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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A PHASE 2, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF SAFETY AND EFFICACY FOLLOWING REPEAT-DOSE ADMINISTRATION OF EVINACUMAB (ANTI-ANGPTL3) IN PATIENTS WITH SEVERE HYPERTRIGLYCERIDEMIA (SHTG) AT RISK FOR ACUTE PANCREATITIS

Compound:	evinacumab (REGN1500)
Clinical Phase:	2
Protocol Number:	R1500-HTG-1522
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Cardiovascular and Metabolism
Clinical Development and Regulatory Affairs
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AMENDMENT 5

The protocol was amended in response to recent nonclinical findings in the rabbit. The table below summarizes the changes and the affected sections:

Change	Sections Changed
In an embryofetal development toxicology study in rabbits, incomplete ossification of the 15th vertebra was observed in some fetuses resulting from the mating of male rabbits exposed to evinacumab with female rabbits not exposed to evinacumab. In male rabbits, there were measurable levels of evinacumab in seminal fluid and, as a safety measure, the current clinical study is amended to require consistent use of a condom for all sexually active males.	Section 3.2.1 Rationale for Study Design Section 6.2.2 Exclusion Criteria, #25 Table 1 Schedule of Events
Updated Scientific/Medical Monitor	Title page

AMENDMENT 4

The table below summarizes the changes and affected sections:

Change	Sections Changed
The descriptions of the cohorts have been updated to use only genotype information in the medical history (or lack of genotype information) for cohort assignment. This change has been made based upon recent data indicating that the baseline measurements of LPL activity may not be sufficiently robust to differentiate individuals in cohorts 2 and 3.	Clinical Study Protocol Synopsis: Objectives, Study Design, Endpoints, Statistical Plan Section 2.1 Primary Objectives Section 2.2 Secondary Objectives Section 2.3 Exploratory Objectives Section 3.1 Hypothesis Section 3.2.1 Rationale for Study Design Section 4.2.1 Primary Endpoint Section 4.2.2 Secondary Endpoints Section 4.2.3 Exploratory Endpoints Section 5.1 Study Description and Duration Section 6.2 Study Population Section 8.2.9.1 Genomics Study Section 10.2 Justification of Sample Size Section 10.4.3.1 Primary Efficacy Analysis Appendix 1 Known LPL and APOC2 Null (Total Loss of Function) Mutations
Updated text regarding blinding for drug product and placebo	Section 7.6.1 Blinding Section 7.7.1 Packaging, Labeling, and Storage
Edits/Clarifications/Updates	Section 6.2.1 Inclusion Criteria, #4 Section 8.2.4.1 18F-FDG PET Section 8.2.6.2 Anti-Drug Antibody Measurements and Samples Section 10.4.3.1 Primary Efficacy Analysis Section 10.4.3.2 Secondary and Exploratory Efficacy Analysis Section 21 References

AMENDMENT 3

The protocol is amended in response to comments from FDA. The table below summarizes the changes and affected sections:

Change	Sections Changed
Updated ADA variables and added a sentence for follow-up of patients whose last sample was positive in the ADA assay	Section 4.4 Anti-Drug Antibody Variables Section 8.2.6.2 Anti-Drug Antibody Measurements and Samples
Modified a secondary objective/endpoint for MRI T2 imaging and added to exploratory objectives/endpoints	Clinical Study Protocol Synopsis: Objectives, Endpoints Section 2.2 Secondary Objectives Section 2.3 Exploratory Objectives Section 4.2.2 Secondary Endpoints Section 4.2.3 Exploratory Endpoints
Allowed more flexibility for a planned interim analysis	Section 5.2 Planned Interim Analysis Section 10.5 Interim Analysis
Allowed other select individuals at the sponsor to have access to unblinded data for safety or other data review. Added text for an unblinded pharmacist/qualified designee	Section 7.6.1 Blinding
Added more specificity to the daily symptom and symptom/dietary impact questionnaires	Table 1 Schedule of Events
Moved collection of the baseline (visit 3) ADA sample to day 1 (visit 5), and added an ADA sample at day 29 (visit 7)	Table 1 Schedule of Events
Expanded list of AESIs for evinacumab	Section 9.4.3 Other Events that Require Accelerated Reporting to Sponsor
Edits/Clarifications	Clinical Study Protocol Synopsis: Study Design Section 3.2.1 Rationale for Study Design Section 5.1 Study Description and Duration Section 6.2 Study Population Section 6.2.2 Exclusion Criteria Section 7.1 Investigational and Reference Treatments

AMENDMENT 2

The following table outlines the changes made to the protocol and the affected sections:

Change	Section Changed
Clarified the age range of the patient population, which was specified in an additional inclusion criterion	Clinical Study Protocol Synopsis: Study Design, Treatment, Population, Statistical Plan
Specified that the screening TG measurements at Visit 1 and Visit 1b should be at least 4 days apart	Section 2.3 Exploratory Objectives
Added measurement of C-peptide and aligned inflammation parameters in schedule of events table with the listings of laboratory tests in other parts of the protocol	Section 3.2.1 Rationale for Study Design
Changed “Study Enrollment” to “Cohort Assignment” in schedule of events to clarify timing of cohort assignment	Section 4.2.3 Exploratory Endpoints
Added line to schedule of events to denote timing of randomization at visit 5	Section 5.1 Study Description and Duration
Renumbered relative timing of visits to make Day 1 correspond to first visit of double blind period	Figure 1 Study Flow Diagram
Extended the screening period to ensure that all required assessments can be completed	Section 6.2 Study Population
Minor alterations of footnotes in schedule of events to improve clarity	Section 6.2.1 Inclusion Criteria #1 and #2
Clarified blinding of lipid measurements and analysis sets	Section 7.1 Investigational and Reference Treatments
Clarifications/Edits	Section 7.2 Run-in Treatment(s)
	Section 7.4.2 Study Drug Discontinuation
	Section 7.6 Method of Treatment Assignment
	Section 7.6.1 Blinding
	Table 1 Schedule of Events
	Section 8.1.1 Footnotes for Schedule of Events Table
	Section 8.1.2 Early Termination Visit
	Section 8.2.4.2 Magnetic Resonance Imaging
	Section 8.2.5.4 Laboratory Testing
	Section 10.3.1 Full Analysis Set
	Section 10.3.2 Safety Analysis Set
	Section 10.3.3 Pharmacokinetics Analysis Set
	Section 10.4.3.1 Primary Efficacy Analysis
	Section 10.4.3.2 Secondary and Exploratory Efficacy Analysis
	Section 10.4.5.1 Adverse Events
	Section 10.4.9.1 First Step: Main Efficacy and Safety Analysis
	Section 10.4.9.2 Second Step: Final Efficacy and Safety Analysis

AMENDMENT 1

The following table outlines the changes made to the protocol and the affected sections:

Change	Section Changed
Sample size increase to "up to 50 patients" to evaluate effect of evinacumab on recurrent acute pancreatitis. Increase number of sites to approximately 20. Changed classification of study from phase 1b to phase 2 Updated and added exploratory objectives and endpoints regarding acute pancreatitis and post heparin LPL activity	Title Page Clinical Study Protocol Synopsis: Title, Site Location, Objectives, Endpoints, Study Design, Population Section 1 Introduction Section 2.2 Secondary Objectives Section 2.3 Exploratory Objectives Figure 1 Study Flow Diagram Section 3.2.1 Rationale for Study Design Section 4.2.2 Secondary Endpoints Section 4.2.3 Exploratory Endpoints Section 5.1 Study Description and Duration Section 5.2 Planned Interim Analysis Section 6.1 Number of Patients Planned Section 6.2 Study Population Section 7.6 Method of Treatment Assignment Section 10.2 Justification of Sample Size Section 10.5 Interim Analysis Section 22 Investigator's Agreement Signature of Sponsor's Responsible Officers
Added explanation regarding the rationale for the single- and double-blind periods	Section 3.2.1 Rationale for Study Design
Inclusion criteria modified to include patients with a history of pancreatitis in the past 10 years Updated inclusion and exclusion criteria regarding alcohol consumption, lipid modifying diets & medication and history of cardio vascular disease Clarified the description of the cohorts Updated enrollment procedure for patients according to genotypes in the medical history and/or LPL activity measurements at visit 2	Clinical Study Protocol Synopsis: Study Design Section 1 Introduction Section 3.2.1 Rationale for Study Design Section 5.1 Study Description and Duration Section 6.2 Study Population Section 6.2.1 Inclusion Criteria: #2, #3, and #5 Section 6.2.2 Exclusion Criteria: #3 and #10

Change	Section Changed
Updated language regarding study drug concentration and anti-drug antibody concentration Added footnote that PK samples will also be used for analysis of total ANGPTL3 concentration and added ANGPTL3 to the drug concentration data Updated visits when ADA samples are taken	Clinical Study Protocol Synopsis: Objectives, Endpoints Section 2.2 Secondary Objectives Section 3.2.2 Rationale for Dose Selection Section 4.2.2 Secondary Endpoints Section 4.3 Pharmacokinetic Variables Section 4.4 Anti-Drug Antibody Variables Table 1 Schedule of Events Section 8.1.1 Footnotes for the Schedule of Events Table: footnote #21 Section 10.3.4 Anti-Drug Antibody Analysis Set Section 10.4.6 Analysis of Drug Concentration Data Section 10.4.7 Analysis of Anti-Drug Antibody Data Table 1 Schedule of Events
Added lomitapide and mipomersen to the list of prohibited medications and disallowed concomitant use during the study. Specified if PCSK9 inhibitors are used as background LMT, the dose should be stable for at least 8 weeks prior to screening. Modified the list of permitted medications and procedures	Clinical Study Protocol Synopsis: Study Design Section 5.1 Study Description and Duration Section 6.2.1 Inclusion Criteria: #3 Section 6.2.2 Exclusion Criteria: #16 Section 7.8.1 Prohibited Medications Section 7.8.2 Permitted Medications and Procedures
Add end of study definition	Section 5.1.1 End of Study Definition
Clarified primary efficacy analysis with respect to baseline Simplified first step analyses. Modified description of interim analysis to allow for planned early analysis of TG efficacy in cohort 1 (FCS)	Clinical Study Protocol Synopsis: Statistical Plan Section 5.2 Planned Interim Analysis Section 10.4.3.1 Primary Efficacy Analysis Section 10.4.9.1 First Step: Main Efficacy and Safety Analysis Section 10.5 Interim Analysis
Updated contraception language to add male contraception and clarified text regarding pregnancy status and contraception. Provide greater detail of study drug discontinuation and early termination, particularly with regards to women of child-bearing potential Added information that sites will provide urine pregnancy tests to female patients of childbearing potential to be used at home. Added pregnancy reporting for female partners of male patients	Clinical Study Protocol Synopsis: Study Design Section 5.1 Study Description and Duration Section 6.2.2 Exclusion Criteria: #25 Section 7.4.2 Study Drug Discontinuation Table 1 Schedule of Events Section 8.1.1 Footnotes for Schedule of Events Table: footnote #23 Section 8.1.2 Early Termination Visit Section 8.2.5.4 Laboratory Testing Section 9.4.3 Other Events That Require Accelerated Reporting to Sponsor Table 1 Schedule of Events
Added an Independent Data Monitoring Committee	Section 5.3.1 Independent Data Monitoring Committee
Sponsor will provide site with retention manual Updated information regarding follow-up of patients who prematurely discontinue the study	Section 6.3 Premature Withdrawal from the Study Section 7.4.2 Study Drug Discontinuation Section 8.1.2 Early Termination Visit

Change	Section Changed
Added Sampson criteria for anaphylaxis	Section 7.5.1.2 Termination of the Infusion Section 21 References
Provide more detail about blinding	Section 7.7.1 Packaging, Labeling, and Storage
Added assessment of "adverse events" at visit 1b in the schedule of events Added urine pregnancy assessments at phone visits	Table 1 Schedule of Events
Updated information on electrocardiograms	Section 8.2.5.3 Electrocardiogram
Added adverse events of special interest (anaphylactic reaction and allergic reaction)	Section 9.4.3 Other Events that Require Accelerated Reporting to Sponsor
Remove the requirement that patients be identified by their initials on CRFs and other documents submitted to the sponsor to preserve patient confidentiality	Section 14.3 Patient Confidentiality and Data Protection
Included information regarding amendments, where applicable, need to be approved by local regulatory agency	Section 15 Protocol Amendments
Updated study drug name from REGN1500 to evinacumab and provided units for TG in mmol/L Made editorial changes for clarity and consistency	Various sections
Update to reference	Section 1 Introduction Section 3.2.1 Rationale for Study Description Section 21 References

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Phase 2, Randomized, Placebo-Controlled Study of Safety and Efficacy, Following Repeat-Dose Administration of Evinacumab (anti-ANGPTL3) in Patients with Severe Hypertriglyceridemia (sHTG) at Risk for Acute Pancreatitis
Site Locations	The study will be conducted at approximately 20 study sites globally.
Principal Investigator	*PI to be determined.*
Objective(s)	Primary Objective: The primary objective of the study is to determine the change in triglycerides (TG) levels following 12 weeks of repeated intravenous (IV) doses of evinacumab in the subset of patients with a documented history of sHTG (TG ≥1000 mg/dL [11.3 mmol/L]), a TG level of at least 500 mg/dL (5.6 mmol/L) at screening, a history of acute pancreatitis and without loss of function (LOF) mutations in genes in the lipoprotein lipase (LPL) pathway; and to assess whether a reduction in TG of at least 40% from the baseline placebo period has been achieved. Secondary Objectives: • To determine the percent change from baseline in TG levels following 2 to 24 weeks of repeated IV doses of evinacumab overall and in subgroups with homozygous or compound heterozygous LOF mutations, heterozygous LOF mutations, and without LOF mutations in genes in the LPL pathway • To assess changes in patient reported abdominal and gastrointestinal (GI) symptoms, dietary habits, and symptom/dietary impact measures • To assess the degree of pancreatic injury/inflammation through ^{18}F-2-Fluoro-2-Deoxy-D glucose positron emission tomography (^{18}F-FDG-PET) imaging at baseline (placebo run-in) and change from baseline following 12 weeks of treatment with evinacumab as assessed by ^{18}F-FDG standardized uptake values SUV_{max} and SUV_{mean} • To assess the degree of pancreatic injury/inflammation through diffusion weighted-magnetic resonance imaging (DW-MRI) at baseline and the change from baseline following 12 and 24 weeks of treatment with evinacumab as assessed by apparent diffusion coefficient (ADC) • To evaluate total evinacumab and total ANGPTL3 concentrations, and anti-drug antibody (ADA) during the evinacumab treatment and follow-up periods • To evaluate the safety and tolerability of evinacumab

Study Design

This is a phase 2, randomized, placebo-controlled study designed to evaluate the efficacy and safety of repeated doses of evinacumab in adult patients with severe hypertriglyceridemia. Up to approximately 50 patients will be enrolled, randomized 2:1 to receive evinacumab or placebo.

The study consists of a screening period of up to 37 days (which includes day -66 to day -59 [visit 1], day -58 to -52 [visit 1b], and day -51 to -39 [visit 2]), a baseline/single-blind placebo run in period (day -28 to day -1), a 12-week double-blind treatment period (day 1 to day 85), a single-blind 12-week treatment period (day 86 to day 169), and an off-treatment follow-up period (week 24 [day 170] to week 44 [day 309]).

The following cohorts will be enrolled based upon information (or lack of information) on genotype in the patient's medical history at screening:

Cohort 1: Familial Chylomicronemia Syndrome (FCS) due to complete LPL deficiency. Approximately 6 to 9 patients will be enrolled. This cohort consists of patients:

- With known homozygous or compound heterozygous null LPL, GPIHBP1, or APOC2 LOF mutations.

Cohort 2: Multifactorial chylomicronemia with partial LPL deficiency. Approximately 9 to 12 patients will be enrolled. This cohort consists of patients:

- with known heterozygous null LPL, GPIHBP1, or APOC2 LOF mutations, or
- with uncharacterized or known non-null LOF LPL pathway gene mutations (LPL, APOC2, APOA5, LMF1 and GPIHBP1)

Cohort 3: Multifactorial chylomicronemia. Approximately 15 to 27 patients will be enrolled. This cohort consists of patients not included in cohorts 1 or 2 above:

- with other monogenic or polygenic causes of sHTG (eg, CGKR, CREB3L3, E2/E2 dysbetalipoproteinemia), or
- without genotype information

For all patients who are enrolled, LPL pathway genotype will also be confirmed using exome sequencing.

Screening (Day -66 to Day -29)

During the screening period, all patients will undergo the informed consent process and standard screening procedures. Laboratory assessments used to determine eligibility may be repeated once during the screening period. Patients who do not meet eligibility criteria during the initial screening may rescreen only once; only the assessments that did not meet eligibility criteria initially are required to be repeated, if rescreening occurs within the

screening period. Patients who are rescreened after the screening window ends must re-consent for study participation and repeat all screening procedures.

After confirmation of eligibility at visit 2, all patients will receive an IV bolus of 60 IU of heparin per kg of body weight and a blood sample will be collected to assess baseline LPL level enzyme activity.

Assignment into 1 of the 3 cohorts and enrollment into the study will occur at visit 3 for patients meeting eligibility criteria.

If enrollment into a specific cohort has reached the maximum number allowed, the patient will not be eligible for enrollment.

Baseline/Single-Blind Placebo Run-in Period (Day -28 to Day -1)

Principal investigators, study site personnel, and the Regeneron study team will be unblinded to treatment, but study patients will not. On day -28, all patients will receive a single IV placebo infusion. Patients will be closely monitored for a minimum of 120 minutes after IV administration of placebo on day -28.

Double-Blind Treatment Period (Day 1 to Day 85)

Principal investigators, study site personnel, study patients and the Regeneron study team will all be blinded to treatment during the double-blind treatment period.

Patients will be randomized 2:1 (evinacumab:placebo) to receive either evinacumab administered IV at a dose of 15 mg/kg or matching placebo every 4 weeks (±4 days) on days 1, 29, and 57. Patients will be closely monitored for a minimum of 120 minutes after IV administration of evinacumab or matching placebo on days 1, 29, and 57.

Stable doses of other triglyceride-lowering therapies such as fibrates, statins, Omega-3s, and niacin are allowed during the study. Patients may not take Glybera®, mipomersen, or lomitapide during the study.

Efficacy and safety procedures and completion of the pancreatitis daily symptom questionnaire and symptom/dietary impact questionnaire will be performed as outlined in the Schedule of Events. Imaging correlates of pancreatic health will be assessed by ^{18}F-FDG PET, by DW-MRI, and by T2-MRI.

Serum samples for the determination of total evinacumab, total ANGPTL3, and anti-drug (anti-evinacumab) antibodies will be collected as outlined in the Schedule of Events.

Serum and plasma samples will be collected for analysis of additional biomarkers, including amylase and lipase.

Single-Blind Treatment Period (Day 86 to Day 169)

	All patients who complete the double-blind treatment period will receive evinacumab administered IV at a dose of 15 mg/kg every 4 weeks (± 4 days) on days 85, 113, and 141. Stable doses of other triglyceride-lowering therapies, such as fibrates, statins, Omega-3s, and niacin are allowed during the study. Glybera®, mipomersen, or lomitapide are prohibited during the study. Efficacy and safety procedures and completion of the pancreatitis daily symptom questionnaire and symptom/dietary impact questionnaire will be performed as outlined in the schedule of events. Patients should fast for a minimum of 8 hours prior to any blood draws. Imaging correlates of pancreatic health will be assessed by DW-MRI. Serum samples for the determination of total evinacumab, total ANGPTL3, and anti-drug (anti-evinacumab) antibodies will be collected. Serum and plasma samples will be collected for analysis of additional biomarkers, including amylase and lipase. ***Off-Drug Treatment Follow-up Period (Day 170 to Day 309 [End-of-Study])*** Efficacy and safety procedures will be performed as outlined in the Schedule of Events. ***Throughout the Study*** Patients will be reminded at visits and during phone calls to adhere to a highly effective birth control method. Pregnancy status of female patients of childbearing potential and the female partners (of childbearing potential) of male patients will be monitored throughout the study and for 24 weeks post the last dose of study drug.
Study Duration	The duration of the study for a patient is approximately 337 days (48 weeks), excluding the screening period.
Population	
Sample Size:	Up to approximately 50 adult male and female patients will be enrolled in the study.
Target Population:	The study population will be males and females ≥18 to 75 years of age with a history of fasting TG ≥1000 mg/dL, a fasting TG ≥500 mg/dL during screening, and a history of acute pancreatitis. Efforts will be made to select sites with a large population of well-characterized patients who have previously undergone gene sequencing and other procedures to understand the etiology of the HTG.
Treatment(s)	

Study Drug Dose/Route/Schedule:	*Double-Blind Treatment Period*: Patients will be randomized to receive either evinacumab 15 mg/kg or matching placebo administered IV every 4 weeks (±4 days) on days 1, 29, and 57. *Single-Blind Treatment Period*: Patients will receive evinacumab administered IV at a dose of 15 mg/kg every 4 weeks (±4 days) on days 85, 113, and 141.
Placebo Route/Schedule:	On day -28, all patients will receive an IV placebo infusion. Placebo matching evinacumab will be prepared in the same formulation as evinacumab, without the addition of protein

Endpoint(s)

Primary:	The primary endpoint is the percent lowering of TG levels from baseline following 12 weeks of repeated IV doses of evinacumab in the subset of patients with a documented history of sHTG (TG ≥1000 mg/dL [11.3 mmol/L]), a TG level of at least 500 mg/dL (5.6 mmol/L) at screening, a history of acute pancreatitis and without LOF mutations in genes in the LPL pathway. (For patients randomized to evinacumab, baseline is defined as the period prior to the double-blind period; for patients randomized to placebo, baseline is defined as the period prior to the single-blind period).
Secondary:	The secondary endpoints of the study are: • Percent TG lowering from baseline following 2 to 24 weeks of repeated IV doses of evinacumab overall and in subgroups with homozygous or compound heterozygous LOF mutations, heterozygous LOF mutations, and without LOF mutations in genes in the LPL pathway. • Changes in patient reported abdominal and GI symptoms, dietary habits, and symptom/dietary impact measures • Degree of pancreatic injury/inflammation through ^{18}F-FDG-PET imaging at baseline (placebo run-in) and change from baseline following 12 weeks of treatment with evinacumab as assessed by ^{18}F-FDG SUV_{max} and SUV_{mean} • Degree of pancreatic injury/inflammation through DW-MRI at baseline (placebo run-in period) and change from baseline following 12 and 24 weeks of treatment with evinacumab as assessed by ADC • The total evinacumab concentrations, total ANGPTL3 concentrations, and ADA during the evinacumab treatment and follow-up periods • Incidence and severity of treatment-emergent adverse event (TEAEs), serious adverse events (SAEs), laboratory abnormalities, and other safety variables in patients treated with evinacumab

Procedures and Assessments	Safety for all patients will be monitored via adverse events (AEs) reported by the patients (including patient reported outcomes on the questionnaires) or observed by the investigator, physical examinations, vital signs (heart rate, systolic and diastolic blood pressure, weight, and body temperature), clinical laboratory tests (biochemistry, amylase, lipase, hematology, urinalysis), and standard 12-lead electrocardiogram automatic reading (HR, PR, QRS, and QT-intervals, and QTc). Efficacy will be assessed by measurement of lipids and lipoproteins. Serum samples for the determination of total evinacumab and total ANGPTL3 concentrations, and anti-drug (anti-evinacumab) antibodies (ADA) will be collected. Serum and plasma samples will be collected for analysis of additional biomarkers, including amylase and lipase. Imaging correlates of pancreatic health will be assessed by ^{18}F-FDG PET, by DW-MRI, and T2-weighted MRI.
Statistical Plan	Descriptive statistics are planned for the primary and secondary outcome measures collected in this study. Statistical analyses will explore data collected across all patients, as well as those patients in the genotype subgroups (as applicable for pharmacodynamic measures). ***Primary analysis:*** The primary analysis is based on percent change from baseline over 12 weeks of evinacumab treatment for the assessment of probability (computed from the likelihood function based on the observed data, which is equivalent to Bayesian posterior probability with uninformative prior) that the mean TG change ≥40% (considered to be a clinically meaningful change) using study data, the point estimates of TG changes between the placebo run-in period and each observation week will be calculated using a Mixed effect Model for Repeated Measures (MMRM) method in the full analysis set population. A natural log transformation will be applied to the TG levels prior to analysis, aiming to provide a relatively normal data distribution (residuals will be examined for normality prior to proceeding with the analysis). The MMRM model will assess within-patient treatment comparisons (using an unstructured covariance matrix), while accounting for baseline TG, study visit, and baseline TG by study visit interaction. Note that study visits will be adjusted to start of evinacumab in order to pool data from both randomized groups of patients for this analysis. Since the comparison of study visits yields the within-patient comparisons of study treatments (ie, week 12 [after 12 weeks of treatment with evinacumab] compared to baseline at week 0 [after 4 weeks of treatment with placebo] in patients randomized to evinacumab and week 24 [after 12 weeks of treatment with evinacumab] compared to baseline at week 12 in patients randomized to placebo), contrast and estimate statements will be used to

assess treatment effects (least squares [LS] means with confidence intervals) and comparisons (LS mean ratio with confidence interval). Within-patient comparisons will include all patients, as well as analyses for the genotype subgroups (to assess relationship with amount of TG reduction while on evinacumab). A graph will depict the relationship of TG over time for each genotype subgroup. Details on the subgroup analyses will be defined in the statistical analysis plan (SAP). Both percent change and raw TG will be descriptively summarized by study visit. In the event the MMRM model covariance matrix does not converge or normality is not achieved with the natural log transformation, then other transformations will be explored, including ranks.

Using the estimate of the log TG mean ratio (week 12/baseline at week 0 for patients randomized to evinacumab and week 24/baseline at week 12 for those randomized to placebo) and the log of the standard deviation derived from the MMRM model, the PP will be calculated using the target change from baseline of 40% reduction (ie, log 0.6) in patients without LOF mutations in genes in the LPL pathway. For the probability calculation (ie, Pr [log TG mean ratio (post/pre)] < log 0.6 conditional on this study's TG results), a non-informative normal distribution prior and a normal distribution of the data is assumed. The probability calculation will yield the probability that the actual mean percent decrease is at least the target 40% value, based on the OBSERVED results from the patients without LOF mutations in genes in the LPL pathway.

Nominal p-values for testing mean change from baseline >0 and ≥40% at each time point in each cohort may be computed for information purposes. Since this is an exploratory study, control of the overall type-I error is not applicable for statistical testing. Any p-values provided for outcome measures are for descriptive purposes only.

Safety data will be summarized.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-Drug Antibody
ADC	Apparent diffusion coefficient
AE	Adverse event
AESI	Adverse event of special interest
AIP	Auto immune pancreatitis
ALT	Alanine aminotransferase
ANGPTL3	Angiopoietin-like 3
APO	Apolipoprotein
AP	Acute pancreatitis
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CABG	Coronary Artery Bypass Grafting
CI	Confidence Interval
CM	Chylomicrons
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CV	Cardiovascular
CVD	Cardiovascular disease
DW-MRI	Diffusion Weighted-Magnetic Resonance Imaging
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
FAS	Full analysis set
FCS	Familial Chylomicronemia Syndrome
FFA	Free fatty acids
^{18}F-FDG PET	^{18}F-2-Fluoro-2-Deoxy-D glucose positron emission tomography
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HTG	Hypertriglyceridemia
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IRB	Institutional Review Board

IV	Intravenous
IWRS	Interactive web response system
Ki	Incorporation rate
Kpatlak	Patlak clearance rate
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LOF	Loss of function
LPL	Lipoprotein lipase
LS	Least squares
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model for repeated measures
MRI	Magnetic resonance imaging
PCI	Percutaneous Coronary Interventions
PK	Pharmacokinetic
PP	Posterior probability
PRO	Patient-Reported Outcomes
PT	Preferred term
Q4W	Every 4 weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SC	Subcutaneous
SD	Standard Deviation
sHTG	Severe hypertriglyceridemia
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
SUV	Standardized uptake value
TBR	Target to background ratio
TE	Echo times
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TIA	Transient Ischemic Attack

T2-MRI	T2-weighted magnetic resonance imaging
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
VLDL	Very-low-density lipoproteins
WBC	White blood cell
WES	Whole exome sequencing
WOCBP	Women of childbearing potential

1. INTRODUCTION

Elevated levels of serum triglycerides (TG) are associated with the development of cardiovascular disease (CVD) and acute pancreatitis (AP). Studies suggest that mild to moderate elevations in TG levels are an independent risk factor for the development of CVD (Hokanson 1996), and recent studies have demonstrated that genetic loss of function (LOF) variants which result in lower TG levels (eg, apolipoprotein C3 (APOC3), ANGPTL3, and ANGPTL4 LOF genetic variants) are associated with a decreased risk of myocardial infarction (Musunura 2010, Stitziel 2016, Dewey 2016, Crosby 2014, Dewey 2017). Patients with severe elevations in TG levels (≥1000 mg/dL) are at increased risk of pancreatitis and current lipid guidelines recommend lifestyle interventions and medications to lower TG levels to prevent AP (Berglund 2012, Jacobson 2015). In most patients who develop AP secondary to sHTG, the condition is mild and self-limiting, but approximately 20% of patients suffer severe attacks associated with prolonged hospitalization and significant morbidity and mortality.

Patients with sHTG often require robust reductions in TG to lower the risk of acute pancreatitis, and a substantial proportion of patients have persistent hypertriglyceridemia, despite the use of multiple medications to lower TG. Current available therapies for lowering TG (eg, statins, fibrates, niacin, omega-3 fatty acids) can provide 20% to 50% reductions in TG in some patients, and minimal effects in other patients, especially patients with mutations in genes in the lipoprotein lipase (LPL) pathway (Brisson 2010). Patients with TG ≥1000 mg/dl typically have chylomicronemia that may be either multifactorial (polygenic & environmental) in origin or due to the presence of highly penetrant gene mutations in the LPL pathway (Brown 2012, Minicocci 2012) as observed in Familial Chylomicronemia Syndrome (also known as Fredrickson Type 1 Hyperlipidemia). Lipoprotein lipase is an endothelial-bound enzyme involved in the hydrolysis of the TG content of very-low-density lipoproteins (VLDL) and chylomicron lipoproteins. Mutations in the LPL gene or other genes that modulate the enzymatic activity of LPL, such as APOC2, and APOA5, LMF1 and GPIHBP1, lead to varying levels of loss of LPL functional activity and elevated levels of plasma TG and especially chylomicrons (Surendran 2012). However, there is a high degree of genetic polymorphism and combinatorial effects of genes, diseases (such as type 2 diabetes), and environment. There is a clear significant unmet medical need for additional treatment options for patients with sHTG to further lower TG levels and the risk of pancreatitis.

Angiopoietin-like 3 acts as a natural inhibitor of LPL and has recently emerged as a potential target for the treatment of elevated levels of TG, and low-density lipoprotein cholesterol (LDL-C). Loss of function of ANGPTL3 in humans has been associated with reductions in TG, LDL-C and high-density lipoprotein-cholesterol (HDL-C) (Minicocci 2013). Deficiency of ANGPTL3 has also been reported to be associated with decreased serum free fatty acids (FFA) and increased insulin sensitivity in patients who are homozygous for LOF mutations in ANGPTL3 (Robciuc 2013). Humans carrying these variants have otherwise appeared healthy and have a reduced risk of coronary artery disease (Dewey 2017).

Evinacumab (REGN1500) is a human IgG4 monoclonal antibody specific for ANGPTL3 and is being developed for treatment of dyslipidemia including hypertriglyceridemia (HTG) and hypercholesterolemia. Evinacumab has been studied in approximately 100 individuals with elevations in LDL-C and TG and has been generally well tolerated up to single doses of 20 mg/kg intravenous (IV), and in multiple subcutaneous (SC) doses up to 450 mg administered weekly and

20 mg/kg IV administered every 4 weeks for approximately 8 weeks. After single doses, evinacumab lowered TG up to ~80% in participants with TG <1000 mg/dL and lowered LDL-C up to 27% in participants with TG <500 mg/dL. In a multiple ascending dose study, evinacumab robustly lowered TG (up to ~72%) and LDL-C (up to ~34%) in patients with TG (150 – 500 mg/dL) and LDL-C >100 mg/dl and had a long durability of treatment effect. However, TG lowering was highly variable in a small cohort of patients with TG ≥1000 mg/dl given a single dose of evinacumab (4 patients received 250 mg SC and 2 patients received 20 mg/kg IV). Although certain individuals exhibited the rapid and substantial lowering of TG (up to 90%), some of the patients with underlying LPL and other mutations did not show robust lowering following single doses of evinacumab. The reason for the mixed response was not clear. Three out of the 6 patients treated with evinacumab and 1 placebo-treated patient in the cohort of patients with baseline TG ≥1000 mg/dL had an occurrence of acute pancreatitis during the study. These serious adverse events (SAEs) were not considered related to evinacumab since all of the patients had a history of prior pancreatitis episodes, had other underlying etiologies, and the events occurred 70 days or later after the single dose of antibody when antibody levels were low or undetectable.

The current study is a phase 2 randomized placebo-controlled study of the effects of multiple doses of evinacumab (anti-ANGPTL3) on safety, on plasma lipids and pancreatic disease biomarkers in patients with sHTG with a history of acute pancreatitis. There are 2 principal aims of this study. The first aim is to evaluate the safety and TG lowering effects of evinacumab in patients with various causes of sHTG including homozygous/heterozygous LPL gene LOF mutations, mutations in other genes in the LPL pathway, and other polygenic/environmental causes of severely elevated TGs. Analyses of the treatment effects among individuals with or without mutations in LPL pathway related genes and across a range of baseline LPL functional activity measurements will allow for a better understanding of the population(s) who will have robust lowering of TG with evinacumab treatment. The second aim of the study is to determine whether patients with sHTG and a history of acute pancreatitis have subclinical evidence of ongoing pancreatic inflammation with or without symptoms. Ongoing pancreatic inflammation may increase the risk of recurrent acute pancreatitis. This novel hypothesis will be tested in a population of patients with a prior history of pancreatitis. Patients with a relatively recent history of pancreatitis (eg, within the past 10 years) will be enrolled to select for a high-risk population that may be more likely to have ongoing pancreatic disease. If patients in this rare patient population, with severe hypertriglyceridemia with a recent history of pancreatitis cannot be enrolled in a reasonable period of time, the study sponsor may allow investigators to enroll patients with history of pancreatitis at any time in the past without the requirement of a time specification. A thorough evaluation of Patient Reported Outcomes (PRO) (eg, patient symptoms, dietary habits), plasma biomarkers and imaging of the pancreas at baseline and after treatment will be performed. In addition, the effects of treatment with evinacumab on pancreatic inflammation biomarkers and the incidence of acute pancreatitis will also be assessed.

Additional background information on the study drug and development program can be found in the Investigator's Brochure.

2. STUDY OBJECTIVES

2.1. Primary Objectives

The primary objective of the study is to determine the change in TG levels following 12 weeks of repeated IV doses of evinacumab in the subset of patients with a documented history of sHTG (TG ≥1000 mg/dL [11.3 mmol/L]), a TG level of at least 500 mg/dL (5.6 mmol/L) at screening, a history of acute pancreatitis and without LOF mutations in genes in the lipoprotein lipase (LPL) pathway; and to assess whether a reduction in TG of at least 40% from the baseline placebo period has been achieved.

2.2. Secondary Objectives

The secondary objectives of the study are:

- To determine the percent change from baseline in TG levels following 2 to 24 weeks of repeated IV doses of evinacumab overall and in subgroups with homozygous or compound heterozygous LOF mutations, heterozygous LOF mutations, and without LOF mutations in genes in the LPL pathway
- To assess changes in patient reported abdominal and gastrointestinal (GI) symptoms, dietary habits, and symptom/dietary impact measures
- To assess the degree of pancreatic injury/inflammation through ^{18}F-2-Fluoro-2-Deoxy-D glucose positron emission tomography (^{18}F-FDG-PET) imaging at baseline (placebo run-in) and change from baseline following 12 weeks of treatment with evinacumab as assessed by ^{18}F-FDG standardized uptake values SUV_{max} and SUV_{mean}
- To assess the degree of pancreatic injury/inflammation through diffusion weighted-magnetic resonance imaging (DW-MRI) at baseline and the change from baseline following 12 and 24 weeks of treatment with evinacumab as assessed by apparent diffusion coefficient (ADC)
- To evaluate the total evinacumab and total ANGPTL3 concentrations, and anti-drug antibody (ADA) during the evinacumab treatment and follow-up periods
- To evaluate the safety and tolerability of evinacumab

2.3. Exploratory Objectives

- To assess the degree of pancreatic injury/inflammation in the placebo run-in period and following treatment with evinacumab, as assessed by biochemical markers (amylase and pancreatic lipase activity [measured without lipemia interference], hsCRP, IL-6, and other inflammation markers)
- To evaluate the effect of evinacumab compared to placebo on the incidence of recurrent acute pancreatitis overall and in subgroups with homozygous or compound heterozygous LOF mutations, heterozygous LOF mutations, and without LOF mutations in genes in the LPL pathway

- To assess medical visits/hospitalizations for abdominal pain or pancreatitis, medical visits/hospitalizations for pancreatitis, and medical visits/hospitalizations for cardiovascular disease
- To assess the degree of pancreatic injury/inflammation through T2-weighted magnetic resonance imaging (T2-MRI) at baseline and the change from baseline following 12 and 24 weeks of treatment with evinacumab as assessed by T2 intensity and T2 relaxation time
- To assess the degree of pancreatic injury/inflammation through 18F-2-Fluoro-2-Deoxy-D glucose positron emission tomography (18F-FDG-PET) imaging at baseline (placebo run-in) and change from baseline following 12 weeks of treatment with evinacumab as assessed by 18F-FDG Ki or Kpatlak
- To evaluate the percent change from baseline of other lipid parameters (eg, total cholesterol [TC], TG, non-HDL-C, LDL-C, HDL-C, APOB, FFA, APOA-I) and lipoprotein subfraction composition (eg, chylomicrons [CM], VLDL, IDL, LDL [low-density lipoprotein], HDL [high-density lipoprotein], particle cholesterol, TG content, and apolipoprotein composition) after ultracentrifugation
- To evaluate change from baseline in metabolic parameters (fasting blood glucose, insulin, C-peptide, HbA1c) after 12 and 24 weeks of evinacumab treatment
- To evaluate change from baseline in post heparin LPL activity after evinacumab treatment.
- To evaluate changes in ^{18}F-FDG-PET in atherosclerotic plaque (target to background ratio [TBR]) in carotids and/or aorta
- To evaluate change from baseline in MRI liver fat signal

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

In patients with a documented history of sHTG (TG ≥1000 mg/dL [11.3 mmol/L]), a TG level of at least 500 mg/dL (5.6 mmol/L) at screening, a history of acute pancreatitis, and without LOF mutations in genes in the LPL pathway, 12 weeks of IV evinacumab administered monthly will reduce serum TG levels from baseline by a mean of at least 40%.

3.2. Rationale

3.2.1. Rationale for Study Design

Principal aims:

This is a phase 2, multicenter, partial-blind, placebo run-in, randomized, placebo-controlled fixed-sequence study, to evaluate the efficacy and safety of repeated doses of evinacumab administered IV for the treatment of patients with a history of sHTG (fasting TGs ≥1000 mg/dL) with a baseline TG ≥500 mg/dL at screening and a history of acute pancreatitis. The primary aim of the study is to evaluate the intrapatient change from baseline in triglyceride concentrations following treatment

with evinacumab in patients with multifactorial and polygenic causes of sHTG as well as in patients with reduced LPL functional activity due to LOF mutations in LPL pathway-related genes. A key secondary aim is to determine whether patients with sHTG at high risk for pancreatitis have evidence of subclinical pancreatic disease as assessed by a panel of plasma/serum biomarkers, imaging biomarkers, and PROs and whether these biomarkers will be impacted by treatment with evinacumab.

Benefit/Risk Assessment:

Elevated blood levels of TGs have been associated with the development of both CVD and acute pancreatitis. Current therapies for lowering TGs (eg, weight reduction, lifestyle changes, statins, fibrates, omega-3 fatty acids) have limited efficacy and/or tolerability issues. Recent studies have demonstrated that patients with genetic LOF mutations that decrease the activity of LPL can result in severe elevations in TG. Because ANGPTL3 acts as a natural inhibitor of LPL, blockade of ANGPTL3 and preventing LPL inhibition is a potential target for the treatment of elevated levels of TGs. Importantly, no identified safety risks from the absence of ANGPTL3 have been reported for the few individuals who are homozygous for LOF mutations in ANGPTL3 (Musunuru 2010, Minicocci 2012). In fact, recent studies have demonstrated that genetic LOF variants which result in lower TG levels (eg, APOC3, ANGPTL3, and ANGPTL4 LOF genetic variants) are associated with a decreased risk of myocardial infarction (Musunuru 2010, Stitziel 2016, Dewey 2016, Crosby 2014, Dewey 2017). A therapeutic targeted to ANGPTL3 could provide beneficial changes in the lipid profile and ultimately in the cardiovascular (CV) risk for patients. Additionally, significant reductions in TGs would also benefit the patient with severe elevations in TGs at risk for pancreatitis. Thus, a significant unmet need exists for additional and improved methods for treating elevated TG levels.

Evinacumab has been evaluated in 3 clinical studies and has been generally well tolerated with no significant clinical safety findings observed to date. No important identified risks have been established. The important potential risks with evinacumab (based on preclinical evaluation, mechanism of action, or risks associated with monoclonal antibody [mAbs] in general) include systemic hypersensitivity reactions, immunogenicity, and embryofetal toxicity. For the potential embryofetal toxicity risk, there is a strict risk mitigation plan, including requirements for consistent use of contraception for sexually active male study participants and sexually active female study participants of child-bearing potential. Currently, the available safety data along with the risk minimization and management activities for all important potential risks support the continued development of this compound.

Population:

Three different cohorts will be enrolled to evaluate the TG lowering effects of evinacumab in the setting of varying levels of LPL functional activity. Since the mechanism of action of evinacumab is to block an endogenous inhibitor of LPL activity in plasma, it is important to understand whether evinacumab will lower TG when the LPL pathway and functional LPL activity is compromised due to partial or total loss of functional mutations in the LPL and LPL pathways genes. Since genetic, environmental factors such as diet and alcohol and disease modifiers (eg, diabetes) can have an impact on LPL functional activity variability, enrollment of patients according to genotype will ensure that the patient population includes patients with a wide range of baseline LPL functional activity. Enrollment of patients at specialized centers, where genetic testing to identify genetic causes of HTG is routinely performed, will be encouraged, and enrollment into the 3

cohorts will be controlled via the Interactive Web Response System (IWRS). If genetic information is not available in a patient's medical history, the patient will be enrolled into cohort 3.

The study will enroll up to approximately 50 adult male and female patients at approximately 20 sites globally. Efforts will be made to select sites with a large population of well characterized patients who have previously undergone gene sequencing and other procedures to understand the etiology of the HTG.

The following cohorts will be enrolled based upon the patient's genotype:

Cohort 1: Familial Chylomicronemia Syndrome (FCS) due to complete LPL deficiency. Approximately 6 to 9 patients will be enrolled. This cohort consists of patients:

- with known homozygous or compound heterozygous null LPL, GPIHBP1, or APOC2 LOF mutations

Cohort 2: Multifactorial chylomicronemia with partial LPL deficiency. Approximately 9 to 12 patients will be enrolled. This cohort consists of patients:

- with known heterozygous null LPL, GPIHBP1, or APOC2 LOF mutations, or
- with uncharacterized or known non-null LOF LPL pathway gene mutations (LPL, APOC2, APOA5, LMF1 and GPIHBP1)

Cohort 3: Multifactorial chylomicronemia. Approximately 15 to 27 patients will be enrolled. This cohort consists of patients not included in cohorts 1 or 2 above:

- with other monogenic or polygenic causes of sHTG (eg, CGKR, CREB3L3, E2/E2 dysbetalipoproteinemia) or
- without genotype information

Lipoprotein lipase activity will be measured in all patients at baseline and at the end of treatment. Lipoprotein lipase enzyme activity will be measured using the assay developed by Imamura (Imamura 2008) in fasting plasma collected from patients during the screening period, after the patient has received an IV bolus of 60 IU of heparin per kg of body weight. Lipoprotein lipase is bound to the luminal side of capillary endothelium by glycosoaminoglycans and the infusion of heparin is required for the disassociation of the bound LPL into the circulation. This will allow a comparison of the treatment effects in different subgroups of patients with varying genetic LOF variants and LPL functional activity. Whole Exome Sequencing (WES) will be done to ascertain or confirm any genetic mutations in LPL and other genes in the LPL pathway (LMF1, APOC2, APOA5, etc).

Patients with a history of pancreatitis due to HTG will be enrolled to increase the probability of observing abnormalities in pancreatic biomarkers at baseline and treatment-related changes in patient-reported outcomes (eg, chronic abdominal complaints, symptom/dietary impact measures), circulating plasma/serum pancreatic/inflammation markers and noninvasive pancreatic imaging inflammation biomarkers. Questionnaires will be administered to patients to evaluate for clinical symptoms of pancreatic inflammation such as nausea, vomiting, abdominal distention, abdominal pain, loss of appetite, and/or self-imposed dietary restrictions. Amylase and lipase, which are typically elevated during episodes of AP, will be measured. Levels of IL6 and C-reactive protein,

frequently elevated during acute pancreatitis episodes, and a panel of inflammation markers will be measured at baseline and post-treatment. Evaluation of subclinical pancreatic injury will be performed using ^{18}F-FDG-PET and DW-MRI and T2-MRI. ^{18}F-2-Fluoro-2-Deoxy-D glucose PET is a molecular imaging modality that has demonstrated high sensitivity in the in vivo detection of glycolytic tissues, including tumors and inflammatory foci. Although ^{18}F-FDG-PET has not been used in this particular setting, it has been utilized to assess low-level pancreatic injury in other settings such as autoimmune pancreatitis (AIP), atherosclerosis and infection (Ozaki 2008, Shreve 1998, Tahara 2007, Vos 2006, Lee 2009, Shigekawa 2010). ^{18}F-FDG PET will be performed at baseline and at week 12 (12 weeks after blinded treatment with evinacumab or placebo). A combination DW-MRI and T2-MRI will also be used to assess pancreatic health at baseline and following treatment with evinacumab. Compared to healthy pancreatic tissue, inflammatory tissue is characterized as having restricted water diffusion (decreased ADCs), while necrotic tissue corresponds to less restricted water diffusion (increased ADCs). With respect to the T2-MRI signal, edematous or inflammatory tissue is hypothesized to possess higher T2-weighted signal intensities in addition to longer T2 relaxation times as a result of higher water content. The implementation of DW-MRI and T2-MRI has been used to assess pancreatic health across pancreatic disease states, including acute, chronic and autoimmune pancreatitis as well as pancreatic cancer (de Freitas Tertulino 2015, Xiao 2010, Tang 2016). DW-MRI and T2-MRI will be performed at the beginning of the placebo run-in period, prior to the randomization visit at the end of the double-blind treatment period (week 12), and at the end of the single blind evinacumab treatment period (week 24).

Study Design:

The current fixed sequence study has a 4-week screening phase, a 4-week single-blind placebo run in phase to obtain additional baseline lipid data, a 12-week double-blind, placebo controlled phase, a 12-week single blind active treatment phase, and an off drug observation phase. Patients with sHTG are very rare and genetically diverse; therefore, it is important to study safety and treatment response in all patients enrolled.

The single-blind placebo run-in period allows for measurement of change from baseline in TG in patients randomized to placebo. The double-blind period allows for an unbiased assessment of the safety of evinacumab compared to placebo. The single-blind period allows for analysis of a treatment effect in patients randomized to placebo. A single-blind period is preferred over an open-label period to allow for unbiased collection of patient reported outcomes by the study participants.

Since fasting TG are highly variable in this population, the geometric mean of TG measurements obtained at specific time-points (day -28, day -14 and week 0) will be used for pre-treatment comparison for the 12-week double blind period. For patients receiving placebo during the double-blind treatment period, the geometric mean obtained at specific time points (week 6, 8, and 12) will be used as the baseline measurements for the single-blind evinacumab treatment period. A placebo controlled double-blind period will allow an unbiased assessment of safety of evinacumab versus placebo. Furthermore, offset kinetics will be observed in patients following withdrawal of active study medication.

3.2.2. Rationale for Dose Selection

An IV dose of 15 mg/kg was selected to test the efficacy of evinacumab with once-monthly administration for this study. The 15 mg/kg IV dose is within the range of doses that has been

shown to be generally well tolerated and markedly efficacious in patients with TG levels of ≥150 mg to 450 mg/dL (Group A) and ≥450 to 1000 mg/dL (Group B) in the single-dose first-in-human study (Study R1500-HV-1214). Ninety to 100 mg/L of evinacumab appears to be the serum concentration of antibody associated with saturation of the target-mediated pathway and to achieve maximal or near-maximal TG lowering. The PK of evinacumab is non-linear, consistent with target-mediated elimination. An evinacumab concentration of >100 mg/L is maintained for approximately 2 weeks for a 10 mg/kg IV dose and for 4 weeks for a 20 mg/kg IV dose with a non-linear PK consistent with target mediated elimination. Pharmacokinetics simulation shows that 15 mg/kg IV will maintain evinacumab concentration above 100 mg/L for 1 month during the 24-week treatment period. Total ANGPTL3 (drug antibody complex) concentration data showed possible target saturation with a limited duration at 20 mg/kg which supports selection of the 15 mg/kg IV monthly regimen. Fifteen mg/kg of evinacumab administered monthly is therefore predicted to provide serum evinacumab concentrations that exceed that required to saturate the target-mediated pathway over the dosing interval.

4. STUDY VARIABLES

4.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height, etc), disease characteristics including detailed cardiovascular and pancreatitis history, medication history, daily symptom Questionnaire, Symptom and Dietary Impact Questionnaire, and screening laboratory measurements for each patient.

4.2. Primary and Secondary Endpoints

4.2.1. Primary Endpoint

The primary endpoint is the percent lowering of TG levels from baseline following 12 weeks of repeated IV doses of evinacumab in the subset of patients with a documented history of sHTG (TG ≥1000 mg/dL [11.3 mmol/L]), a TG level of at least 500 mg/dL (5.6 mmol/L) at screening, a history of acute pancreatitis, and without LOF mutations in genes in the LPL pathway. (For patients randomized to evinacumab, baseline is defined as the period prior to the double-blind period; for patients randomized to placebo, baseline is defined as the period prior to the single-blind period.)

4.2.2. Secondary Endpoints

The secondary endpoints of the study are:

- Percent TG lowering from baseline following 2 to 24 weeks of repeated IV doses of evinacumab overall and subgroups with homozygous or compound heterozygous LOF mutations, heterozygous LOF mutations, and without LOF mutations in genes in the LPL pathway
- Changes in patient reported abdominal and GI symptoms, dietary habits, and symptom/dietary impact measures

- Degree of pancreatic injury/inflammation through ^{18}F-FDG-PET imaging at baseline (placebo run-in) and change from baseline following 12 weeks of treatment with evinacumab as assessed by ^{18}F-FDG standardized uptake values SUV_{max} and SUV_{mean}
- Degree of pancreatic injury/inflammation through DW-MRI at baseline (placebo run-in period) and the change from baseline following 12 and 24 weeks of treatment with evinacumab as assessed by ADC
- The total evinacumab concentrations, total ANGPTL3 concentrations, and ADA during the evinacumab treatment and follow-up periods
- Incidence and severity of treatment-emergent adverse event (TEAEs), SAEs, laboratory abnormalities, and other safety variables in patients treated with evinacumab

4.2.3. Exploratory Endpoints

The exploratory endpoints of the study are:

- Change from baseline in pancreatic injury/inflammation in the placebo run-in period and following treatment with evinacumab as assessed by biochemical markers (amylase, lipase, hsCRP, IL-6 and other inflammatory markers)
- Incidence of recurrent acute pancreatitis overall and in subgroups with homozygous or compound heterozygous LOF mutations, heterozygous LOF mutations, and without LOF mutations in genes in the LPL pathway
- Incidence of medical visits/hospitalizations for abdominal pain or pancreatitis, medical visits/hospitalizations for pancreatitis, and medical visits/hospitalizations for cardiovascular disease
- Degree of pancreatic injury/inflammation through T2-MRI at baseline (placebo run-in period) and the change from baseline following 12 and 24 weeks of treatment with evinacumab as assessed by T2 intensity and T2 relaxation time
- Degree of pancreatic injury/inflammation through 18F-FDG-PET imaging at baseline (placebo run-in) and change from baseline following 12 weeks of treatment with evinacumab as assessed by 18F-FDG Ki or Kpatlak
- Percent change from baseline in lipid parameters (eg, TC, TG, non-HDL-C, LDL-C, HDL-C, APOB, FFA, APOA-I) and lipoprotein subfraction composition (eg, CM, VLDL, IDL, LDL, HDL, particle cholesterol, TG content, and apolipoprotein composition) after ultracentrifugation at 16 weeks and 28 weeks
- Change from baseline in metabolic parameters (fasting blood glucose, insulin, C-peptide, HbA1c) after 12 and 24 weeks of evinacumab treatment
- Percent change from baseline in post heparin LPL activity after evinacumab treatment overall and by LPL gene mutations
- Change from baseline in ^{18}F-FDG-PET in atherosclerotic plaque (TBR) in carotids and/or aorta
- Change from baseline in liver fat fraction as measured by MRI

4.3. Pharmacokinetic Variables

Pharmacokinetic variables may include, but are not limited to, the following:

- Total evinacumab concentrations in serum over time
- C_{max}
- C_{trough}

4.4. Anti-Drug Antibody Variables

Anti-drug antibody variables include status (positive or negative) and titer as follows:

- Treatment emergent - defined as any post-dose positive ADA assay response when the pre-dose baseline ADA results are negative
- Treatment-boosted - defined as any post-dose positive ADA assay response that has titer at least 9-fold over the pre-dose baseline titer when pre-dose baseline ADA results are positive

The definition of persistent and transient ADA will be defined a priori in the statistical analysis plan (SAP).

- Titer values
- Titer category
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)
  - High (titer >10,000)

Samples positive in the ADA assay will be assessed for neutralizing activity.

5. STUDY DESIGN

5.1. Study Description and Duration

This is a phase 2, randomized, placebo-controlled, study designed to evaluate the efficacy and safety of repeated doses of evinacumab in adult patients with severe HTG. Up to approximately 50 patients will be enrolled, randomized 2:1 (evinacumab:placebo) to receive evinacumab or placebo.

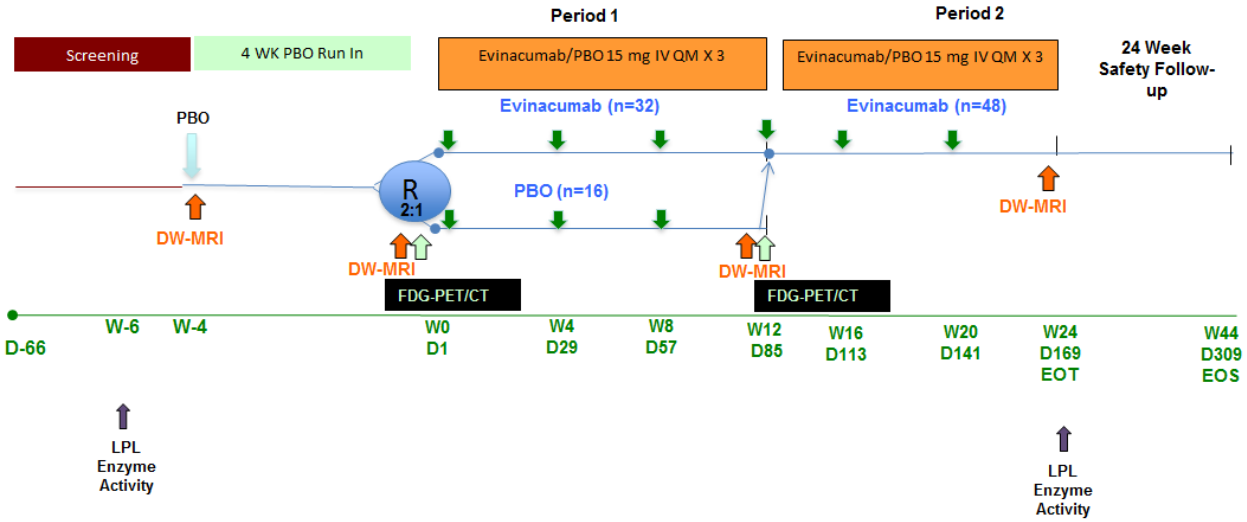
The study consists of a screening period of up to 37 days (which includes day -66 to day -59 [visit 1], day -58 to -52 [visit 1b], and day -51 to -39 [visit 2]), a baseline/single-blind placebo run in period (day -28 to day -1), a 12-week double-blind treatment period (day 1 to day 85), a single-blind 12-week treatment period (day 86 to day 169), and an off-treatment follow-up period (week 24 [day 170] to week 44 [day 309]).

The following cohorts will be enrolled based upon information (or lack of information) on genotype in the patient's medical history at screening:

1. Cohort 1: FCS due to complete LPL deficiency. Approximately 6 to 9 patients will be enrolled. This cohort consists of patients:
   - with known homozygous or compound heterozygous null LPL, GPIHBP1, or APOC2 LOF mutations
2. Cohort 2: Multifactorial chylomicronemia with partial LPL deficiency. Approximately 9 to 12 patients will be enrolled. This cohort consists of patients:
   - with known heterozygous null LPL, GPIHBP1, or APOC2 LOF mutations, or
   - with uncharacterized or known non-null LOF LPL pathway gene mutations (LPL, apoC2, apoA5, LMF1 and GPIHBP1)
3. Cohort 3: Multifactorial chylomicronemia. Approximately 15 to 27 patients will be enrolled. This cohort consists of patients not included in cohorts 1 or 2 above:
   - with other monogenic or polygenic causes of sHTG (eg, CGKR, CREB3L3, E2/E2 dysbetalipoproteinemia), or
   - without genotype information

A study flow diagram is in Figure 1.

Figure 1: Study Flow Diagram



Screening (Day -66 to Day -29)

During the screening period, all patients will undergo the informed consent process and standard screening procedures. Laboratory assessments used to determine eligibility may be repeated once during the screening period. Patients who do not meet eligibility criteria during the initial screening may rescreen only once; only the assessments that did not meet eligibility criteria initially are required to be repeated, if rescreening occurs within the screening period. Patients who are rescreened after the screening window ends must re-consent for study participation and repeat all screening procedures.

After confirmation of eligibility at visit 2, all patients will receive an IV bolus of 60 IU of heparin per kg of body weight and a blood sample will be collected to assess baseline level of LPL enzyme activity.

Assignment into 1 of the 3 cohorts and enrollment into the study will occur at visit 3 for patients meeting eligibility.

If enrollment into a specific cohort has reached the maximum number allowed, the patient will not be eligible for enrollment.

Baseline/Single-Blind Placebo Run-in Period (Day -28 to Day -1)

Principal investigators, study site personnel, and the Regeneron study team will be unblinded to treatment, but study patients will not. On day -28, all patients will receive a single IV placebo infusion. Patients will be closely monitored for a minimum of 120 minutes after IV administration of placebo on day -28.

Double-Blind Treatment Period (Day 1 to Day 85)

Principal investigators, study site personnel, study patients and the Regeneron study team will all be blinded to treatment during the double-blind treatment period.

Patients will be randomized 2:1 (evinacumab:placebo) to receive either evinacumab administered IV at a dose of 15 mg/kg or matching placebo every 4 weeks (±4 days) on days 1, 29, and 57. Patients will be closely monitored for a minimum of 120 minutes after IV administration of evinacumab or matching placebo on days 1, 29, and 57.

Stable doses of other triglyceride-lowering therapies, such as fibrates, statins, omega-3s, and niacin are allowed during the study. Patients may not take Glybera®, mipomersen, or lomitapide during the study.

Efficacy and safety procedures and completion of the pancreatitis daily symptom questionnaire and symptom/dietary impact questionnaire will be performed as outlined in the schedule of events. Imaging correlates of pancreatic health will be assessed by ^{18}F-FDG PET, by DW-MRI, and by T2-MRI.

Serum samples for the determination of total evinacumab, total ANGPTL3, and anti-drug (anti-evinacumab) antibodies (ADA) will be collected.

Serum and plasma samples will be collected for analysis of additional biomarkers, including amylase and lipase.

Single-Blind Treatment Period (Day 86 to Day 169)

All patients who complete the double-blind treatment period will receive evinacumab administered IV at a dose of 15 mg/kg every 4 weeks (± 4 days) on days 85, 113, and 141.

Stable doses of other triglyceride-lowering therapies, such as fibrates, statins, omega-3s, and niacin are allowed during the study. Glybera®, mipomersen, or lomitapide are prohibited during the study.

Efficacy and safety procedures and completion of the pancreatitis daily symptom questionnaire and symptom/dietary impact questionnaire will be performed as outlined in the schedule of events. Patients should fast for a minimum of 8 hours prior to any blood draws. Imaging correlates of pancreatic health will be assessed by DW-MRI.

Serum samples for the determination of total evinacumab, total ANGPTL3, and anti-drug (anti-evinacumab) antibodies (ADA) will be collected.

Serum and plasma samples will be collected for analysis of additional biomarkers, including amylase and lipase.

Off-Drug Treatment Follow-up Period (Day 170 to Day 309 [End-of-Study])

Efficacy and safety procedures will be performed as outlined in the Schedule of Events.

Throughout the Study

Patients will be reminded at visits and during phone calls to adhere to a highly effective birth control method. Pregnancy status of female patients of childbearing potential and of female partners (of child-bearing potential) of male patients will be monitored throughout the study and for 24 weeks post the last dose of study drug.

5.1.1. End of Study Definition

The end of study for this study is defined as the last visit of the last patient.

5.2. Planned Interim Analysis

Interim analyses may be conducted during the course of the study by the unblinded team to assess efficacy, safety, and futility. If the timing of this analysis falls within a few weeks of the first-step analysis, only the first-step analysis will be performed. Enrollment (up to a maximum of approximately 50 patients) may be halted if the incidence of pancreatitis is much lower than anticipated, making the evaluation of a treatment effect on pancreatitis futile. Details of the interim analysis will be provided in the SAP.

5.3. Study Committees

5.3.1. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC), composed of members who are independent from the sponsor and the study investigators, will monitor patient safety by conducting formal reviews of accumulated safety data that will be blinded by treatment group; if requested, the IDMC may have access to the treatment allocation code or any other requested data for the purposes of a risk-benefit assessment.

The IDMC will provide the sponsor with appropriate recommendations on the conduct of the clinical study to ensure the protection and safety of the patients enrolled in the study. The IDMC will also institute any measures that may be required for ensuring the integrity of the study results during the study execution.

All activities and responsibilities of the IDMC are described in the IDMC charter.

6. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

6.1. Number of Patients Planned

The study will enroll up to approximately 50 patients at approximately 20 study sites globally.

6.2. Study Population

The study population will be males and females ≥18 to 75 years of age with a history of fasting TG ≥1000 mg/dL, a fasting TG ≥500 mg/dL during screening, and a history of pancreatitis. The study will enroll up to approximately 50 adult male and female patients at approximately 20 sites globally. Efforts will be made to select sites with a large population of well-characterized patients who have previously undergone gene sequencing and other procedures to understand the etiology of the HTG.

The following LPL pathway cohorts will be enrolled based upon the patient's genotype:

1. Cohort 1: FCS due to complete LPL deficiency. Approximately 6 to 9 patients will be enrolled. This cohort consists of patients:
   - With known homozygous or compound heterozygous null LPL, GPIHBP1, or APOC2 LOF mutations
2. Cohort 2: Multifactorial chylomicronemia with partial LPL deficiency. Approximately 9 to 12 patients will be enrolled. This cohort consists of patients:
   - with known heterozygous null LPL, GPIHBP1, or APOC2 LOF mutations, or
   - with uncharacterized or known non-null LOF LPL pathway gene mutations (LPL, APOC2, APOA5, LMF1 and GPIHBP1)
3. Cohort 3: Multifactorial chylomicronemia. Approximately 15 to 27 patients will be enrolled. This cohort consists of patients not included in cohorts 1 or 2 above:
   - with other monogenic or polygenic causes of sHTG (eg, CGKR, CREB3L3, E2/E2 dysbetalipoproteinemia), or
   - without genotype information

6.2.1. Inclusion Criteria

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Males and females ≥18 to 75 years of age at screening
2. Previous documentation in the patient's medical records of a fasting serum TG measurement ≥ 1000 mg/dL (11.3 mmol/L) on more than 1 occasion, and all fasting TG values ≥500 mg/dL (5.6 mmol/L) at screening

   NOTE: TGs will be measured at least twice and at least 4 days apart during the screening period.

3. History of a hospitalization and diagnosis of acute pancreatitis in the past 10 years. (Sponsor may elect to drop the time specification if sufficient enrollment does not occur within a reasonable period of time).
4. On a stable lipid-modifying diet with or without medications (eg, statins, niacin, omega-3 fatty acids). Lipid-modifying diet and doses of medications should be stable for at least 4 weeks (6 weeks for fibrates, 8 weeks for PCSK9 inhibitors) prior to screening
5. BMI index of 18-40 kg/m^2
6. Willing to consume no more than an average of 2 standard alcoholic drinks per day and a maximum of 15 standard alcoholic drinks per week for the duration of the study. (A standard alcoholic drink is the equivalent of 12 ounces (355 mL) of beer, 5 ounces (148 mL) of wine, or 1.5 ounces (44 mL) of hard liquor)
7. Willing to refrain from consumption of alcohol for 24 hours prior to each study visit
8. Willing to refrain from cigarette smoking for 24 hours prior to each study visit
9. Willing to consistently maintain previously recommended diet and exercise regimen for duration of the study
10. Willing and able to comply with clinic visits and study-related procedures
11. Provide signed informed consent
12. Able to understand and complete study-related questionnaires

6.2.2. Exclusion Criteria

A patient who meets any of the following criteria will be excluded from the study:

1. A hospital or clinic discharge diagnosis of acute pancreatitis within 12 weeks of screening
2. Lipid apheresis or plasma exchange treatment within the last 4 weeks or plans to undergo apheresis or plasma exchange during the time frame of the study
3. History of class 3/4 heart failure at any time in the past, or hospitalization for heart failure, diagnosis of a myocardial infarction, stroke, TIA, unstable angina, CABG, PCI, carotid surgery/stenting within 3 months before the screening visit
4. History of bleeding disorders, esophageal varices, heparin induced thrombocytopenia, or contraindications to receiving heparin (eg, allergic reaction to heparin)
5. New clinically significant findings on 12-lead electrocardiogram (ECG) that would place the patient at risk or interfere with participation in the study
6. Dose(s) of any permitted concomitant medications that have changed in the time period prior to screening as described in Section 7.8.2
7. Presence of any clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins

   NOTE: Patients on thyroid replacement therapy are eligible if the dosage of thyroxine has been stable for at least 12 weeks prior to screening visit

8. Use of systemic corticosteroids, unless used as replacement therapy for pituitary/adrenal disease (in which case must be a stable regimen for at least 6 weeks prior to the screening visit)

   NOTE: Topical, intra-articular, nasal, inhaled and ophthalmic steroid therapies are not considered as 'systemic' and are allowed

9. Calculated eGFR <45 ml/min (according to 4-variable MDRD study equation)
10. History of drug or alcohol abuse (including binge drinking which typically involves consumption of approximately 4 drinks for women and 5 drinks for men in a few hours) within 1 year of screening
11. Exposure to another investigational drug or therapy within 30 days or within at least 5 half-lives (whichever is longer) prior to the screening visit
12. Blood donation of any volume within 1 month prior to administration of study drug
13. Known hypersensitivity to monoclonal antibody therapeutics. Known sensitivity to any of the components of the investigational product formulation
14. History of malignancy within 5 years prior to screening (other than successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and or localized carcinoma in situ of the cervix)
15. Any medical or psychiatric condition that, in the opinion of the investigator, would place patient at risk, interfere with participation in the study or interfere with the interpretation of the study results (eg, cirrhosis or chronic active hepatitis, nephrotic syndrome, uncontrolled diabetes, uncontrolled hypertension)
16. Previous treatment with Glybera® in the past 5 years or treatment with lomitapide or mipomersen in the past 6 months
17. Positive serum hCG pregnancy test at the screening visit
18. Creatine phosphokinase (CPK) ≥3x upper limit of normal (ULN) at the screening visit
19. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3x ULN
20. Thyroid-stimulating hormone (TSH) >1.5 ULN or < lower limit of normal
21. Platelet count <75,000
22. Any patient who is the investigator or any sub-investigator, research assistant, study coordinator, or other staff directly involved in the conduct of the protocol, or a family member of staff involved in the conduct of the protocol
23. Pregnant or breast feeding women
24. Women of childbearing potential (WOCBP)* who are unwilling to practice a highly effective birth control method prior to the initial dose, during the study, and for 24 weeks after the last dose of study drug. Highly effective contraceptive measures include:

    - Stable use of combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening:

  - oral
  - intravaginal
  - transdermal
- Stable use of progestogen-only hormonal contraception associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening:
  - oral
  - injectable
  - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal ligation
- Vasectomized partner. Note: Vasectomized partner is a highly effective birth control method provided that the partner is the sole sexual partner of the woman of child bearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success
- Sexual abstinence. Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with study treatments.

*Postmenopausal women must be amenorrheic for at least 12 months in order **not** to be considered of childbearing potential. Postmenopausal status will be confirmed by measurement of follicle-stimulating hormone (FSH). Pregnancy testing and contraception are not required for women with documented hysterectomy and/or oophorectomy.

25. Men who are sexually active with WOCBP and are unwilling to consistently use condoms during the study drug treatment period and for 24 weeks after the last injection of study drug, regardless of vasectomy status. Sperm donation is prohibited during the study and for up to 24 weeks after the last injection of study drug.

6.3. Premature Withdrawal from the Study

A patient has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and/or sponsor have the right to withdraw a patient from the study if it is no longer in the interest of the patient to continue in the study, or if the patient's continuation in the study places the scientific outcome of the study at risk (eg, if a patient does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. The site will be provided a retention manual outlining the best practices for patient retention.

Patients who are withdrawn prematurely from the study will be asked to complete study assessments, as described in Section 8.1.2.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 7.4.2.

6.4. Replacement of Patients

Patients prematurely discontinued from the study/ study drug will not be replaced.

7. STUDY TREATMENTS

7.1. Investigational and Reference Treatments

Sterile evinacumab drug product will be provided in a 20 mL single-use glass vial at a concentration of 150 mg/mL.

***Double-Blind Treatment Period*:** Patients will be randomized to receive either evinacumab 15 mg/kg or matching placebo administered IV every 4 weeks (±4 days) on days 1, 29, and 57.

***Single-Blind Treatment Period*:** All patients will receive evinacumab administered IV at a dose of 15 mg/kg every 4 weeks (±4 days) on days 85, 113, and 141.

Instructions on management of infusion reactions are provided in Section 7.5.

Instructions on dose preparation are provided in the pharmacy manual.

7.2. Run-in Treatment(s)

On day -28, all patients will receive an IV placebo infusion. Placebo will be supplied in vials that match evinacumab, but do not contain the protein.

7.3. Pretreatment(s)

After confirmation of eligibility, patients will receive an IV bolus of 60 IU of heparin per kg of body weight at screening visit 2.

7.4. Dose Modification and Study Treatment Discontinuation Rules

7.4.1. Dose Modification

Dose modification for an individual patient is not allowed.

7.4.2. Study Drug Discontinuation

Patients who permanently discontinue from study drug before entering the double-blind treatment period (day 1, week 0) will be contacted to assess any adverse events (AEs) but will not be asked to return for the remaining study visits.

Patients who permanently discontinue from study drug during the double-blind treatment period will be asked to return to the clinic within 5 days for an early termination visit consisting of week 12 study assessments; these patients will then enter the off-drug treatment follow-up period.

Patients who are permanently withdrawn from study drug during the single-blind treatment period will be asked to return to the clinic for an early termination visit consisting of week 24 study

assessments. After the early termination visit, patients will enter the off-drug treatment follow-up period.

Patients who are unable or unwilling to attend the study visits as described above should still be followed for at least 24 weeks from the last dose of study drug or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last. The assessments completed should include pregnancy testing for WOCBP. A final end of study visit should take place with assessments as specified in the end of study visit (ie, follow up visit) at 24 weeks after the premature discontinuation of study drug.

Sexually active males and WOCBP who discontinue the study prematurely should be reminded at the early termination visit following treatment discontinuation to maintain the contraceptive measures (as described in Section 6.2.2) for 24 weeks after the last dose of study drug. At this visit, WOCBP will be provided a sufficient number of urine pregnancy tests with instructions to test for pregnancy 4 weeks after this visit and every 4 weeks (Q4W) thereafter. The patient will also be notified of Q4W follow-up phone calls to confirm continued contraception use, to obtain results of urine pregnancy tests, and to obtain information on whether pregnancy has occurred in WOCBP and in female partners of male patients.

The investigator should make the best effort to contact any patient (eg, contacting patient's family or private physician, review available registries or health care database) who fails to return to the site, and to determine health status. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

7.4.2.1. Reasons for Permanent Discontinuation of Study Drug

Study drug dosing will be permanently stopped in the event of:

- Evidence of pregnancy
- Acute systemic injection reactions with AEs including, but not limited to, anaphylaxis, laryngeal/pharyngeal edema, severe bronchospasm, chest pain, seizure or severe hypotension
- Withdrawal of patient consent

7.4.2.2. Reasons for Temporary Discontinuation of Study Drug

The investigator may temporarily discontinue study drug dosing at any time, even without consultation with the medical monitor if the urgency of the situation requires immediate action and if this is determined to be in the patient's best interest. However, the Regeneron medical monitor should be contacted as soon as possible in any case of temporary or permanent study drug discontinuation. If a patient requires a prohibited medication at any time during the study, the principal investigator should contact the Regeneron medical monitor. Based on the discussions, study drug may be continued or temporarily or permanently discontinued.

7.4.2.3. Management of Suspected Cases of Acute Pancreatitis

Patients enrolled in this study have an increased risk of acute and recurrent pancreatitis due to HTG. A key objective of this study is to determine whether patients with sHTG have evidence of

subclinical pancreatitis by collecting information on abdominal symptoms and biochemical tests such as amylase and pancreatic lipase on a regular basis throughout the study. Development of or worsening abdominal pain with or without elevations in amylase and/or pancreatic lipase may signify the development of acute pancreatitis in this susceptible population. Investigators may elect to perform additional diagnostic and laboratory testing. If a clinical diagnosis of acute pancreatitis is made, investigators may elect to temporarily discontinue study drug.

7.5. Management of Acute Reactions

7.5.1. Acute Infusion Reactions

Emergency equipment and medication for the treatment of infusion reactions must be available for immediate use. All infusion reactions must be reported as AEs (as defined in Section 9.4.1) and graded using the grading scales as instructed in Section 9.5.1.

7.5.1.1. Interruption of the Infusion

The infusion should be interrupted if any of the following AEs are observed:

- cough
- rigors/chills
- rash, pruritus (itching)
- urticaria (hives, welts, wheals)
- diaphoresis (sweating)
- hypotension
- dyspnea (shortness of breath)
- vomiting
- flushing

The reaction(s) should be treated symptomatically. If investigators feel there is a medical need for treatment or discontinuation of the infusion other than described above, they should use clinical judgment to provide the appropriate response according to typical clinical practice.

7.5.1.2. Termination of the Infusion

The infusion should be terminated and NOT restarted if any of the following AEs occur:

- Anaphylaxis*
- laryngeal/pharyngeal edema
- severe bronchospasm
- chest pain
- seizure
- severe hypotension

- other neurological symptoms (confusion, loss of consciousness, paresthesia, paralysis, etc)
- any other symptom or sign that, in the opinion of the investigator, warrants discontinuation of the infusion

*Consider anaphylaxis if the following is observed (Sampson 2006): acute onset of an illness (minutes to several hours) with the involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula AND AT LEAST ONE OF THE FOLLOWING:

a. respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia);
b. reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).

7.6. Method of Treatment Assignment

Up to approximately 50 patients will be treated in this partial-blind, randomized, placebo-controlled, fixed-sequence study; all will receive an IV placebo infusion on day -28. Patients will be randomized 2:1 to receive either evinacumab 15 mg/kg or matching placebo administered IV every 4 weeks (±4 days) on days 1, 29, and 57 (double-blind treatment period). All patients will receive evinacumab administered IV at a dose of 15 mg/kg every 4 weeks (±4 days) on days 85, 113, and 141, (single-blind treatment period).

7.6.1. Blinding

Study patients will remain blinded to the sequence of study drug administration in this partial-blind study. Investigators, Regeneron Study Director, Medical Monitor, Study Monitor, and any other Regeneron and contract research organization (CRO) personnel who are in regular contact with the study site will be blinded to treatment assignment during the double-blind treatment period of the study and blinded to blood lipid measurements during the double-blind and single-blind treatment periods.

Selected individuals at Regeneron not involved in the conduct of the study may have access to unblinded data, as needed, for safety review or other data review.

Although there is a slight color difference between the drug product and placebo product for IV infusion bag preparation, the color difference is not detectable when the investigational product is added to the IV infusion bag. Further details are provided in the pharmacy manual.

7.6.2. Emergency Unblinding

Unblinding of treatment assignment for a patient may be necessary due to a medical emergency or any other significant medical event (eg, pregnancy) during the double-blind treatment period.

If unblinding is required:

- Only the investigator will make the decision to unblind the treatment assignment.
- Only the affected patient will be unblinded.
- The investigator or their designee for the site will unblind the patient.

- The investigator will notify Regeneron and/or designee before unblinding the patient, whenever possible.

Treatment assignment is not to be provided to site personnel at any time during the conduct of the study except in the case of a true emergency.

7.7. Treatment Logistics and Accountability

7.7.1. Packaging, Labeling, and Storage

A medication numbering system will be used to label blinded investigational study drug. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging. In order to maintain the blind, these lists will not be accessible to individuals involved in study conduct.

Study drug will be stored at the site at a temperature of 2°C to 8°C; storage instructions will be provided in the pharmacy manual.

7.7.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2°C to 8°C to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be returned to the sponsor or designee.

7.7.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication

- dispensed to each patient,
- returned from each patient (if applicable), and
- returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

7.7.4. Treatment Compliance

All doses of study drug will be administered in the clinic. All drug compliance records must be kept current and made available for inspection by the sponsor and regulatory agency inspectors.

7.8. Concomitant Medications

Any treatment administered from the time the informed consent is signed to the final study visit will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study.

7.8.1. Prohibited Medications

The following concomitant medications and procedures are prohibited during the study:

- Glybera®
- Lipid apheresis or plasma exchange
- Lomitapide
- Mipomersen and other antisense lipid therapies
- Systemic corticosteroids, unless used as replacement therapy for pituitary/adrenal disease with a stable regimen for at least 6 weeks prior to the screening visit

7.8.2. Permitted Medications and Procedures

The use of medications and nutritional supplements known to lower triglycerides, including statins, fibrates, niacin, omega-3s are permitted as long as that therapy has been stable for at least 4 weeks (6 weeks for fibrates, 8 weeks for PCSK9 inhibitors) prior to the screening visit. Patients should continue taking their background medical lipid-modifying therapy for the duration of the study starting at screening and through the end of treatment visit.

Patients on thyroid replacement therapy can be included if the dosage of thyroxine has been stable for at least 12 weeks prior to the screening visit.

Topical, intra-articular, nasal, inhaled and ophthalmic steroid therapies are not considered as 'systemic' and are allowed.

8. STUDY SCHEDULE OF EVENTS AND PROCEDURES

8.1. Schedule of Events

Study assessments and procedures are presented by study period and visit in Table 1.

Table 1: Schedule of Events

	Screening Period			Placebo run-in[1]/ Baseline		Double-Blind Treatment Period[2]						Single-Blind Treatment Period[3]		
Study Procedure	**Visit 1**	**Visit 1b[4]**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10[5]**	**Visit 11**	**Visit 12**	**End of Treat-ment Visit 13**
Day	**-66 to -59**	**-58 to -52**	**-51 to -39**	**-28 +4d**	**-14 ± 4d**	**1 ± 4d**	**15 ± 4d**	**29 ± 4d**	**43 ± 4d**	**57 ± 4d**	**85 ± 4d**	**113 ± 4d**	**141 ± 4d**	**169 ± 5d**
Week						**0**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**
Screening/Baseline:														
Inclusion/Exclusion	X		X	X										
Informed Consent	X													
Medical History[6]	X													
Demographics	X													
FT4, TSH	X													
FSH (for women only)	X													
PT/PTT, INR	X													
Cohort Assignment				X										
Randomization						X								
Treatment:														
Heparin[7]			X[8]											X
Administer Placebo				X[9,10]										
Administer Study Drug (evinacumab or placebo)						X[9,10]		X[9,10]		X[9,10]				
Administer evinacumab											X[9,10]	X[9,10]	X[9,10]	
Concomitant Medications and treatment	X		X	X	X	X	X	X	X	X	X	X	X	X
Efficacy:														
Lipids and lipoproteins[11,12]	X[13]	X[13]		X	X	X	X	X	X	X	X	X	X	X
HbA1c, Insulin, C-peptide, and Homa[11]				X		X					X			X
Post-heparin LPL, EL, HL activity assay and HL mass assay[11]			X[14]											X
Pre-heparin LPL and EL mass assay [11]			X											X
Train/dispense ePRO device			X											
Daily Symptom Questionnaire (Hypertriglyceridemia and Acute Pancreatitis Signs and Symptoms)[15]				X		X[16]		X[16]		X[16]	X[16]	X[16]	X[16]	X[16]

	Screening Period			Placebo run-in[1]/ Baseline		Double-Blind Treatment Period[2]						Single-Blind Treatment Period[3]		
Study Procedure	**Visit 1**	**Visit 1b[4]**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10[5]**	**Visit 11**	**Visit 12**	**End of Treat-ment Visit 13**
Day	**-66 to -59**	**-58 to -52**	**-51 to -39**	**-28 +4d**	**-14 ± 4d**	**1 ± 4d**	**15 ± 4d**	**29 ± 4d**	**43 ± 4d**	**57 ± 4d**	**85 ± 4d**	**113 ± 4d**	**141 ± 4d**	**169 ± 5d**
Week						**0**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**
Symptom/Dietary Impact Questionnaire (Hypertriglyceridemia and Acute Pancreatitis Dietary Behavior)[15]				X		X[16]		X[16]		X[16]	X[16]	X[16]	X[16]	X[16]
Site review of questionnaires for compliance				X		X		X		X	X	X	X	X
Safety:														
Vital Signs	X		X	X[10]	X	X[10]	X	X[10]	X	X[10]	X[10]	X[10]	X[10]	X
Physical Examination	X			X		X					X			X
Weight	X		X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram[17]	X					X					X			X
Adverse Events[18]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Confirm required contraception use and reminder of pregnancy status reporting in women of child bearing potential and female partners of male patients[19]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Remind male patients to use condoms				X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing:														
Hematology[11]	X			X		X	X	X	X	X	X	X	X	X
Blood Chemistry[11]	X			X		X	X	X	X	X	X	X	X	X
Pregnancy Test	serum			urine		urine		urine		urine	urine	urine	urine	serum
Urinalysis	X			X		X					X			X
Imaging and Other Assessments:														
DW-MRI[20]				X	X						X			X
^{18}F-FDG-PET[20]					X						X			
PK/Drug Concentration and ADA Samples:														
PK/Drug conc. Sample[21]						X[22]		X[22]		X[22]	X[22]		X[22]	X
ADA sample						X		X			X			X
Biomarkers:														
Biomarker serum/plasma				X	X	X	X	X	X	X	X	X	X	X
Amylase, lipase[11]	X			X	X	X	X	X	X	X	X	X	X	X
APOC2, APOC3, APOA5, NEFA[11]						X					X			X

	Screening Period			Placebo run-in[1]/ Baseline		Double-Blind Treatment Period[2]						Single-Blind Treatment Period[3]		
Study Procedure	**Visit 1**	**Visit 1b[4]**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10[5]**	**Visit 11**	**Visit 12**	**End of Treat-ment Visit 13**
Day	**-66 to -59**	**-58 to -52**	**-51 to -39**	**-28 +4d**	**-14 ± 4d**	**1 ± 4d**	**15 ± 4d**	**29 ± 4d**	**43 ± 4d**	**57 ± 4d**	**85 ± 4d**	**113 ± 4d**	**141 ± 4d**	**169 ± 5d**
Week						**0**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**
Inflammation Panel (eg, IL-1, IL-6, IL-8, TNFα)				X		X					X			X
hs-CRP				X		X					X			X
Lipid sub-fractions by UC						X					X			X
Genomic DNA sample:														
Whole blood DNA sample				X										

Schedule of Events (continued)

	Off-Drug Treatment Follow-Up Period				
Study Procedure	**Visit 14**	**Phone Call**	**Visit 16**	**Phone Call**	**End of Study Visit 18**
Day	**197± 5d**	**225± 5d**	**253± 5d**	**281± 5d**	**309± 5d**
Week(s)	**28**	**32**	**36**	**40**	**44**
Treatment:					
Concomitant Medications and treatment	X	X	X	X	X
Efficacy:					
Lipids and lipoproteins[11,12]	X		X		X
HbA1c, Insulin, C-peptide, and Homa[11]					X
Daily Symptom Questionnaire (Hypertriglyceridemia and Acute Pancreatitis Signs and Symptoms)[15]	X[16]		X[16]		X[16]
Symptom/Dietary Impact Questionnaire (Hypertriglyceridemia and Acute Pancreatitis Dietary Behavior)[15]	X		X		X
Site review of responses to questionnaires	X		X		X
Safety:					
Vital Signs	X		X		X
Physical Examination					X
Weight	X		X		X
Electrocardiogram[17]					X
Adverse Events	X	X	X	X	X
Confirm required contraception use and reminder of pregnancy status reporting in women of child bearing potential and female partners of male patients[19]	X	X	X	X	X
Remind male patients to use condoms	X	X	X	X	
Laboratory Testing:					
Hematology[11]	X		X		X
Blood Chemistry[11]	X		X		X
Pregnancy Test[19]	Urine	Urine	urine	urine	serum
Urinalysis					X
Imaging and Other Assessments:					
Amylase, lipase[11]	X		X		X
PK/Drug Concentration and ADA Samples:					
PK/Drug conc. Sample[21]	X		X		X
ADA sample					X
Biomarkers:					
Inflammation Panel (eg, IL-1, IL-6, IL-8, TNFα)					X
hs-CRP					X

8.1.1. Footnotes for the Schedule of Events Table

1. Patients who are permanently withdrawn from study drug before entering the double-blind treatment period (day 1, week 0) will be contacted to assess any AEs.
2. Patients who are permanently withdrawn from the study drug during double-blind period will be asked to return to the clinic for an early termination visit consisting of week 12 study assessments. After the early termination visit, patients will enter the off-drug treatment follow-up period.
3. Patients who are permanently withdrawn from study drug during the single-blind treatment period will be asked to return to the clinic for an early termination visit consisting of week 24 study assessments. After the early termination visit, patients will enter the off-drug treatment follow-up period.
4. Visit 1b must occur at least 4 days after visit 1.
5. Patients will undergo end of double-blind treatment period assessments at the week 12 visit, which is the first visit of administration of single-blind evinacumab.
6. Medical history should include detailed cardiovascular and pancreatitis history.
7. The patient should be fasting for at least 8 hours prior to the post-heparin procedure for measurement of LPL activity. The patient should not consume any alcohol 48 hours prior to the post-heparin plasma blood draw. Heparin (60 U/kg body weight) should be administered IV by bolus injection. Venous blood should be collected 10 minutes after the bolus injection. Prior to discharge from the clinic, patients should then be observed for 1 hour post-heparin administration for any AEs.
8. Following the screening period and confirmation of eligibility, patients will receive an IV bolus of 60 IU of heparin per kg of body weight at visit 2.
9. At dosing visits, all assessments (including urine or serum pregnancy tests for WOCBP) should be performed and all blood samples should be collected before the dose of study drug is administered.
10. Vital signs should also be measured and AEs monitored pre-dose, at the end of study drug infusion, between 30 to 60 minutes post dose, and at approximately 120 minutes post dose. Patients will be closely monitored for a minimum of 120 minutes after IV administration of study drug.
11. Patients should fast for a minimum of 8 hours prior to all blood draws. For patients with diabetes, investigators may hold a patient's morning diabetes medications until labs are drawn and the patient has eaten.
12. Lipids and lipoproteins, total cholesterol, LDL-C, HDL-C, TG, APOB, APOA1, and Lp(a) will be measured except at visit 1 and 1b.
13. At visit 1 and visit 1b, only total cholesterol, LDL-C, HDL-C, and TG will be measured.
14. Lipoprotein lipase level enzyme activity will be measured in fasting plasma collected at visit 2 only after eligibility has been confirmed by screening procedures at visit 1 and visit 1b.

15. Questionnaires should be completed daily for 7 days prior to each visit except for visit 3 (to be completed daily for the duration between visit 2 and visit 3).
16. Patients should be reminded by phone call 1 week prior to their visit to complete questionnaires.
17. Electrocardiogram should be performed before blood is drawn during visits that require blood draws.
18. In addition to assessment of adverse events at each visit, investigators should also ask patients if they have had any changes in abdominal symptoms and/or medical clinic visits for abdominal symptoms.
19. Confirm required contraception use and pregnancy status of female patients of childbearing potential and female partners (of child-bearing potential) of male patients will be monitored at clinic visits and by phone call for 24 weeks post the last dose of study drug. Women of childbearing potential will be provided urine pregnancy tests with instructions to test for pregnancy on days corresponding to phone call visits or Q4W if patients do not attend regularly scheduled visits.
20. Imaging may be performed up to 1 week prior to the visit and may be on the same day of the visit (for visit 3, MRI can be done on the same day or up to 4 days after visit 3). If done on the day of the visit, vital signs, ECG and blood draws after an 8-hour fast should be completed prior to the imaging procedures. Imaging procedures should be performed prior to study drug infusion.
21. PK samples will also be used for the analysis of total ANGPTL3.
22. In addition to the PK sample collected prior to drug administration, a PK sample should be obtained immediately after the end of each infusion.

8.1.2. Early Termination Visit

Patients who are permanently withdrawn before entering the double-blind treatment period (day 1, week 0) will be contacted to assess any adverse events. Patients who are permanently withdrawn from study drug during the double blind treatment period will be asked to return to the clinic for an early termination visit consisting of week 12 study assessments described in Table 1. After the early termination visit, patients will enter the off-drug treatment follow-up period as described in Table 1. Patients who are permanently withdrawn from study drug during the single blind treatment period will be asked to return to the clinic for an early termination visit consisting of week 24 study assessments described in Table 1. After the early termination, patients will enter the off-drug treatment follow-up period as described in Table 1. Efforts should be made to contact patients by phone to assess for AEs for patients who do not wish to return for clinic visits (as described above) after discontinuation from study drug.

All patients who prematurely discontinue study treatment (either in the double-blind period or in the single blind period) should be followed for at least 24 weeks from the last dose of study drug, and a final end of study visit can take place with assessments as specified in the end of study visit (ie, follow-up visit).

Sexually active males and WOCBP who discontinue the study prematurely should be reminded at the unscheduled early termination visit following treatment discontinuation to maintain highly

effective contraceptive measures for 24 weeks (as described in Section 6.2.2) for 24 weeks after the last dose of study drug. At this visit, WOCBP will be provided a sufficient number of urine pregnancy tests with instructions to test for pregnancy 4 weeks after this visit and Q4W thereafter. The patient will also be notified of Q4W follow-up phone calls to confirm continued contraception use and pregnancy reporting, to obtain the results of the pregnancy tests, and to obtain information on whether pregnancy has occurred in WOCBP and in female partners of male patients.

If a WOCBP is lost to follow-up, sites should attempt a minimum of 2 telephone calls. If the patient cannot be reached on the second attempt, a formal letter will be issued from the site to the patient that reminds the patient of the importance of continued use of highly effective contraception use for at least 6 months after the last dose of study drug.

8.1.3. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted.

8.2. Study Procedures

8.2.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population: FT4, TSH, FSH (to verify postmenopausal status - for women only), and PT/PTT/INR.

8.2.2. Efficacy Procedures

Fasting blood samples will be collected at specified time points listed in Table 1 for assessment of the lipid profile, including plasma triglycerides, LDL-C by ultra-centrifugation, HDL-C, non-HDL-C, total cholesterol and other assays. The TG and total cholesterol will be assessed by an enzymatic colorimetric assay run on Beckman-Coulter chemistry analyzers. HDL-C will be assayed by precipitation, which involves precipitating all non-HDL-C (IDL, LDL and Lp[a]) using 50kDa Dextran sulfate with magnesium ions as the precipitating agent followed by determination of the HDL-C in the supernatant on the Beckman-Coulter analyzers using an adapted method for determining total-cholesterol. Low-density lipoprotein cholesterol will be calculated after separation of the VLDL/CM sub-fraction by ultra-centrifugation, measurement of the cholesterol in the infranatant measured by the enzymatic colorimetric assay and subtraction of the HDL-C (also known as beta-quantification). APOA1 and APOB will be assessed by nephelometry on a Siemens BNII nephelometer. Serial ultra-centrifugation will be performed to separate lipoprotein subfractions (CM, VLDL, IDL, LDL, HDL) and lipids (eg, TG, cholesterol, phospholipids) and proteins (eg, APOB, A1, C2, C3, A5, etc) will be measured in the fractions by established methods. Samples for assessment of lipids and lipoproteins and HbA1c will be collected at time points according to Table 1.

8.2.3. Daily Symptom Questionnaire and Symptom/Dietary Impact Questionnaire

Patients will complete a daily symptom questionnaire recording sub-clinical/clinical pancreas-related symptoms such as nausea vomiting, abdominal distention, abdominal pain, loss

of appetite, and self-imposed dietary restrictions daily for 7 days prior to each visit except for visit 3 (the questionnaire should be completed daily for the duration between visit 2 and visit 3) (Table 1).

Patients will also complete a symptom/dietary impact questionnaire after the weekly signs and symptoms questionnaire daily for 7 days prior to each visit except for visit 3 (the questionnaire should be completed daily for the duration between visit 2 and visit 3) (Table 1).

8.2.4. Imaging

Imaging provides a non-invasive means of evaluating tissue-specific changes that may not be detectable by assays performed on blood samples. ^{18}F-FDG PET provides a sensitive way to evaluate tissue-specific inflammatory changes. This is achieved through signal enhancement driven by increased blood vessel permeability and presence of hypermetabolic infiltrating immune cells. Pancreatic ^{18}F-FDG PET signal may be susceptible to drastic changes in blood glucose, and could be affected by clearance changes of the tracer induced by therapeutic intervention. While the DW-MRI signal depends on the water diffusion through tissue and is not affected by the metabolic state of the patient, the T2-MRI signal in soft tissue is dependent upon the degree of localized water content. Respiratory motion artifacts and presence of abdominal fat may present challenges for quantitative MRI. Compared to other imaging modalities, there is more cross-sectional published data on the utilization of MRI in acute pancreatic states. However, more examples in the literature exist where ^{18}F-FDG PET was implemented to longitudinally assess pancreatic inflammation. Thus, both imaging modalities appear promising for the detection of pancreatic inflammation or injury. Taken together, these factors point to the advantage an imaging strategy where both modalities are incorporated, as they may each provide complementary information, or only one may be the primary source of pancreatic injury data due to technical/operational challenges that cannot be fully predicted at this time.

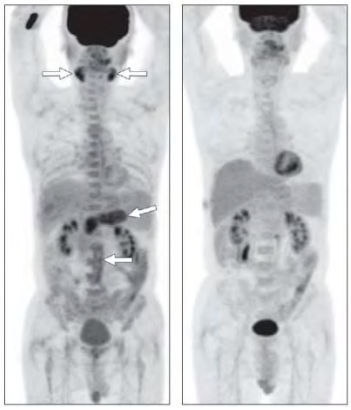
8.2.4.1. ^{18}F-FDG-PET

^{18}F-FDG-PET will be performed at baseline (placebo run-in period) and following 12 weeks of study treatment (double-blind treatment period) as a method to measure inflammation in the pancreas.

Although ^{18}F-FDG-PET has not been used to detect subclinical pancreatic inflammation in patients with HTG, it has been utilized to assess low-level pancreatic injury in other settings. We plan to assess subclinical pancreatic injury through ^{18}FDG-PET measures (maximal standardized uptake value, SUV_{max}, SUV_{mean}, and incorporation rates, Ki or Kpatlak at baseline and following 12 weeks of treatment). Although ^{18}FDG-PET has not been used in this particular setting, it has been utilized to assess low-level pancreatic injury in other settings. ^{18}F-FDG PET is a molecular imaging modality that has demonstrated high sensitivity in the in vivo detection of glycolytic tissues, including tumors and inflammatory foci. ^{18}F-FDG PET has been applied in a clinical setting to the assessment of inflammation for a variety of indications, including AIP, atherosclerosis and infection (Ozaki 2008, Shreve 1998, Glaudemans 2013,Tahara 2007, Vos 2006). ^{18}F-FDG PET has shown the capability of measuring longitudinal patient inflammatory response in the context of AIP, where patients who present with pancreatitis symptoms and high baseline pancreatic PET signal were treated with corticosteroids. These studies demonstrated the within-patient normalization of PET signal after treatment (see Figure 2) (Lee 2009). While normal pancreas has

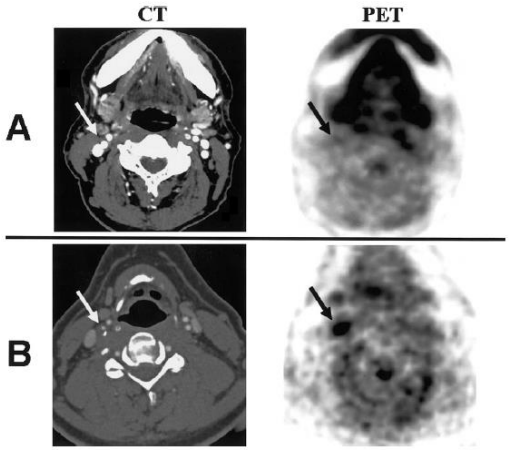
a PET uptake signal with an SUV_{mean} = 2.0±0.5 (mean ± SD), patients with AIP show enhanced pancreatic PET uptake with an SUV_{mean} = 4.0±1.2, providing a substantial signal window (SUV = a normalized measure of activity concentration in tissue, SUV_{max} is the maximum SUV within a region of interest). Given the test/re-test variability in PET signal (CV = 15%), a mean ~10% change in mean pancreatic SUV signal should be readily detectable in this study. Studies in patients undergoing corticosteroid treatment for AIP experienced consistent reductions of ~40% pancreatic signal and normalization of ^{18}F-FDG pancreatic uptake (Lee 2009, Shigekawa 2010). A 30% reduction in ^{18}F-FDG pancreas uptake should be deemed as clinically significant. In one study (N=12), 50% of patients with pancreatitis and positive ^{18}F-FDG PET scans showed normal amylase and lipase levels (Shreve 1998), suggesting that ^{18}F-FDG PET may have better sensitivity for detection of pancreatic inflammation than traditional markers of pancreatitis.

Figure 2: ^{18}F-FDG PET showing decrease of signal in areas of AIP inflammation (pancreas, salivary glands and retroperitoneum) after up to 2 months of prednisolone treatment (0.5 mg/kg, baseline on the left, post-treatment on the right) (Lee 2009).



^{18}F-FDG PET has been shown to be able detect inflamed/vulnerable atherosclerotic plaque in the carotid of patients (Figure 3) (Tawakol 2006) and to detect ~15% reductions in signal following 12 weeks of treatment with high-dose statin (versus low dose statin) in N=34 patients (Tawakol 2013). Since the acquisitions with ^{18}F-FDG PET in the present study will include the neck and thoracic regions, it will be possible to assess suspect areas of atherosclerotic plaque in the carotid and aorta of patients. Reduction of signal (target to background ratio - TBR) in these areas would indicate a potential beneficial effect of ANGPTL3 inhibition on atherosclerotic lesions. ANGPTL3 inhibition in rodents has led to reductions in atherosclerotic plaque. Since ^{18}F-FDG-PET can detect inflammation in atherosclerotic lesions, we plan to explore imaging of the carotids and aorta before and after treatment, without any further isotope dosing or radiation exposure.

Figure 3: **Axial CT and co-registered PET images from 2 patients. Patient A showed low ^{18}F-FDG uptake in the region of the carotid plaque, while Patient B had high uptake in the region of the carotid plaque. The uptake difference was consistent with high inflammatory infiltration in the atherosclerotic plaque of patient B compared to patient A as determined from excised tissue samples.**



^{18}F-FDG PET scans (including a low-dose CT scan) result in typical effective radiation doses of 7 to 10 mSv per study for an adult (19 microSv/MBq) (ICRP 80). The maximum recommended allowed effective dose for a research patient in a single year is 50 mSv (21CFR361.1). Two ^{18}F-FDG PET studies would result in an approximate dose of 20 mSv, or 40% of the recommended maximum allowed dose. Risk and management of radiation exposure will be disclosed to patients in the informed consent form. ^{18}F-FDG PET will be performed at week 2 and at week 16 (12 weeks after initiation of evinacumab treatment).

8.2.4.2. Magnetic Resonance Imaging

MRI will be used to assess pancreatic injury/inflammation at baseline and after treatment with evinacumab. With MRI, there is no ionizing radiation dose to the patient that would limit the number of imaging studies that could be performed. Pancreatic MRI is planned for day -28, week -2, week 12 and week 24. Week 12 and 24 scans will allow for short-term and long-term inflammatory response assessments (Klauss 2015). During early stages of pancreatic injury or inflammation, acinar cell injury, activation of pancreatic stellate cells and an invasion by leukocytes, neutrophils and macrophages are all known to exist (Whitcomb 2004). Such intra-and extracellular pathological events modulate microstructural properties of affected pancreatic tissue, and in turn, alter the Brownian motion of water molecules in cellular compartment. In DW-MRI, the random diffusion of water molecules occurring within intracellular, extracellular and intravascular spaces is measured, enabling detection of macroscopic soft tissue pathology such as edema, necrosis and fibrosis. The apparent diffusion coefficient (ADC, units of mm^2/sec) is a principal metric quantified in DW-MRI experiments, where ADC values can be mapped across a region of interest at a spatial resolution of ~3 x 3 x 5 mm^3. Compared to healthy pancreatic tissue, inflammatory tissue is characterized as having restricted water diffusion (decreased ADCs), while necrotic tissue corresponds to less restricted water diffusion (increased ADCs). Normal pancreas ADCs are (1.77±0.32) X 10^3 mm^2/sec while acute pancreatitis ADCs are (1.32±0.32) X 10^3

mm^2/sec showing a significant window for measuring the projected inflammatory changes in the pancreas. Given a test/re-test variability of 18%, a signal change of 20% should be detectable in the present study.

Measurement of ADCs has been used to assess pancreatic health across pancreatic disease states, including acute, chronic and autoimmune pancreatitis as well as pancreatic cancer. Confirming earlier observations, de Freitas Turtulino recently reported a ~20% difference in ADC between healthy (N=15) and mild acute (N=13) pancreas states (de Freitas Tertulino 2015) (Figure 4). Lower ADCs were also detected in indications possessing pancreatic inflammation such as in cases of chronic obstruction of the main pancreatic duct known to exist in pancreatic cancer (Hayano 2016). Here, a ~12% difference in ADCs between large and small main pancreatic duct diameter cohorts was observed (Mann-Whitney U test [P=0.03]). For review of implementation of DW-MRI in pancreatic disease see Barral 2015.

DW-MRI can be combined with T2-weighted and T2 mapping MRI, the latter of which can further inform on the presence, but not clear differentiation of edema, hyperemia or inflammatory cell infiltration within a region of interest (Figure 5). Moreover, pancreatic lesions can be assesses in combination with whole organ or regional (head, neck, body and tail) pancreatic volume, which can be modulated in a disease state. In the current study, ADCs, T2-weighted intensities and T2 relaxations times will be reported for the whole pancreas in addition for each pancreatic sub-region (head, neck, body and tail). Outside of disease states affecting pancreatic health, a combined diffusion-weighted and T2-MRI approach is commonly utilized for early detection of lesions following stroke, monitoring of hepatic metastases across oncology indications and detection of focal renal lesions known to exist in metabolic diseases such as chronic kidney disease. Thus, the combined DW-MRI and T2-MRI approach is commonly implemented and validated across multiple indications (Mashhood 2013).

Magnetic resonance imaging is used in the measurement of hepatic fat fraction. A multi-echo gradient-recalled echo sequence acquiring axial images to cover the entire liver is recommended. The echo times shall be such that at successive echo times (TEs), fat and water alternate between out-of-phase and in-phase. To minimize motion artifacts, these should be acquired under breath hold (not to exceed 20 seconds), and 3 separate breath hold acquisitions covering different sections of the liver (superior-middle-inferior) will need to be acquired. The full acquisition should take 3 to 5 minutes.

Figure 4: **ADC values as measured by DW-MRI differentiate normal pancreas from acute pancreatic disease states. ~20% difference between normal and mild acute pancreas. Kruskal-Wallis test across cohorts (P < 0.001). Sample Size: Normal (N=15), mild acute (N=13) and necrotizing acute (N=8) pancreas (de Freitas Tertulino 2015).**

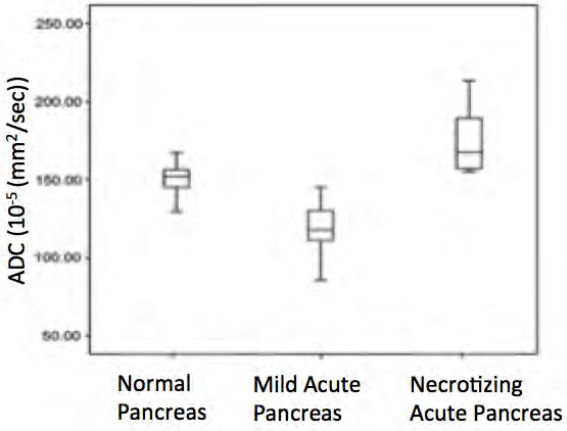
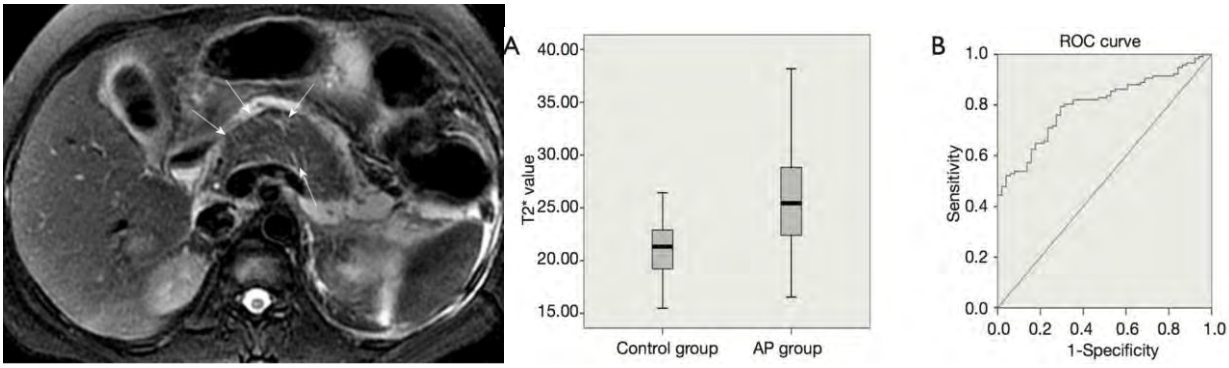


Figure 5: **Axial T2-weighted MRI with fat-suppression demonstrated intrapancreatic threadlike hyperintense structures consistent with interlobular septal inflammation (arrows). Data collected from a 42-year-old male, acute pancreatitis patient (Xiao 2010). Boxplots of the control (N=51) and acute pancreatitis (N=117) groups shows higher T2 values in the patient cohort owing to presence of edematous pancreatic tissue. Calculation of the ROC curve demonstrated good diagnostic value of T2 MRI for diagnosis of acute pancreatitis (Tang 2016).**



8.2.5. Safety Procedures

8.2.5.1. Vital Signs

Vital signs, including temperature, sitting blood pressure, pulse, and respiration will be collected pre-dose at time points according to Table 1.

8.2.5.2. Physical Examination

A thorough and complete physical examination will be performed at time points according to Table 1. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history. Medical history should include detailed cardiovascular and pancreatitis history.

8.2.5.3. Electrocardiogram

Electrocardiograms should be performed before blood is drawn during visits requiring blood draws. A standard 12-lead ECG will be performed at time points according to Table 1. A 12-lead ECG should be performed in the supine position after resting for at least 10 minutes. For each ECG recording throughout the study, the electrodes should be positioned in the same place as much as possible. The ECG will be interpreted locally by the investigator. Heart rate will be recorded from the ventricular rate, and the PR, QRS, RR, QTcB and QTcF intervals will be recorded. Any clinically significant abnormality should be documented as an AE/SAE as applicable. Each ECG tracing will be analyzed in comparison with the screening record trace. The ECG strips or reports will be retained with the source.

8.2.5.4. Laboratory Testing

Hematology, chemistry, urinalysis, and serum pregnancy testing samples will be analyzed by a central laboratory. Urine pregnancy testing samples will be analyzed locally (patients will use a pregnancy test provided by the site for phone visits in the follow-up). Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

Samples for laboratory testing will be collected at visits according to Table 1. Tests will include:

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin
Potassium	Creatinine	Total cholesterol*
Chloride	Blood urea nitrogen (BUN)	Triglycerides
Carbon dioxide	Aspartate aminotransferase (AST)	Uric acid
Calcium	Alanine aminotransferase (ALT)	Creatine phosphokinase (CPK)
Glucose	Alkaline phosphatase	Phosphorus
Albumin	Lactate dehydrogenase (LDH)	Magnesium

*(low-density lipoprotein [LDL] and high-density lipoprotein [HDL])

Hematology

Hemoglobin	Differential:
Hematocrit	Neutrophils
Red blood cells (RBCs)	Lymphocytes
White blood cells (WBCs)	Monocytes
Red cell indices	Basophils
Platelet count	Eosinophils

Urinalysis

Color	Glucose	RBC
Clarity	Blood	Hyaline and other casts
pH	Bilirubin	Bacteria
Specific gravity	Leukocyte esterase	Epithelial cells
Ketones	Nitrite	Crystals
Protein	WBC	Yeast

Other Laboratory Tests

Samples will also be collected for assessment of LPL enzyme activity after administration of heparin at screening visit 2 and at visit 13. Other laboratory tests include HbA1C, insulin, C-peptide, Homa, inflammation biomarker panel (eg, hs-CRP, IL-1, IL-6, IL-8, and TNFα), amylase, lipase, APOC2, APOC3, APOA5, and NEFA, and lipid sub-fractions by UC.

Abnormal Laboratory Values and Laboratory Adverse Events

- All laboratory values must be reviewed by the investigator or authorized designee.
- Significantly abnormal test results that occur after start of treatment must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the medical monitor must be consulted.
- The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 9.4.5.

8.2.6. Pharmacokinetic and Anti-Drug Antibody Procedures

8.2.6.1. Drug Concentration Measurements and Samples

Samples for drug concentration will be collected at time points listed in Table 1.

[redacted].

8.2.6.2. Anti-Drug Antibody Measurements and Samples

Serum samples for ADA assessment will be collected at time points listed in Table 1. They will be collected pre-dose on days when study drug is administered. [redacted].

Patients who exhibit a treatment emergent or treatment boosted positive ADA assay response in their last sample analyzed will be followed until the titers are less than 240 or within 2 dilution steps from the pre-dose baseline titer levels.

8.2.7. Biomarker Procedures

Biomarker samples will be collected at time points according to Table 1.

Lipoprotein lipase enzyme activity will be measured using the assay developed by Imamura et al, (Imamura 2008) in fasting plasma collected from patients at visit 2 (after eligibility has been confirmed by screening procedures at visit 1 and 1b and the patient has received an IV bolus of 60 IU of heparin per kg of body weight), and at visit 13 (after administration of an IV bolus of 60 IU of heparin per kg of body weight). Lipoprotein lipase is bound to the luminal side of capillary endothelium by glycosoaminoglycans and the infusion of heparin is required for the disassociation of the bound LPL into the circulation. The heparin infusion is generally considered to be safe and well tolerated.

8.2.8. Biochemical Measures of Pancreatic Health

Amylase and pancreatic lipase are clinical measures of pancreatic health, which are elevated during episodes of AP and will be measured at every visit. Levels of IL6 and CRP have been demonstrated to be elevated during AP episodes and are considered exploratory measures due to limited clinical evidence and therefore will only be measured at baseline and during the treatment period. Research samples will be collected at every visit for any post-hoc analyses of biochemical markers for correlation with clinical symptoms of AP and may include trypsinogen, pancreatic isoamylase, pancreatic elastase, serum trypsin, phospholipase A2, carboxypeptidase B.

[redacted]

8.2.9.1. Genomics Study

To better understand the response to inhibition of ANGPTL3 in patients with sHTG, this study will enroll patients with LPL deficiency (as assessed by genotype) as well as those with relatively intact LPL activity. Lipoprotein lipase deficiency can be caused by LOF mutations in LPL or other genes that modulate the enzymatic activity of LPL, such as APOC2, and APOA5. APOC2 serves as an activator protein of LPL and APOA5 is thought to stabilize the lipoprotein enzyme complex and enhance lipolysis.

Loss of function mutations in LPL (eg, deletions or duplications) lead to levels of undetectable LPL activity and mass in plasma (Monsalve 1990) and heterozygotes who have a G215E mutation have mean levels of LPL at about 50% of normal though individually their levels overlap with normal levels (Wilson 1993). Other genetic causes of sHTG include homozygous mutations in LMF1 and GPIHBP1, which are genes in the LPL pathway. In a study of 86 sHTG patients (both Type 1 and Type 5 with TGs > 10 mmol/L), with a range of LPL enzyme activity levels, 35% had rare causative mutations in LPL, 11% had mutations in APOA5, APOC2, LMF1 and GPIHBP1,

and the rest had either common variants in these genes or no identified mutations (Surendran 2012). Based on the data from this Dutch study, not all LOF mutations in the LPL pathway resulted in diminished LPL enzyme activity.

DNA will be collected for all patients and sequencing performed to confirm mutations if previously genotyped and analysis will be done to identify mutations in genes in the LPL pathway eg, LPL, APOC2, APOA5 as well as other genes known to be associated with sHTG.

9. SAFETY DEFINITIONS, REPORTING, AND MONITORING

9.1. Obligations of Investigator

The investigator must promptly report to the Institutional Review Board (IRB)/Ethics Committee (EC) all unanticipated problems involving risks to patient. This includes death from any cause and all SAEs related to the use of the study drug. It is recommended that all SAEs be reported to the IRB/EC, regardless of assessed causality.

9.2. Obligations of Sponsor

During the course of the study, the sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to the study drug (suspected unexpected serious adverse reaction [SUSAR]), to the health authorities, IRBs/ECs as appropriate, and to the investigators.

Any AE not listed as an expected event in the Investigator's Brochure or in this protocol will be considered as unexpected. Any worsening of or new onset of symptoms related to sHTG which occur during the screening period prior to study drug administration will be considered expected.

In addition, the sponsor will report in an expedited manner all SAEs that are expected and at least reasonably related to the study drug to the health authorities, according to local regulations.

At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the clinical study report to health authorities and IRBs/ECs as appropriate.

9.3. Definitions

9.3.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug, which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease, which is temporally associated with the use of a study drug, whether or not considered related to the study drug.

An AE also includes any worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug.

9.3.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** - includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** - in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

9.3.3. Infusion Reactions

Infusion reactions are defined as any AE that occurs during the infusion or within 2 hours after the infusion is completed. All infusion reactions must be reported as AEs (defined in Section 9.4.1) and graded using the grading scales as instructed in Section 9.5.1.

9.4. Recording and Reporting Adverse Events

9.4.1. Adverse Events

The investigator (or designee) will record all AEs that occur from the time the informed consent is signed until the end of study. Refer to the study reference manual for the procedures to be followed.

Information on follow-up for AEs is provided in Section 9.4.6. Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs as outlined in Section 9.4.5.

9.4.2. Serious Adverse Events

All SAEs, regardless of assessment of causal relationship to study drug, must be reported to the sponsor (or designee) within 24 hours. Refer to the study reference manual for the procedure to be followed.

Information not available at the time of the initial report must be documented in a follow-up report. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested.

In the event the investigator is informed of an SAE after the patient completes the study, the following will apply:

- SAE with an onset within 30 days of the end of study or within 24 weeks of last study drug administration if the patient terminated from the study early - the SAE will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome until the event is considered chronic and/or stable.
- SAE with an onset day greater than 30 days from the end of study or 24 weeks from the early termination visit for patients who terminate from the study early - only fatal SAEs and those deemed by the investigator to be drug-related SAEs will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of a drug-related SAE until the event is considered chronic and/or stable.

9.4.3. Other Events that Require Accelerated Reporting to Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

Symptomatic Overdose of Study Drug: Accidental or intentional overdose of at least 2 times the intended dose of study drug within the intended therapeutic window, if associated with an AE.

Pregnancy: Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female patient, or female partner of a male patient, during the study or within 24 weeks of the last dose of study drug. Any complication of pregnancy affecting a female study patient, or the female partner of a male study patient, and/or fetus and/or newborn that meets the SAE criteria

must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

Adverse Events of Special Interest: All AESI, serious and nonserious, must be reported within 24 hours of identification using the same reporting process as for SAE reporting, per Section 9.4.2. Adverse events of special interest for this study include the following:

- Anaphylactic reactions
- Allergic reactions and/or local injection site reactions that require consultation with another physician for further evaluation
- Increase in ALT or AST: ≥3 x ULN (if baseline <ULN), or ≥2 times the baseline value (if baseline ≥ ULN)
- Pregnancy
- Symptomatic overdose with evinacumab
- Neurocognitive events
- New onset of diabetes: The definition of new onset of diabetes will be the following:
  - Type 1 or type 2 diabetes TEAE (grouping of Medical Dictionary for Regulatory Activities [MedDRA®] terms will be specified in the SAP)

  and/or

  - At least 2 values of HbA1c ≥6.5% during the TEAE period. **NOTE**: For patients with only a single measurement available during the TEAE period, a single value ≥6.5% will be considered and qualify the patient as new onset of diabetes by default. For patients with several HbA1c measurements but only with the last one ≥6.5%, this single value ≥6.5% will be considered and qualify the patient as new onset of diabetes by default.

  and/or

- At least 2 values of fasting glucose ≥126 mg/dL (7.0 mmol/L). NOTE: For patients with only a single measurement available during the TEAE period, a single value ≥126 mg/dL (7.0 mmol/L) will NOT be considered and will NOT qualify the patient as new onset of diabetes. For patients with several fasting glucose measurements but only with the last one ≥126 mg/dL (7.0 mmol/L), this single value ≥ 126 mg/dL (7.0 mmol/L) will NOT be considered and will NOT qualify the patient as new onset of diabetes
- Pancreatitis

Refer to the study manual for the procedures to be followed.

9.4.4. Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a patient's withdrawal from the study must be reported to the sponsor's medical monitor within 30 days.

Refer to the study reference manual for the procedures to be followed.

9.4.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results

The criteria for determining whether an abnormal objective test finding should be reported as an AE include:

- the test result is associated with accompanying symptoms, and/or
- the test result requires additional diagnostic testing or medical/surgical intervention, and/or
- the test result leads to a change in dosing (outside of protocol-stipulated dose adjustments), discontinuation from the study, significant additional concomitant drug treatment, or other therapy

Contact the medical monitor in the event the investigator feels that an abnormal test finding should be reported as an AE, although it does not meet any of the above criteria.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Evaluation of severity of laboratory abnormalities will be assessed according to the scale outlined in Section 9.5.1.

9.4.6. Follow-up

Adverse event information will be collected until the patient's last study visit.

Serious adverse event information will be collected until the event is considered chronic and/or stable.

9.5. Evaluation of Severity and Causality

9.5.1. Evaluation of Severity

The severity of AEs will be graded according to the following scale:

- **Mild:** Does not interfere in a significant manner with the patient normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms, but may be given because of personality of the patient.
- **Moderate:** Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.
- **Severe:** Produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health. Treatment for symptom may be given and/or patient hospitalized.

If a laboratory value is considered an AE, its severity should be based on the degree of physiological impairment the value indicates.

Infusion Reactions

The severity of infusion reactions will be graded according to the following scale (semi-colon indicates "or" within description of the grade):

- **Mild**: Mild transient reaction; infusion interruption not indicated; intervention not indicated.
- **Moderate**: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.
- **Severe**: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae; life-threatening consequences; urgent intervention indicated; death.

9.5.2. Evaluation of Causality

Relationship of Adverse Events to Study Drug:

The relationship of AEs to study drug will be assessed by the investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the study drug?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the study drug

Related: There is a reasonable possibility that the event may have been caused by the study drug

A list of factors to consider when assessing the relationship of AEs to study drug is provided in Appendix 2.

The investigator should justify the causality assessment of each SAE.

Relationship of Adverse Events to Study Conduct:

The relationship of AEs to study conduct will be assessed by the investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by study conduct?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by study conduct

Related: There is a reasonable possibility that the event may have been caused by study conduct

A list of factors to consider when assessing the relationship of AEs to study conduct is provided in Appendix 2.

The investigator should justify the causality assessment of each SAE.

Relationship of Adverse Events to study drug infusion:

The relationship of AEs to the infusion procedure will be assessed by the investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the infusion procedure?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the infusion procedure

Related: There is a reasonable possibility that the event may have been caused by the infusion procedure

A list of factors to consider in assessing the relationship of AEs to infusion procedure is provided in Appendix 2.

The sponsor will request information to justify the causality assessment of SAEs, as needed.

9.6. Safety Monitoring

The investigator will monitor the safety of study patient at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The medical monitor will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Pharmacovigilance and Risk Management; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

9.7. Investigator Alert Notification

Regeneron (or designee) will inform all investigators participating in this clinical trial, as well as in any other clinical trial using the same investigational drug, of any SAE that meets the relevant requirements for expedited reporting (an AE that is serious, unexpected based on the Investigator's Brochure or this protocol, and has a reasonable suspected causal relationship to the medicinal/study drug).

10. STATISTICAL PLAN

This section provides the basis for the SAP for the study. The SAP may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the database is locked.

Analysis variables are listed in Section 4.

10.1. Statistical Hypothesis

There is no formal statistical hypothesis testing planned for this trial, as the primary objective is to estimate the magnitude of treatment effect on TG lowering.

10.2. Justification of Sample Size

Percent change in TG is analyzed based on log (post/pre) transformation, allowing for a normal distribution of the data. Standard deviations (SD) of raw percent changes up to 13% are akin to moderate SD on the log scale (30-40%). For the statistical precision calculations, a log-scale SD of 0.5 was used based on available evinacumab phase 1 data, and is assumed to be conservative. With N=10 patients, the 90% confidence interval (CI) for an estimated mean reduction in triglycerides of 40% is approximately 20% to 55%. With N=12, the CI is 22% to 54%. A sample size of 24 is considered adequate to analyze the percent change in TG in the 3 genetic cohorts. Assuming a 20% drop out rate, approximately 30 patients will be needed to assess TG. Additional patients (up to a maximum of approximately 50 patients) will be enrolled with the intent to explore the effect of evinacumab on development of pancreatitis.

For the FDG-PET uptake signal SUV_{max}, prior data on steroid-treated patients yielded a natural log-scale SD of change of 0.66 (Shigekawa 2010). This yields 80% power to yield a statistically significant (alpha=0.05, 1-sided) change from baseline within the N=16 evinacumab-treated patients if the TRUE underlying geometric mean ratio (post/pre) is 0.65 (back-transformed from the log-scale; ~35% reduction). For comparison to the N=8 placebo-treated patients, assuming log-scale SD=0.15 for placebo based on reproducibility data, and 0.66 for evinacumab, there is 80% power if the TRUE underlying geometric mean ratio (GMR) of GMR's (evinacumab post/pre divided by placebo post/pre) is 0.64 (~36% reduction).

For the key MRI endpoint "mean f", which is the weighting coefficient between contrasting MRI regions (Klauss 2015) reported summary statistics which yield an SD estimate at most 5.96 for change from baseline. With this assumed SD, the N=24 patients with evinacumab post- and pre-values have 80% power to yield a statistically significant (alpha=0.05, 1-sided) change from baseline if the TRUE underlying mean change is 3.12 (~30% from baseline 10.5, which was observed by Klauss [Klauss 2015]). For the between-treatment comparison (N=16 evinacumab vs N=8 placebo), there is 80% power if the TRUE difference is 6.62 (~63% of the 10.5 baseline value observed by Klauss [Klauss 2015]).

10.3. Analysis Sets

10.3.1. Full Analysis Set

The full analysis set (FAS) includes all randomized patients who receive any randomized study drug; it is based on the treatment assigned (as randomized). Only observed data will be analyzed/summarized; no missing data will be imputed. Efficacy endpoints and baseline characteristics will be analyzed using the FAS.

10.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized patients who received any randomized study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

10.3.3. Pharmacokinetics Analysis Set

The PK analysis set includes all treated patients who received any randomized study drug and who had at least 1 non-missing result following the first dose of study drug.

10.3.4. Anti-Drug Antibody Analysis Set

The ADA analysis set includes all treated patients who had at least 1 qualified non-missing post-dose ADA result.

10.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean and/or geometric mean, median, SD or log-scale SD, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

10.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients: met the inclusion criteria regarding the target indication and signed the informed consent form (ICF)
- The total number of patients in each analysis set (eg, FAS, provided in Section 10.3.1)
- The total number of patients who discontinued the study, and the reasons for discontinuation
- A listing of patients enrolled and treated with at least 1 dose of evinacumab, and patients enrolled but not treated with at least 1 dose of evinacumab
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation

10.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group, and by all patients combined.

10.4.3. Efficacy Analyses

10.4.3.1. Primary Efficacy Analysis

The primary analysis is based on percent change from baseline in TG over 12 weeks of evinacumab treatment. For the assessment of probability (computed from the likelihood function based on the observed data, which is equivalent to Bayesian posterior probability with uninformative prior) that

mean TG percent change ≥40% (considered to be a clinically meaningful change) using study data, the point estimates of TG percent changes between the placebo run-in period and each observation week will be calculated using a Mixed-effect Model for Repeated Measures (MMRM) method in the FAS population. A natural log transformation will be applied to the TG levels prior to analysis, aiming to provide a relatively normal data distribution (residuals will be examined for normality prior to proceeding with the analysis). The MMRM model will assess within-patient treatment comparisons (using an unstructured covariance matrix), while accounting for-baseline TG, study visit, and baseline TG by study visit interaction. Note that study visits will be adjusted to start of evinacumab in order to pool data from both randomized groups of patients for this analysis. Since the comparison of study visits yields the within-patient comparisons of study treatments (ie, week 12 [after 12 weeks of treatment with evinacumab] compared to baseline at week 0 [after 4 weeks of treatment with placebo] for patients randomized to evinacumab and week 24 [after 12 weeks of treatment with evinacumab] compared to baseline at week 12 for those randomized to placebo), contrast and estimate statements will be used to assess treatment effects (least squares [LS means with confidence intervals) and comparisons (LS mean ratio with CI). Within-patient comparisons will include all patients, as well as analyses for the genotype subgroups (to assess relationship with amount of TG reduction while on evinacumab). A graph will depict the relationship of TG over time for each genotype subgroup. Details on the subgroup analyses will be defined in the SAP. Both percent change and raw TG will be descriptively summarized by study visit. In the event the MMRM model covariance matrix does not converge or normality is not achieved with the natural log transformation, then other transformations will be explored, including ranks.

To reduce variability of TG baseline measurements, baseline at week 0 for patients randomized to active treatment is the geometric mean of the last 2 measurements during the placebo run-in (day -28, day -14) and week 0. Baseline at week 12 for patients switching from placebo to active is the geometric mean of the last 2 measurements during the placebo phase (weeks 6, 8) and first measurement prior to active infusion (week 12). Additional exploratory analyses may be carried out using the average of all available TG observations prior to first dose of active treatment, if no trend over time in those measurements is discernable.

Using the estimate of the log TG mean ratio (week 12/baseline at week 0 for patients randomized to evinacumab and week 24/baseline at week 12 for those randomized to placebo) and the log of the standard deviation derived from the MMRM model, the PP will be calculated using the target percent change from baseline of 40% reduction (ie, log 0.6) in patients without LOF mutations in genes in the LPL pathway. For the probability calculation (ie, Pr [log TG mean ratio (post/pre)] < log 0.6 conditional on this study's TG results), a non-informative normal distribution prior and a normal distribution of the data is assumed. The probability calculation will yield the probability that the actual mean percent decrease is at least the target 40% value, based on the OBSERVED results from the patients without LOF mutations in genes in the LPL pathway.

This fixed sequence design assumes no carryover effect from the placebo run-in period into the active treatment period. This assumption will be verified by assessment of the time course of TG observations during the run-in period. A generally flat or non-decreasing trend over time in the placebo run-in period will be evidence of no carryover effect into the active treatment period and of a useful valid baseline benchmark against which to compare treatment effects based on within-patient comparisons (active treatment period to placebo run-in period). As a sensitivity analysis, the TG reduction and posterior probability analyses of the combined sequence groups will be repeated using the same baseline at week 0. Note that the follow-up period is expected to have

carryover effects from the active treatment period and is included to estimate the time course of those effects. Such carryover effects may also be interpreted as evidence of treatment effects.

Nominal p-values for testing mean change from baseline >0 and >40% at each time point in each cohort may be computed for information purposes. Since this is an exploratory study, control of the overall type-I error is not applicable for statistical testing. Any p-values provided for outcome measures are for descriptive purposes only.

10.4.3.2. Secondary and Exploratory Efficacy Analysis

Continuous secondary and exploratory endpoints will be analyzed similarly to the primary endpoint, except PP will not be computed. Binary endpoints will be summarized by counts and percents. Triglyceride mean percent change from baseline at each observation week will be summarized. Triglyceride mean percent change from baseline at each observation week will be analyzed and estimated for genetic mutations affecting LPL function (eg, homozygous LPL null [total LOF], heterozygous LPL null, with no LPL null gene mutations subgroups).

For the FDG-PET endpoint, comparisons will be within the evinacumab-treated patients in the double-blind period (week 12 vs week -2 for post/pre) and between the treatment groups in the double-blind period (week 12 vs week -2 for evinacumab in comparison to week 12 vs week -2 for placebo). In order to yield corresponding results, the MRI readout will be analyzed similarly as the FDG-PET endpoint. In addition, combining all evinacumab post/pre observations from the double-blind period (week 12 vs week -2) and the single-blind post/pre (week 24 vs week 12) for the patients who received placebo in the double-blind period, and post/pre (week 24 vs week -2 and week 24 vs week 12) for patients randomized to evinacumab during the double-blind period.

Summary statistics may be computed for time points beyond week 12 for the TG and continuous and exploratory endpoints in the patients randomized to evinacumab.

Summary statistics will be computed for the End of Day symptom diary and the symptom and dietary impact measure. These measures will also be psychometrically analyzed; this will be outlined in a separate psychometric analysis plan.

10.4.4. Analysis of Symptoms

The signs and symptoms questionnaire along with the symptom/dietary impact questionnaire will be analyzed using total aggregate scores.

10.4.5. Safety Analysis

10.4.5.1. Adverse Events

Definitions

For safety variables, 3 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug
- The treatment period is defined as the day from first dose of randomized study drug to end of the study

- The double-blind treatment period is defined as the day from first dose of study drug in the double-blind treatment period to the day prior to the administration of single-blind evinacumab

Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the on-treatment period.

Analysis

All AEs reported in this study will be coded using the currently available version of MedDRA. Coding will be to lowest level terms. The verbatim text, the preferred term (PT), and the primary system organ class (SOC) will be listed.

Summaries of all TEAEs will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 9.5.1), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT

All deaths, SAEs and TEAEs overall and events leading to permanent treatment discontinuation will be listed will be listed.

10.4.5.2. Other Safety

Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Laboratory Tests

Laboratory test results by baseline, change from baseline to each scheduled assessment time, and number and percentage of patients with a potentially clinically significant value (PCSV) at any time point will be summarized with descriptive statistics

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

Listings will be provided with flags indicating the out of laboratory range values.

10.4.5.3. Treatment Exposure

The duration of exposure during the study will be presented and calculated as:

(Date of last evinacumab injection - date of first evinacumab injection) + 24 weeks (length of follow-up period)

The number (%) of patients enrolled and exposed to evinacumab will be presented by specific time periods. The time periods of interest will be specified in the SAP.

In addition, duration of exposure during the study will be summarized using number of patients, means, SD, minimums, medians, and maximums. A summary of the number of doses will be provided.

10.4.5.4. Treatment Compliance

Treatment compliance will be assessed via the summary of treatment exposure as described in Section 10.4.5.3.

10.4.6. Analysis of Drug Concentration Data

Summary of total evinacumab concentrations and total ANGPTL3 concentrations will be presented by nominal time point. Plots of individual concentration will be presented by actual time (linear and log scales). Plots of mean or median concentrations will be presented by nominal time (linear and log scales).

10.4.7. Analysis of Anti-Drug Antibody Data

Listings of ADA positivity and titers presented by patient, time point, and dose group will be provided. Prevalence of treatment-emergent and treatment-boosted ADA response will be assessed as absolute occurrence (N) and percent of patients (%), grouped by study cohorts.

The influence of ADAs on drug concentrations will be evaluated. Assessment of impact of ADA on safety and efficacy may be provided.

10.4.8. Analysis of Biomarker Data

All exploratory biomarker data analyses will be performed on the FAS and no multiplicity adjustment is planned. Detailed analyses of exploratory biomarker endpoints will be provided in the SAP.

10.4.9. Timing of Statistical Analysis

The analyses will be conducted in 2 steps.

10.4.9.1. First Step: Main Efficacy and Safety Analysis

The first analysis will be conducted when all enrolled patients have completed the double-blind period. This will consist of the final analysis of the primary and secondary endpoints up to week 12. The safety analysis will be performed on all safety data collected and validated at the time of the first analysis.

10.4.9.2. Second Step: Final Efficacy and Safety Analysis

The second analysis will be conducted at the end of the study and will consist of the final analysis of week 44 efficacy endpoints and final safety analysis.

10.5. Interim Analysis

Interim analyses may be conducted during the course of the study by the unblinded team to assess efficacy, safety, and futility. If the timing of this analysis falls within a few weeks of the first-step analysis, only the first-step analysis will be performed. Enrollment (up to a maximum of approximately 50 patients) may be halted if the incidence of pancreatitis is much lower than anticipated, making the evaluation of a treatment effect on pancreatitis futile. Details of the interim analysis will be described in the SAP.

10.6. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

Definition of baseline:

- The baseline assessment will be the latest, valid pre-dose assessment available.

General rules for handling missing data:

- If the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the intake of study medication, except if an incomplete date (eg, month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the intake of study medication date, then the start date by the study medication intake date will be imputed; otherwise, the missing day or month by the first day or the first month will be imputed.
- No imputations for missing laboratory data, ECG data, vital signs data, or physical examination data will be made

Visit windows:

- Assessments taken outside of protocol allowable windows will be displayed according to the case report form (CRF) assessment recorded by the investigator

Unscheduled assessments:

- Extra assessments (laboratory data or vital signs associated with nonprotocol clinical visits or obtained in the course of investigating or managing AEs) will be included in listings, but not summaries. If more than 1 laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings

10.7. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 16.1.

11. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

11.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation, cleaning, correcting, releasing) will be maintained and stored at Regeneron.

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical history/surgical history) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected using an electronic data capture (EDC) tool, Medidata Rave.

11.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IVRS/IWRS system – randomization, study drug supply
- EDC system – data capture
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database

12. STUDY MONITORING

12.1. Monitoring of Study Sites

The study monitor and/or designee (eg, contract research organization) will visit each site prior to enrollment of the first patient, and periodically during the study.

12.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents).

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

12.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic CRFs within the EDC system by trained site personnel. All required CRFs must be completed for each patient enrolled in the study. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each patient CRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

13. AUDITS AND INSPECTIONS

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately

- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the International Council for Harmonisation (ICH) guidelines for GCP and applicable regulatory requirements.

14.2. Informed Consent

The principles of informed consent are described in ICH guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC -approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF
- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the patient’s study record and a copy must be given to the patient.

14.3. Patient Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by a patient identification number, only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The patient's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

14.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

15. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC -approved amendment. Where required under local regulations, regulatory approval will also be sought.

16. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

16.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

16.2. Close-out of a Site

The sponsor and the investigator have the right to close out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of patients required for the study are enrolled earlier than expected

In all cases, the appropriate IRB/EC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

17. STUDY DOCUMENTATION

17.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the eCRF must be signed electronically by the investigator. This signed declaration accompanies each set of patient final eCRF that will be provided to the sponsor.

17.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The investigator must consult with the sponsor before discarding or destroying any essential study documents following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor and the relevant records will be transferred to a mutually agreed-upon destination.

18. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

19. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

20. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

21. REFERENCES

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22. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Phase 2, Randomized, Placebo-Controlled Study of Safety and Efficacy Following Repeat-Dose Administration of Evinacumab (anti-ANGPTL3) in Patients with Severe Hypertriglyceridemia (sHTG) at Risk for Acute Pancreatitis, and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

APPENDIX 1. KNOWN LPL AND APOC2 NULL (TOTAL LOSS OF FUNCTION) MUTATIONS

This list of LPL and APOC2 mutations is not comprehensive and is for reference only. Inclusion in the study is not limited to mutations in this list.

	LPL	Variant	HGVS Nomenclature	Nucleotide Change	State	Reference
1	1	Met-27Ile	M1I	3G>C	Homozygous	Yu XH 2006
2	1	Trp-14Ter	W14X	42G>A	Homozygous	Nakamura T 1996
3	1	pQ-12E>11X	46_47del2		Compound Heterozygous	Wang J 2007
4	Intron	IVS1+1G>C			Homozygous	Chimienti G 1992
5	Intron	89-4_89-2del3			Compound Heterozygous	Hölzl B 2000
6	2	133_143del11			Compound Heterozygous	Reina M 1992
7	2	Cys27Ter	C54X	162C>A	Compound Heterozygous	Chan AO 2006
8	2	183dup1			Homozygous	Benlian P AJHG 1996
9	2	Asn43Ser	N70S	209A>G	Homozygous	Kobayashi J 1994
10	Intron	IVS2+1G>A			Homozygous	Gotoda T 1991
11	Intron	IVS2-1G>A			Compound Heterozygous	Hata A 1990
12	3	Tyr61Ter	Y88X	264T>A	Homozygous	Gotoda T 1991
13	3	Trp64Ter	W91X	272G>A	Compound Heterozygous	Sprecher DL 1992
14	3	287_288del2			Compound Heterozygous	Foubert L 1998
15	3	290_293del4ins2			Compound Heterozygous	Benlian P 1996
16	3	Tyr73Ter	Y100X	300A>C	Compound Heterozygous	Wilson DE 1993
17	3	Arg75Ser	R102S	306A>C	Compound Heterozygous	Wilson DE 1993
18	3	Trp86Arg	W113R	337T>C	Compound Heterozygous	Ishimura-Oka K 1992
19	3	384del1ins6			Homozygous	Henderson HE 1990

	LPL	Variant	HGVS Nomenclature	Nucleotide Change	State	Reference
20	3	Gly105Arg	G132R	394G>A	Compound Heterozygous	Ikeda Y 2000
21	3	Gln106Ter	Q133X	397c>t	Homozygous	Emi M AJHG 1990
22	4	440_443del4			Compound Heterozygous	Ma Y 1993
24	4	Gly139Ser	G166S	496G>A	Homozygous	Bijvoet S 1994
25	4	Gly142Glu	G169E	506G>A	Homozygous	Ameis D 1991
26	4	Gly154Ser	G181S	541G>A	Homozygous	Bruin T JLR 1993
27	5	Gly154Val	G181V	542G>T	Compound Heterozygous	Ikeda Y 2001
28	5	Asp156Asn	D183N	547G>A	Compound Heterozygous	Ma Y 1992
29	5	Asp156Gly	D183G	548A>G	Homozygous and Compound Heterozygous	Ma Y 1992, Faustinella F 1991
30	5	Pro157Arg	P184R	551C>G	Homozygous	Bruin T 1992
31	5	Ala158Thr	A185T	553G>A	Homozygous	Mailly F 1997
32	5	Ala176Thr	A203T	607G>A	Homozygous	Beg OU 1990
33	5	Asp180Glu	D207E	621C>G	Homozygous	Haubenwallner S 1993
34	5	His183Asp	H210D	628C>G	Compound Heterozygous	Hölzl B 2000
35	5	Gly188Arg	G215R	643G>A	Homozygous	Benlian P 1996
36	5	Gly188Glu	G215E	644G>A	Homozygous	Emi M JBC 1990, Monsalve MV 1990
37	5	Arg192Ter	R219X	655C>T	Homozygous	Zhang Q 1997
38	5	Ser193Arg	S220R	658A>C	Compound Heterozygous	Mailly F 1997
39	5	Ile194Thr	I221T	662T>C	Homozygous	Henderson HE 1991
40	5	Gly195Glu	G222E	665G>A	Homozygous	Hata A 1992
41	5	Asp204Glu	D231E	693C>G	Homozygous	Gotoda T 1991
42	5	Ile205Ser	I232S	695T>G	Homozygous	Reina M 1992
43	5	Pro207Leu	P234L	701C>T	Homozygous and Compound Heterozygous	Ma Y 1991, Yang Y 2007
44	5	Cys216Ser	C243S	727T>A	Compound Heterozygous	Ma Y 1992

	LPL	Variant	HGVS Nomenclature	Nucleotide Change	State	Reference
45	5	742del1			Homozygous	Takagi A 1992
46	5	Ile225Thr	I252T	755T>C	Compound Heterozygous	Henderson HE 1993
47	6	Cys239Ter	C266X	798C>A	Homozygous	Takagi A 1994
48	6	Cys239Trp	C266W	798C>G	Homozygous	Hoffmann MM 2000
49	6	Arg243His	R270H	809G>A	Homozygous and Compound Heterozygous	Gotoda T 1991, Dichek HL 1991
50	6	Ser244Thr	S271T	811T>A	Compound Heterozygous	Hata A 1990
51	6	Asp250Asn	D277N	829G>A	Homozygous	Ma Y 1992
52	6	835_836del2			Homozygous	Mailly F 1997
53	6	Ser251Cys	S278C	833C>G	Compound Heterozygous	Bijvoet SM 1996
54	6	Leu252Val	L279V	835C>G	Compound Heterozygous	Chan L 2000
55	6	Leu252Arg	L279R	836T>G	Compound Heterozygous	Chan L 2000, Ma Y 1994
56	6	Ser259Arg	S286R	858T>A	Homozygous	Foubert L 1997
57	6	Tyr262His	Y289H	865T>C	Homozygous	Rouis M 1996
58	6	Cys264Tyr	C291Y	872G>A	Homozygous	Murugasu CG 1998
59	6	Phe270Leu	F297L	891T>G	Homozygous	Takagi A 2000
60	6	Leu276Phe	L303F	909G>C	Homozygous	Saika Y 2003
61	6	Leu286Pro	L313P	938T>C	Compound Heterozygous	Benlian P 1996
62	6	Tyr288Ter	Y315X	945T>A	Homozygous	Causeret AS 2001
63	6	953del1			Compound Heterozygous	Kobayashi J 1999
64	6	Tyr302Ter	Y329X	987C>A	Homozygous	Bertolini S 2000
65	Intron	IVS6-3C>A			Homozygous and Compound Heterozygous	Hölzl B 1994
66	8	Trp382Ter	W409X	1227G>A	Homozygous	Gotoda T 1991
67	8	1227del1			Homozygous	Gotoda T 1991, Maruyama T 2004
68	8	1314_1315del2			Homozygous	Nierman MC 2006

	LPL	Variant	HGVS Nomenclature	Nucleotide Change	State	Reference
69	Intron	IVS8+2T>C			Compound Heterozygous	Ikeda Y 2001

LPL	Variant	HGVS Nomenclature	Nucleotide Change	State	Reference

APOC2	Exon	Variant/HGVS-Nomenclature	Nucleotide Change	Mutation Type	State	Reference
1	Prom	7.5 kb promoter + ex. 1 Deletion		Gross Deletion	Homozygous	Fu J 2013
2	Prom	-25 relative to transcription initiation site		Regulatory	Homozygous	
3	1	M1V	1A>G	Missense	Homozygous	
4	1	R4X	10C>T	Nonsense	Homozygous	
5	Intron	55+1G>C	55+1G>C	Splicing	Homozygous	
6	2	70delC		Small Deletion	Homozygous	
7	2	118delG		Small Deletion	Homozygous	
8	2	K41T	122A>C	Missense	Homozygous	
9	2	W48R	142T>C	Missense	Homozygous	
10	2	Y59X	177C>A	Nonsense	Homozygous	
11	2	E60K	178G>A	Missense	Homozygous	
12	3	Y85X	255C>A	Nonsense	Homozygous	
13	3	270delT		Small Deletion	Homozygous	
14	3	Q92X	274C>T	Nonsense	Homozygous	
15	3	274dupC		Small Insertion		
16	3	L94P	281T>C	Missense	Homozygous	

APPENDIX 2. FACTORS TO CONSIDER IN ASSESSING THE RELATIONSHIP OF ADVERSE EVENTS TO STUDY DRUG AND STUDY CONDUCT

Is there a reasonable possibility that the event may have been caused by the study drug or study conduct?

No:

- due to external causes such as environmental factors or other treatment(s) being administered
- due to the patient's disease state or clinical condition
- do not follow a reasonable temporal sequence following the time of administration of the dose of study
- do not reappear or worsen when dosing with study drug is resumed
- are not a suspected response to the study drug based upon preclinical data or prior clinical data

Yes:

- could not be explained by environmental factors or other treatment(s) being administered
- could not be explained by the patient's disease state or clinical condition
- follow a reasonable temporal sequence following the time of administration of the dose of study drug
- resolve or improve after discontinuation of study drug
- reappear or worsen when dosing with study drug is resumed
- are known or suspected to be a response to the study drug based upon preclinical data or prior clinical data

NOTE: This list is not exhaustive.

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Scientific/Medical Monitor, Regulatory Representative, Clinical Study Team Lead, and Biostatistician)

To the best of my knowledge, this protocol accurately describes the conduct of the study.

Study Title: A Phase 2, Randomized, Placebo-Controlled Study of Safety and Efficacy, Following Repeat-Dose Administration of Evinacumab (anti-ANGPTL3) in Patients with Severe Hypertriglyceridemia (sHTG) at Risk for Acute Pancreatitis

Protocol Number: R1500-HTG-1522

Protocol Version: R1500-HTG-1522 Amendment 5

See appended electronic signature page

Sponsor's Responsible Scientific/Medical Monitor

See appended electronic signature page

Sponsor's Responsible Regulatory Representative

See appended electronic signature page

Sponsor's Responsible Clinical Study Team Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00089259 v1.0

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