

6.1 Description of Study Treatments

The study drug to be used in this study is outlined in Table 2.

Study treatments are described in Section 6.4.

Table 2: Study Drugs

Treatment	Treatment Type	Study Drug Name	Study Drug Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/Treatment Period	Use	IMP/ NIMP/ AxMP	Sourcing
Moderate HI (Group 1)	Experimental	MK-0616 / sodium caprate	Drug	Tablet (FMF)	MK-0616 20 mg/ [redacted]	20 mg/ [redacted]	Oral	Single dose, Day 1	Test product	IMP	Sponsor
Healthy Control (Group 2)											
Mild HI (Group 3; optional)											

Abbreviations: FMF = final market formulation, HI = hepatic impairment, IMP = investigational medicinal product, NIMP/AxMP = non-investigational/auxiliary medicinal product.

All study drugs will be administered orally with approximately 240 mL of water.

Participants will be instructed not to crush, split, or chew the study drug.

The pharmacy at the CRU will provide each dose in individual unit dose containers for each participant and for each study period.

The exact clock time of dosing will be recorded.

6.2 Drug Supplies, Storage, and Accountability

The Sponsor will supply sufficient quantities of enlicitide decanoate to allow completion of this study. The lot numbers and expiration dates (where available) of the study drugs supplied will be recorded in the Clinical Study Report.

All study drugs must be stored in a secure, temperature controlled, and monitored area in accordance with the study drugs storage requirements, with access limited to the PI and designated CRU personnel.

Records will be made of the receipt and dispensing of the study drugs supplied. At the conclusion of the study, any unused study drug will be retained by Celerion, returned to the Sponsor or designee, or destroyed, as per Sponsor instructions.

6.3 Study Dose Modification

Refer to Section 4.3.

6.3.1 Stopping Rules

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

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

1. An individual participant reports an SAE considered related to the study drug by the PI or designee.
2. Two (2) or more participants report Severe Nonserious AEs considered related to the study drug by the PI or designee.

6.4 Participant Assignment and Randomization

All participants will receive a single oral dose of 20 mg enlicitide/[redacted]
(1 x 20 mg enlicitide/[redacted]) on Day 1.

Each participant will be assigned a unique identification number upon the screening visit. Participants who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique identification number, different from the screening number, and will receive the corresponding product.

No randomization will be performed in this study. All participants will receive the treatment on one occasion.

6.5 Blinding

This is an open-label study.

6.6 Study Treatment Compliance

A qualified designee will be responsible for monitoring the administration of the timed oral doses. Once a participant has finished the dosing water, the qualified designee will use a flashlight and a tongue depressor to check the participant's mouth to ensure that the participant has swallowed the study drug. Participants' hands will also be verified to ensure that the study drug was ingested.

6.7 Concomitant Therapy

Prior medications (including prescription and non-prescription medications, herbal remedies, or vitamin supplements) will be prohibited as listed below and in the exclusion criteria in Section 5.2 and throughout the study with the exception of the ones listed below and in Section 5.3.4.2.

Participants with Moderate HI (Group 1) and Mild HI (Group 3):

In general, the use of any concomitant medication/therapy required to treat the current disease of a participant may be permitted following consultation with the Sponsor (except when specifically prohibited).

Participants who are taking medications to treat manifestations of hepatic disease or medications needed to treat stable diseases (e.g., angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers, diuretics, metformin, insulin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase-4 inhibitors, alpha-glucosidase inhibitors, sodium-glucose cotransporter 2 inhibitors) that are common in patients with HI will be allowed to participate in the study at the discretion of the PI or designee and following consultation with the Sponsor. Participants must be on a stable dose (steady dose, drug, and regimen) for at least 14 days before enlicitide dosing (at least 28 days prior to enlicitide dosing for diuretic treatment, and at least 3 months prior to enlicitide dosing for

thyroid hormone replacement medication) and able to withhold the use of their maintenance medication for at least 4 hours prior to enlicitide dosing until at least 4 hours after enlicitide dosing.

Phosphate binders containing aluminum, calcium, or lanthanum salts; iron supplements or other metal cations; H2-receptor antagonists (except cimetidine); or multivitamins containing iron or zinc must be withheld at least 8 hours before enlicitide dosing and at least 4 hours postdose. Any medication (including over-the-counter) that would significantly alter eGFR, which, by the determination of the PI or designee, might interfere with the study (e.g., cimetidine) must be discontinued at least 2 weeks prior to enlicitide dosing and throughout the study.

Changes to medication that require frequent dose adjustments, such as insulin, furosemide (Lasix), spironolactone (Aldactone), or analgesic, may be made at least 14 days prior to enlicitide dosing and may be considered if medically necessary thereafter, at the discretion of the PI and following consultation with the Sponsor.

If a participant is prescribed prohibited medication, upon discussion between the Sponsor and the PI, the PI may substitute the previously prescribed medication to an allowed one for the purpose of this study.

Healthy Control Participants (Group 2):

Any drugs, including prescription and non-prescription medications (with the exception of oral contraception, hormone replacement therapy, and thyroid hormone replacement medication), vitamins, or herbal and dietary supplements, are prohibited beginning 14 days prior to enlicitide dosing and until after the last PK sample collection. However, healthy participants who are on stable medication for at least 30 days prior to enlicitide dosing may be enrolled upon approval by the PI or designee and the Sponsor.

Certain medications may be deemed acceptable at the discretion of the PI and following consultation with the Sponsor, but participants must be on a stable regimen for at least 28 days prior to enlicitide dosing. If a participant is prescribed prohibited medication, upon discussion between the Sponsor and the PI, the PI may substitute the previously prescribed medication to an allowed one for the purpose of this study.

All Participants:

Birth control methods are allowed as described in Section 5.3.4.2.

Hormone replacement therapy and thyroid hormone replacement medication will be allowed, if the participant has been on the same stable dose for at least 3 months prior to dosing.

After dosing, acetaminophen (up to 2 g per 24-hour period) may be administered at the discretion of the PI or designee. Administration of other concomitant medication will be permitted for the treatment of AEs, only when deemed necessary and when agreed by the PI

and Sponsor, unless appropriate medical care necessitates that therapy should begin before the PI and Sponsor can be consulted.

COVID-19 vaccines may be allowed if administered at least 72 hours before dosing or at least 48 hours after dosing. Other vaccines are prohibited from 14 days prior to dosing and through 30 days after dosing.

If deviations occur, the PI or designee in consultation with the Sponsor, if needed, will decide on a case-by-case basis whether the participant may continue participation in the study.

All medications taken by participants beginning 2 weeks prior to screening and during the course of the study will be recorded.

7 DISCONTINUATION OF STUDY DRUG AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Drug

Not applicable.

7.2 Participant Withdrawal from the Study

Participants are free to withdraw from the study at any time for any reason. If a participant withdraws from the study, they will no longer receive study drug or be followed at scheduled protocol visits.

In addition, participants may be withdrawn from the study by the PI or designee or the Sponsor for the following reasons but not limited to:

- AEs.
- Pregnancy.
- Difficulties in blood collection.
- Positive drug or alcohol test.
- Enrollment into the study is inappropriate.
- Non-compliance.
- Protocol violation.
- Study terminated by Sponsor.

The PI or designee must notify the Sponsor when a participant has discontinued or withdrawn from the study. If a participant discontinues or withdraws prior to study completion, efforts should be made to perform all procedures scheduled for early termination as outlined in the Schedule of Activities (Section 1.3).

7.2.1 Withdrawal from Future Biomedical Research

Participants may withdraw their consent for future biomedical research (FBR). Participants may withdraw consent at any time by contacting the PI or designee. If medical records for the study are still available, the PI or designee will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for FBR will be withdrawn. A letter will be sent from the Sponsor to the PI confirming the withdrawal. It is the responsibility of the PI or designee 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 (e.g., if the PI 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.

7.3 Lost to Follow-up

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

- The CRU 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 PI or designee must make every effort to regain contact with the participant at each missed visit (e.g., 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

The Schedule of Activities (Section 1.3) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures will be carried out as per CRU standard operating procedures and are described briefly below. Additional evaluations/testing may be deemed necessary by the PI or designee and/or the Sponsor for reasons related to participant safety.

For this study, the blood collection for enlicitide is the critical parameter and needs to be performed as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior or after the prescribed/scheduled time.

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

8.1 Screening Assessments and Procedures

Within 28 days prior to dosing, medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), BMI (kg/m^2), and tobacco use (including number of cigarettes smoked per day) will be recorded. At the screening visit each participant will be assessed by collection of clinical laboratory tests, temperature, respiratory rate, orthostatic blood pressure and heart rate, 12-lead ECG, and a physical examination.

8.1.1 Hepatic Function Assessment

A baseline Child-Pugh score will be obtained by taking the mean of the Child-Pugh score obtained from the screening visit and from historical values within a 6-month period prior to the screening visit. If no historical measurement is available, a second baseline Child-Pugh score will be taken during the screening period (> 72 hours apart) and the mean of the 2 values will be used for HI group assignment; the second Child-Pugh score may be obtained at the time of check-in (Day -1).

In Group 1 (moderate HI), at least 4 participants must have a score of 2 or higher on at least 1 of the laboratory parameters (i.e., albumin, INR, and bilirubin) on the Child-Pugh scale.

8.1.2 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. The data from participants who fail at screening will not be reported in the case report forms (CRFs).

8.2 Participant Identification Card

Prior to discharge from the CRU, participants who received any portion of study drug will be given a participant identification card identifying them as participants in a research study. The card will contain the identification number and CRU contact information (including direct telephone numbers) to be used in the event of an emergency.

8.3 Safety Assessments and Procedures

8.3.1 Physical Examination

A full physical examination will be performed as outlined in the Schedule of Activities (Section 1.3). Additional physical examinations may be performed at other times, if deemed necessary by the PI or designee.

8.3.2 Standard Vital Signs

Single measurements of body temperature and respiratory rate, and triplicate measurements of blood pressure and heart rate will be performed as outlined in the Schedule of Activities (Section 1.3). If the last value of the triplicate measurement is out of range, one recheck will be performed.

Triplicate measurements of blood pressure and heart rate will be measured approximately 1 minute apart. The median of the three measurements will be used to determine participants' eligibility and baseline values.

Additional vital signs may be taken at any other times, if deemed necessary by the PI or designee.

Blood pressure and heart rate measurements will be performed with participants in a semi-recumbent position for approximately 5 minutes, except when they are supine or seated because of study procedures and/or AEs (e.g., nausea, dizziness) or if deemed necessary by the PI or designee.

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

When scheduled predose, triplicate blood pressure and heart rate and single body temperature and respiratory rate will be measured within 3 hours prior to dosing. When scheduled postdose, body temperature and respiratory rate will be performed within ±20 minutes of the scheduled time point.

8.3.3 Orthostatic Vital Signs

Orthostatic vital signs (i.e., heart rate and blood pressure) will be measured as outlined in the Schedule of Activities (Section 1.3). Measurements will be collected with participants in a semi-recumbent position and then collected when in a standing position.

Additional orthostatic blood pressure and heart rate may be taken at any other times, if deemed necessary by the PI or designee.

When scheduled predose, orthostatic blood pressure and heart rate will be measured within 3 hours prior to dosing in each period. When scheduled postdose, orthostatic blood pressure and heart rate will be performed within ±20 minutes of the scheduled time point.

8.3.4 Electrocardiograms

Single and triplicate 12-lead ECGs will be performed as outlined in the Schedule of Activities (Section 1.3). Additional ECGs may be taken at any other times, if deemed necessary by the PI or designee.

Triplicate 12-lead ECGs will be performed within an approximately 6-minute time window, at the time points indicated in the Schedule of Activities (Section 1.3). The 3 individual ECG tracings at each time point should be obtained approximately 1 minute apart. The mean value from the 3 ECG tracings collected prior to first dosing will be considered the baseline ECG.

ECGs will be performed with participants in a supine position for at least 5 minutes.

All ECG tracings will be reviewed by the PI or designee.

Triplicate ECGs will be measured within 3 hours prior to dosing. When scheduled postdose, single ECGs will be performed within ±20 minutes of the scheduled time point.

8.3.5 Clinical Laboratory Assessments

All tests listed below will be performed as outlined in the Schedule of Activities (Section 1.3). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the PI or designee.

Hematology
- Hemoglobin
- Hematocrit
- Total and differential leukocyte count
- Red blood cell count
- Platelet count

Coagulation
- Prothrombin time / INR
- Activated partial thromboplastin time

Serum Chemistry *
- Blood urea nitrogen
- Bilirubin (total, direct, and indirect)
- Alkaline phosphatase
- AST
- ALT
- Albumin
- Sodium
- Potassium
- Chloride
- Glucose (fasting)
- Creatinine **
- Creatine phosphokinase
- Cholesterol
- Triglycerides

Urinalysis
- pH
- Specific gravity
- Protein ***
- Glucose
- Ketones
- Bilirubin
- Blood ***
- Nitrite***
- Urobilinogen
- Leukocyte esterase ***

Additional Tests
- HIV
- HBsAg
- HCV (if antibody is positive, confirm RNA)
- COVID-19 screen
- Urine/saliva drug screen
  - Opiates
  - Opioids
  - Amphetamines
  - Cocaine
- Urine/breath alcohol screen
- Serum/urine pregnancy test (for females only)
- Serum FSH (for PMP females only)

* Serum chemistry tests will be performed after a fast of at least 12 hours; however, in case of dropouts or rechecks, participants may not have fasted for 12 hours prior to when the serum chemistry sample is taken.

** At the screening visit, eGFR will be calculated.

*** If urinalysis is abnormal for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

8.3.6 Adverse Events and Serious Adverse Events

8.3.6.1 Definition of Adverse Event

An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE will be considered treatment-emergent if the onset date and time is at the time of or after study drug administration.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Note: For purposes of AE definition, study drug 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 treatment), 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 (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the PI or designee.
- 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 drug 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 as determined by the PI or designee.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication as determined by the PI or designee.
- 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.”

Events NOT meeting the AE definition

- Medical or surgical procedure (e.g., 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.

8.3.6.2 Definition of Serious Adverse Event

An SAE is any AE or suspected adverse reaction that in the view of either the PI or designee or Sponsor, results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening is defined as an AE or suspected adverse reaction that in the view of the PI or designee or Sponsor, its occurrence places the patient or participant at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

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 a Sponsor product and is documented in the participant's medical history.

Unexpected is defined as an AE or suspected adverse reaction that is not listed in the IB or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

8.3.6.3 Monitoring

Participants will be monitored for adverse reactions to the study drugs and/or procedures from the time of signing the ICF until the follow-up visit. Prior to release, participants will be asked how they are feeling. Participants will be queried with an open-ended question such as: 'How have you been feeling since your last visit?'

AEs (whether serious or non-serious) and clinically significant abnormal laboratory test value(s) will be evaluated by the PI or designee and treated and/or followed up until the symptoms or value(s) return to normal, or acceptable levels, as judged by the PI or designee.

Treatment of serious adverse events (SAEs) will be performed by a licensed health care professional, either at Celerion or at a nearby hospital emergency room where appropriate medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as fatal, not recovered/not resolved, recovered/resolved, recovered/resolved with sequelae, or recovering/resolving.

8.3.6.4 Reporting

All AEs that occur during this clinical study will be recorded. All clinically significant abnormal laboratory results should be reported as AEs.

AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before dosing, must be reported by the PI or designee 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 treatment, including but not limited to washout or discontinuation of usual therapy, diet, placebo, or a procedure.

From the time of dosing through approximately 14 days after cessation of dosing of study drug, all AEs, SAEs, and other reportable safety events must be reported by the PI or designee.

Additionally, any SAE brought to the attention of the PI 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 drug.

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

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

Assessment of causality

- Did the study drug cause the AE?
- The determination of the likelihood that the study drug caused the AE will be provided by a PI who is a qualified physician. The PI'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 PI 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 drug and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study drug caused the AE:**
    - **Exposure**: Is there evidence that the participant was actually exposed to the study drug 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 drug? 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 drug 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 drug; (3) the study is a single-dose drug study; or (4) study drug(s) is/are only used 1 time.)
    - **Rechallenge**: Was the participant re-exposed to the study drug in this study?
        - If yes, did the AE recur or worsen?
        - If yes, this is a positive rechallenge.
        - If no, this is a negative rechallenge.

(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) study drug(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 DRUG, OR IF RE-EXPOSURE TO THE STUDY DRUG 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.

- **Consistency with study drug profile**: Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study drug or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the CRFs/worksheets by a PI 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 drug relationship).
  - Yes, there is a reasonable possibility of study drug relationship:
    - There is evidence of exposure to the study drug. The temporal sequence of the AE onset relative to the administration of the study drug is reasonable. The AE is more likely explained by the study drug than by another cause.
  - No, there is not a reasonable possibility of study drug relationship:
    - Participant did not receive the study drug OR temporal sequence of the AE onset relative to administration of the study drug is not reasonable OR the AE is more likely explained by another cause than the study drug. (Also entered for a participant with overdose without an associated AE.)
- The PI 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 PI has minimal information to include in the initial report to the Sponsor. However, it is very important that the PI always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The PI 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.

Assessment of intensity/toxicity

Each sign or symptom reported will be graded on a 3-point severity scale (mild, moderate, or severe), and the date of onset, time of onset, and outcome of each event will be noted.

The following definitions will be used for rating the severity of AEs:

Mild	The AE is easily tolerated and does not interfere with daily activity.
Moderate	The AE interferes with daily activity, but the participant is still able to function. Medical intervention may be considered.
Severe	The AE is incapacitating and requires medical intervention.

8.3.6.5 Reporting for SAEs

If any AEs are serious, as defined by the Food and Drug Administration (FDA) Code of Federal Regulations (CFR), Chapter 21, special procedures will be followed. All SAEs will be reported to the Sponsor via fax or e-mail within 24 hours of becoming aware of the event, whether or not the serious events are deemed drug-related. This will be followed by the SAE Report within 24 hours. All serious event reporting will adhere to 21 CFR 312.32 for Investigational New Drugs (IND) and to the Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE, dated December 2012. The IRB will be notified of the Alert Reports as per FDA regulations.

If an SAE occurs to a participant on this study, contact the Sponsor personnel listed in the Additional Key Contacts for the Study section.

8.3.7 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.

8.3.8 Events of Clinical Interest

Selected serious and nonserious AEs are also known as events of clinical interest (ECIs) and must be reported to the Sponsor.

ECIs for this study include:

1. An overdose of study drug, as defined in Section 8.3.9.
2. Potential drug-induced liver injury events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3x the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2x the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2x the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based 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 PI 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.

8.3.9 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose of any study drug administered that exceeds the dose prescribed by the protocol. It is up to the PI or the reporting physician to decide whether a non-study drug dose (e.g., rescue or concomitant medication) is to be considered an overdose, in consultation with the Sponsor.

Refer to the IB for specific treatment of overdose. Decisions regarding dose interruptions or modifications will be made by the PI or designee in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

8.4 Pharmacokinetic Assessments

8.4.1 Blood Sampling and Processing

For all participants, blood samples for the determination of enlicitide will be collected at scheduled time points as delineated in the Schedule of Activities (Section 1.3).

Instructions for blood sampling, collection, processing, and sample shipment will be provided separately. Blood samples collected may be stored and further analysis may be performed, if required.

The allowed window for PK blood sampling is indicated in Table 3.

Table 3: Window for PK Blood Sample Collection

Nominal Time	Allowed Window
Predose	Within 30 minutes prior to dosing
> 0 to < 1 hour	≤ ± 5 minutes
1 to < 2 hours	≤ ± 10 minutes
2 to < 24 hours	≤ ± 15 minutes
24 to < 48 hours	≤ ± 1 hour
48 to ≤ 168 hours	≤ ± 4 hours

8.4.2 Pharmacokinetic Parameters

The following PK parameters for plasma enlicitide will be calculated, as appropriate:

AUC0-24:	Area under the concentration versus time curve from 0 to 24 hours after dosing
AUC0-last:	Area under the concentration versus time curve from 0 to the time of the last quantifiable (above lower limit of quantitation) sample
AUC0-inf:	Area under the concentration versus time curve from 0 to infinity after single dosing
AUC%extrap:	Percent of AUC0-inf extrapolated
Cmax:	Maximum observed drug concentration after the administration of a given dose
Tmax:	Time to maximum observed plasma drug concentration
λz:	Lambda z, Apparent terminal elimination rate constant
t½:	Apparent terminal half-life
CL/F:	Apparent clearance
Vz/F:	Apparent volume of distribution during terminal phase

No value for AUC0-inf, AUC%extrap, λz, t½, CL/F, or Vz/F will be reported for cases that do not exhibit a terminal log-linear phase in the concentration-time profile.

PK parameters will not be calculated for participants with less than 3 consecutive postdose time points with quantifiable concentrations.

8.4.3 Long Term Storage and Use

Residual PK samples may be stored by the Sponsor or bioanalytical facility for up to 15 years after dosing and may be used for future analyses (e.g., PK assessment). Tubes will be identified with a barcode using an appropriate label. No diseases/conditions, DNA, or RNA will be the focus of these analyses. The analyses will only focus on analytes/biomarkers. Samples will not be submitted to a public database. The Sponsor and contract research organizations involved in the clinical conduct, bioanalytical analyses and PK and statistical analyses of the data will have access to the samples and/or the data that resulted from the analysis, if performed. By signing the ICF, participants agree to the possible future analysis of these samples. Any additional research on these samples unspecified by this protocol will require approval from the participants.

8.4.4 Analytical Method

Samples from all participants will be assayed even if the participants do not complete the study.

Samples will be analyzed for plasma enlicitide using validated bioanalytical methods.

If indicated, these samples may also be measured and/or pooled for assay in an exploratory manner for metabolites and/or additional PD markers.

8.5 Planned Exploratory Biomarker Research

8.5.1 Planned Exploratory Biomarkers

The mechanism of action of many new therapeutics is not completely understood and much remains to be learned regarding how best to leverage new drugs in treating participants. Thus, to aid future participants, it is important to investigate the determinants of response or resistance to the treatments administered, as well as determinants of AEs in the course of our clinical studies. These efforts may identify novel predictive/pharmacodynamic biomarkers and generate information that may better guide single-agent and combination therapies. To identify novel biomarkers, biospecimens (e.g., blood components, tissue material) will be collected to support analyses of cellular components (e.g., protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include, but are not limited to the following:

Germline genetic analyses (e.g., SNP analyses, whole exome sequencing, whole genome sequencing)

This research may evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. Genome and exome wide approaches may be used for this effort. In addition, epigenetic characterization techniques (i.e., DNA methylation status, histone profiling) may also be explored. If genetic and/or

epigenetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population.

Blood protein biomarker analyses

Blood samples from this study may undergo protein-based biomarker analyses using a variety of platforms that could include, but are not limited to; immunoassays (e.g., enzyme-linked immunosorbent assay) liquid chromatography/mass spectrometry, cytometry, and immunohistochemistry. These approaches may be used to quantify soluble, cell- and/or tissue-based analytes to further elucidate therapy mechanism of action and/or assess disease-related parameters. For immunohistochemical analyses information on spatial context and cellular distribution may also be included. Correlation of protein expression to response to therapy may be performed to identify novel predictive biomarkers that could aid in patient selection for therapy. This research would serve to develop such assays for future clinical use.

8.5.2 Biomarkers

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

- Blood for genetic analysis
- Blood for plasma PD markers (Free PCSK9)

8.5.2.1 Planned Genetic Analysis Sample Collection

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

The planned genetic analysis sample should be obtained predose on Day 1 of Period 1, but may be collected at the next scheduled blood draw, if needed. Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the operations/laboratory manual.

8.5.3 Future Biomedical Research

FBR 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 FBR.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for 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. The details of FBR research are presented in Appendix 1.

8.5.3.1 Future Biomedical Research Sample Collection

All sample collections for study-specific assessments shown in the Schedule of Activities (Section 1.3) are described within the main informed consent.

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

- Leftover samples listed in Section 8.5.1

8.6 Pharmacodynamic Assessments

Blood samples for the determination of plasma free PCSK9 will be collected at scheduled time points as delineated in the Schedule of Activities (Section 1.3). Blood samples collected may be stored and further analysis may be performed, if required. Exploratory PD parameters may be assessed in samples described in Section 8.5.2.

Instructions for blood sampling, collection, processing, and sample shipment will be provided separately.

8.7 Blood Volume Drawn for Study Assessments

Table 4: Blood Volume during the Study

Sample Type	Number of Time Points	Approximate Volume per Time Point * (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, serology, and coagulation), FSH (for PMP female participants only) and serum pregnancy (for female participants only)	1	16	16
Blood for planned genetic analysis	1	8.5	8.5
On-study hematology, serum chemistry (this includes serum pregnancy for female participants only when scheduled at the same time), and coagulation	3	16	48
Blood for enlicitide	15	4	60
Blood for plasma PD markers (free PCSK9)	5	3	15
		Total blood volume (mL)→	147.5 **

* A smaller or larger collection tube size may be used if the present collection tube size is not available.

** If additional blood is needed for PK and/or PD analysis, additional blood may be collected (up to a maximum of 500 mL for the study).

9 STATISTICAL CONSIDERATIONS

Data will be handled and processed according to Celerion Standard Operating Procedures, which are written based on the principles of GCP.

9.1 Sample Size Determination

Data from healthy participants in the fasted state after administration of a single oral dose of 20 mg enlicitide [redacted] from the following protocols was used to estimate between participant variance: MK-0616-005, MK-0616-009 (18 mg enlicitide), MK-0616-020 (preliminary data), MK-0616-022 (preliminary data), and MK-0616-024 (preliminary data). The approximate 90% CI of the expected geometric mean ratio (GMR) estimate for the GMRs listed below would be:

Table 5: Approximate 90% CI of the Expected GMR Estimate

GMR	AUC0-inf 90% CI	Cmax 90% CI
0.8	(0.63, 1.01)	(0.66, 0.97)
0.9	(0.71, 1.14)	(0.74, 1.09)
1.0	(0.79, 1.27)	(0.82, 1.21)
1.1	(0.87, 1.39)	(0.91, 1.34)
1.2	(0.95, 1.52)	(0.99, 1.46)
1.25	(0.99, 1.58)	(1.03, 1.52)
Assumes a between-participant coefficient of variation of 41.1% for AUC0-inf, 33.4% for Cmax. Confidence intervals calculated for 10 participants per group.		

If the true AUC0-inf adjusted geometric means following administration of a single 20 mg oral dose of enlicitide for both the participants with moderate hepatic insufficiency and their matched healthy control group are the same (GMR=1.0), then a sample size of n=10 moderate hepatic insufficiency participants and n=10 participants in the matched healthy control group provide this study with 96.6% probability of observing the 90% CI for the GMR to be contained within [0.50, 2.00].

9.2 Population for Analyses

Safety Population: The Safety Population will include all participants who received any portion of study drug.

PK Population: The PK Population will include all participants in the Safety Population who completed at least 1 PK blood draw sample.

PK Analysis Population: The PK Analysis Population, a subset of the PK Population, will include all participants who comply sufficiently with the protocol and have ample PK data to display an evaluable PK profile (e.g., exposure to treatment, availability of measurements, and absence of major protocol violations). The PK Analysis Population will be used in concentration summaries, PK parameter summaries, and statistical analyses.

Note: If participants experience issues that affect exposure to study drug (e.g., emesis, dosing errors, incomplete data, significant drug carryover, important protocol violation, sample processing errors), data will be reviewed by the study pharmacokineticist and evaluated for exclusion from the PK Analysis Population on a case-by-case basis. All participants excluded from the PK Analysis Population will be documented.

All available data will be included in the concentration and PK parameter listings/tables to the extent possible.

PD Population: The PD population will include all participants in the Safety Population who have at least one predose and one postdose PD result (i.e., free PCSK9). The PD Population will be used in the PD data summary and statistical analyses, if applicable.

9.3 Statistical Analyses

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP). The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate.

9.3.1 Pharmacokinetic Analyses

9.3.1.1 Descriptive Statistics

The plasma enlicitide concentrations and the PK parameters listed in Section 8.4.2 will be summarized using the appropriate descriptive statistics which will be fully outlined in the SAP.

9.3.1.2 Model-based PK Analysis

Individual values of plasma PK (AUC0-inf, AUC0-24, AUC0-last, Cmax, CL/F, Vz/F) after a single oral dose of enlicitide to participants with moderate HI and healthy matched control participants will be natural log-transformed and evaluated with a linear fixed effects model containing a fixed effect for population (participants with moderate HI and healthy matched control participants).

Ninety-five percent (95%) CIs for the least-squares means (LSMs) for each population will be constructed on the natural log scale and will reference the t-distribution. Exponentiating

the LSMs and their corresponding 95% CIs will yield estimates for the population geometric means and CIs about the geometric means on the original scale.

To compare participants with moderate HI to the healthy control participants, a 2-sided 90% CI for the true difference in means (moderate HI - healthy) will be calculated for each PK parameters of interest using the mean square error from the model and referencing a t-distribution. The confidence limits will be exponentiated to obtain the 90% CI for the true ratio of geometric means (moderate HI/healthy) for each PK parameter. If the 90% CI for the AUC0-inf ratio is contained within 0.50 and 2.00, then no clinically significant difference between participants with moderate HI compared to healthy matched control participants will be concluded.

Figures showing individual PK values with geometric means (95% CIs) by population, plotted on the natural log scale, will be provided for AUC0-inf, AUC0-last, and Cmax.

If Part 2 (mild HI) is conducted, the same analysis as described above for the moderate HI group (Part 1) will be applied for the mild HI group.

9.3.1.3 Relationship Between Impaired Hepatic Function and PK

The relationship between selected enlicitide PK parameters and hepatic function parameters (e.g., albumin, prothrombin time, overall Child-Pugh scores) may be examined in an exploratory manner graphically. Details will be provided separately.

9.3.2 Safety Analyses

AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities® available at Celerion and summarized by group for the number of participants reporting the TEAE and the number of TEAEs reported. A by-participant AE data listing including verbatim term, coded term, treatment, severity, action, and relationship to treatment will be provided.

Safety data including clinical laboratory results, standard and orthostatic vital sign assessments, and 12-lead ECGs will be summarized by group and time point of collection.

Quantitative safety data as well as the change from baseline, when appropriate, will be summarized using the appropriate descriptive statistics.

Concomitant medications will be listed by participant and coded using the most current version of World Health Organization Drug Dictionary available at Celerion.

Medical history will be listed by participant.

9.3.3 Pharmacodynamic Analysis

The plasma free PCSK9 concentrations will be summarized using the appropriate descriptive statistics which will be fully outlined in the SAP. Free PCSK9 analysis may be triggered following review of PK data. Reduction of free PCSK9 relative to baseline may also be determined in an exploratory manner. More details will be provided separately.

9.3.4 Interim Analysis

Safety and PK data from Part 1 (i.e., participants with moderate HI [Group 1] and their matched healthy control participants [Group 2]) will be reviewed before determining to proceed with Part 2 (i.e., participants with mild HI [Group 3]).

10 STUDY ADMINISTRATION

10.1 Ethics

10.1.1 Institutional Review Board

This protocol will be reviewed by an IRB and the study will not start until the IRB has approved the protocol or a modification thereof. The IRB is constituted and operates in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56). The IRB is ICH compliant.

10.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, 21 CFR Parts 50, 56, and 312, the ethical principles set forth in the Declaration of Helsinki, GCP, and the ICH harmonized tripartite guideline regarding GCP (E6[R2] Good Clinical Practice: Integrated Addendum to E6 [R1], November 2016).

10.1.3 Participant Informed Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the participants in non-technical terms. Participants will be required to read, sign and date an ICF summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

10.1.3.1 General Informed Consent

Informed consent given by the participant 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 and of the person conducting the consent discussion.

A copy of the signed and dated ICF will be given to the participant before participating in the study.

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB's approval/favorable opinion in advance of use. 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.

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

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

10.1.3.2 Consent and Collection of Specimens for Future Biomedical Research

The PI or designee will explain the optional FBR consent to the participant, answer all of their questions, and obtain documented informed consent before performing any procedure related to FBR.

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

The original FBR, 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 should be informed in a timely manner.

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

10.1.4 Confidentiality

All clinical sites and vendors will have signed confidentiality agreements with Celerion. By signing this protocol, the PI and CRU staff will regard all information provided by the Sponsor and all information obtained during the course of the study as confidential.

The clinical site and Celerion must guarantee the privacy of the participants taking part in the study. Participants will be identified throughout documentation and evaluation by a unique participant study number. Throughout the study, a participant's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. If participant name appears on any study document, it must be redacted before the copy of the documents is supplied to the Sponsor. Any information concerning the participants (clinical notes, identification numbers, etc.) must be kept on file by the PI or designee who will ensure that it is revealed only to the Sponsor, IRB, or regulatory authorities for the purposes of trial monitoring, auditing or official inspections. As required, in the case of an event where medical expenses are the responsibility of the Sponsor, personal information i.e., full name, social security details etc. may be released to the Sponsor. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information in strictest confidence and in accordance with local data protection laws.

10.2 Study Termination

The CRU(s) reserves the right to terminate the study in the interest of participant welfare.

The Sponsor reserves the right to suspend or terminate the study at any time.

10.3 Data Management

Data management activities will be detailed in the Data Management Plan (DMP). Each vendor involved with this study will adhere to Good Documentation Practices and their standard operating procedures covering their respective activities relevant to participation in this study, as applicable. The PI or designee will ensure that all data related to the conduct of this study is attributable, legible, contemporaneous, original, accurate, enduring, and readily accessible.

Standard operating procedures are available for all activities performed at the CRU relevant to the quality of this study. Designated personnel of the CRU will be responsible for implementing and maintaining quality assurance (QA) and quality control systems to ensure that the study is conducted, and that data are generated, documented and reported in compliance with the study protocol, and GCP requirements as well as applicable regulatory requirements and local laws, rules and regulations relating to the conduct of the clinical study.

The Clinical Study Report will be audited by the QA department and the QA audit certificate will be included in the Clinical Study Report.

10.3.1 Data Entry and Verification

Data will be transcribed from original sources by the PI or designee into the CRF. Data received from external sources, as applicable, will be integrated into the Clinical Data Interchange Standards Consortium study data tabulation model datasets.

10.3.2 Data Validation

After the data have been entered, various edit checks (including manual review of listings) will be performed to ensure the accuracy, integrity and validation of the database against the CRF as described in the DMP.

Inconsistencies that arise from these edit checks will be resolved with the PI or designee.

10.3.3 Database Lock

Upon study completion, after data entry is complete, the data has been pronounced clean, and the PI has reviewed and provided approval via signature, the database will be locked and final write access will be removed.

The Sponsor will be required to provide database lock approval.

Any changes to the data following database lock will be documented and approved by the Sponsor prior to unlocking the database to make changes to the data.

The final transfer of all study data to the Sponsor will be in SAS format with supporting documentation as described in the DMP.

10.4 Direct Access to Source Data/Documents

All CRUs and vendors will ensure that the Sponsor, IRB and inspection by domestic and foreign regulatory authorities will have direct access to all study-related sites, source data/documents, and reports for the purpose of monitoring and auditing (ICH[E6][R2] 5.1.2 & 6.10). In the event that other study-related monitoring should be done by other parties, they will be required to sign a confidentiality agreement prior to any monitoring and auditing.

10.5 Reporting of the Study

10.5.1 Case Report Forms

A CRF is completed for each dosed participant whether or not the participant has completed the study. The PI will assure complete and accurate entries on the forms. Each CRF will be reviewed and signed by the PI. The final signed CRFs will be archived electronically at the end of study in a document repository system. Final CRFs will be provided to the Sponsor in the format and transfer method as decided between Celerion and the Sponsor which will be documented in the DMP.

10.5.2 Record Keeping

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

It is the responsibility of the Sponsor to inform the PI/Institution as to when these documents no longer need to be retained.

10.5.3 Report Format

According to the ICH Harmonized Tripartite Guideline (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the ICH M2 Expert Working Group), the final clinical study report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

10.6 Publication Policy

All unpublished information given to Celerion and/or the CRU by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

The data generated by this study are considered confidential information and the property of the Sponsor. This confidential information may be published only in collaboration with participating personnel from the Sponsor or upon Sponsor's written consent to publish the article.

11 REFERENCES

EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS); Mortensen A, Aguilar F, Crebelli R, Di Domenico A, et al. Re-evaluation of fatty acids (E 570) as a food additive. EFSA J. 2017;15(5):e04785.

European Medicines Agency (EMA). Guideline on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired Hepatic Function (Feb 2005). Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-pharmacokinetics-medicinal-products-patients-impaired-hepatic-function_en.pdf

Food and Drug Administration: Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function - Study Design, Data Analysis, and Impact on Dosing and Labeling (May 2003). Available at: https://www.fda.gov/media/71311/download

Food and Drug Administration. Salts of fatty acids. In: Food additives permitted for direct addition to food for human consumption. 21CFR172.863 (Dec 2023). Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=172.863

Fox KM, Tai MH, Kostev K, Hatz M, Qian Y, Laufs U. Treatment patterns and low-density lipoprotein cholesterol (LDL-C) goal attainment among patients receiving high- or moderate-intensity statins. Clin Res Cardiol. 2018;107(5):380-388.

Praluent® (alirocumab) injection for subcutaneous use, full prescribing information (electronic monograph) published on the FDA website (document revised: 04/2021).

Repatha® (evolocumab) injection for subcutaneous use, full prescribing information (electronic monograph) published on the FDA website (document revised: 02/2021).

12 APPENDICES

12.1 Appendix 1: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

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

The specimens consented and/or collected in this study as outlined in Section 8.5.3 will be used in various experiments to understand:

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

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

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

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

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in FBR.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants, at a study visit by the PI or designee. Informed consent for FBR should be presented to the participants on the visit designated in the Schedule of Activities (Section 1.3). If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

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

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for FBR will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for FBR will be performed as outlined in the Schedule of Activities (Section 1.3). In general, if additional blood specimens are being collected for FBR, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

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

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

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

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

5. Biorepository Specimen Usage [3, 4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses using the FBR specimens may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The PI 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 FBR protocol and consent. FBR specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

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

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

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

7. Retention of Specimens

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

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

8. Data Security [3, 4]

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

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

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

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

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

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

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

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

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

12. Questions

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

13. References

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

12.2 Appendix 2: 12-Lead Electrocardiogram Evaluation Criteria

	Screen Failure Criteria	Potentially Significant Postrandomization Findings (Clarification on Action to Take)
RHYTHM		
Sinus Tachycardia	>110 bpm	HR >110 bpm and HR increase of ≥25 bpm from baseline
Sinus Bradycardia	<40 bpm	HR <40 bpm and HR decrease of ≥5 bpm from baseline
Sinus Pause/Arrest	>2.0 seconds	>2.0 seconds
Atrial Premature Complex	>1 beat	≥3 beats
Ventricular Premature Complex	All	≥3 beats
Ectopic Atrial Rhythm	None	None
Junctional Rhythm	Junctional Rhythm with HR <40 bpm	Junctional Rhythm with HR <40 bpm
Idioventricular Rhythm	All	All
Atrial Fibrillation	All	All
Atrial Flutter	All	All
Supraventricular Tachycardia	All	All
Ventricular Tachycardia	All	All
AXIS		
Left Axis Deviation	RBBB with LAHB	New Onset LAHB
Right Axis Deviation	RBBB with LPHB	New Onset LPHB
CONDUCTION		
1st Degree AV Block	PR ≥230 ms	PR ≥230 ms + Increase of >15 ms; or PR Increase of >25%
2nd Degree AV Block	Mobitz Type II	Mobitz Type II
3rd Degree AV Block	All	All
LBBB	All	All
RBBB	RBBB with LAHB/LPHB as defined above	New Onset RBBB (Not Including Rate-related)
ICRBBB (QRS <120 ms)	No Exclusion	Nothing
Short PR/Preexcitation Syndrome	Delta Wave + PR <120 ms	Delta Wave + PR <120 ms
Other Intra-Ventricular Conduction Delay	QRS ≥130 ms	QRS ≥130 ms + Increase of ≥10 ms
QTcF		
Male	QTcF ≥470 ms	QTcF ≥500 ms or Increase of ≥60 ms From Baseline
Female	QTcF ≥480 ms	QTcF ≥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
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 Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
T-wave Inversions Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
Non-specific ST-T Changes (in 2 or More Leads)	No exclusion	In 2 or more contiguous leads
PACEMAKER	All	All

Abbreviations: AV = atrioventricular; bpm = beats per minute; HR = heart rate; ICRBBB = incomplete right bundle branch block; LAHB = left anterior hemiblock; LPHB = left posterior hemiblock; LVH = left ventricular hypertrophy; mm = millimeter; ms = milliseconds; PR = pulse rate; QTcF = QT correction using Fridericia formula; RBBB = right bundle branch block; ST/T = ST segment/T wave.
Baseline is defined as Predose on Day 1 in each period.

12.3 Appendix 3: Algorithm for Assessing Out of Range Laboratory Values

For all laboratory values obtained at the screening visit and/or predose evaluation:

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

2. 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.

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

    a. The participant may be excluded from the study.

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

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

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

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

        ii. If the repeat test value is still abnormal, the PI 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.

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