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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Evinacumab in Patients with Severe Hypertriglyceridemia for the Prevention of Recurrent Acute Pancreatitis

Compound:	REGN1500 (evinacumab)
Clinical Phase:	2b
Protocol Number:	R1500-HTG-20118
Protocol Version:	R1500-HTG-20118 Amendment 2
Amendment 2 Date of Issue:	*See appended electronic signature page*
Amendment 1 Date of Issue:	21 Apr 2021
Original Date of Issue:	22 March 2021
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AMENDMENT HISTORY

Amendment 2

Overall rationale for Amendment 2

The purpose of this protocol amendment is to implement revisions to protocol inclusion criteria to enhance enrollment.

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

Description of Change	Brief Rationale	**Section # and Name**
Revised the definition of the study population	Broadened the inclusion criteria for the trial. In addition to enrolling patients with TG value >880 mg/dL at the screening visit, also allowing patients with a TG value at screening >500 mg/dL if they have a prior fasting measurement >1000 mg/dL or if they have had 2 or more episodes of pancreatitis in the past 24 months.	Clinical Study Synopsis, Target Population, Statistical Plan Section 3.2.1 Rationale for Study Design Section 2.1 Primary Objective Section 6.1 Study Description and Duration Figure 1 Study Flow Diagram Section 7.2.1 Inclusion Criteria, #3
Broadened the entry criteria with regard to fasting TG values at study entry and consequently removed Visit 2 during the Screening Period; Extended the time period for patients having a documented history of HTG from 15 to 24 months of screening	See rationale above. Since requiring only a single TG screening value, eliminating visit 2 which had the purpose of checking a second screening value. This decreases the burden on participants and sites, while still enrolling patients who have demonstrated high fasting TG values.	Clinical Study Protocol Synopsis, Objectives, Study Design, Study Duration Section 2.1 Primary Objective Section 3.1 Hypotheses Section 3.2.1 Rationale for Study Design Section 6.1 Study Description and Duration Section 7.2.1 Inclusion Criteria, Criterion #2 Table 1 Schedule of Events for DBTP Section 11.4.3.1 Primary Efficacy Analysis
Broadened the entry criteria with regard to BMI at study entry	Feedback from investigators and experts in this area have stated that a BMI range of 18-40 is too restrictive. Therefore the upper limit was increased to 45.	Section 7.2.1 Inclusion Criteria, Criterion #5
Added exclusion criterion for patients with a history of hypersensitivity to study drug or excipients, and for patients having received COVID-19 vaccination within 1 week of start of study medication.	The exclusion for hypersensitivity was an omission in the last version of the protocol that is now being updated. The exclusion for COVID-19 was added as the study drug has not been tested together with vaccines for COVID-19.	Section 7.2.2 Exclusion Criteria, new criteria #20, and #21 Section 8.9.1 Prohibited Medications

Reduced the off-drug follow-up period from 48 weeks to 20 weeks and the total study duration from 100 weeks to 72 weeks	Feedback from investigators, experts, and potential patients has been that a 48-week off-drug follow-up period is excessive and discourages participation. Other studies have demonstrated that evinacumab serum concentrations are minimal (ie, <1 ug/mL and <1% of C_{max}) by 24 weeks after the last drug administration	Clinical Study Protocol Synopsis, Study Design, Study Duration Section 3.2.1 Rationale for Study Design Section 6.1 Study Description and Duration Figure 1 Study Flow Diagram Section 8.3.2 Study Drug Discontinuation Table 1 Schedule of Events for the DBTP Table 2 Schedule of Events for the Off-Drug Follow-up Period
Revised definition of study follow-up period	Patient disposition summaries were adjusted to align with the 20-week follow-up period. Simplified the definition of screened patients. Simplified the descriptions of TEAE summaries that will be provided.	Section 11.4.1 Patient Disposition Section 11.4.5.1 Adverse Events
Distinguished separate timepoints for collection of lipids and special lipids	This was an oversight in the last version of the protocol. Special Lipids (ApoC3, ApoB48, ApoB100, and ApoB Total) collections were reduced as was the original intention.	Table 1 Schedule of Events for the DBTP Table 2 Schedule of Events for the Off-Drug Follow-up Period Section 9.1.1.1 Footnotes for Table 1 Schedule of Events (DBTP), #6 Section 9.1.1.2 Footnotes for Table 2 Schedule of Events (Off Drug Follow-up Period), #1 Section 9.2.2.2 Fasting Blood Samples for Assessment of Lipid Profile (For Efficacy and PD Variables)
Specified that immunogenicity sample collection should occur prior to infusion	This corrects an error in the prior version. Immunogenicity only needs to be sampled prior to infusion.	Section 9.1.1.2 Footnotes for Table 2 Schedule of Events (Off Drug Follow-up Period), #6
Removed eligibility criteria redundant text	To minimize repetition of identical text to avoid discrepancies and enhance readability	Clinical Study Protocol Synopsis, Study Design
Added APOE genotypes to the list of genes encoding proteins in the LPL pathway	APOE genotypes will be explored when patients are sequenced to assess their response to evinacumab	Section 1 Introduction
Revised screening language to allow the potential for patients who failed screening to be rescreened following a discussion with the medical monitor	To enhance enrollment	Section 6.1 Study Description and Duration
Editorial change related to genotypic or other biomarker differences	Revised for clarity	Section 2.3 Exploratory Objectives

Amendment 1

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

Description of Change	Brief Rationale	Section # and Name
The schedule of events were updated to add "weight" at each dosing visit and during in-person visits in the off-drug follow up period. Correspondingly, weight was added as an assessment in the Safety Procedures section.	Body weight measurement is needed for treatment dosing which is weight-based, and for safety assessment. Weight was inadvertently omitted in the original protocol.	Table 1. Schedule of Events for the DBTP Table 2. Schedule of Events for the Off-Drug Follow-Up Period Section 9.2.3.1 Vital Signs and Body Weight

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANGPTL3	Angiopoietin-like 3
APAC	Acute Pancreatitis Adjudication Committee
APO	Apolipoprotein
AP	Acute pancreatitis
AST	Aspartate aminotransferase
β-HCG	Human chorionic gonadotrophin
BMI	Body mass index
BUN	Blood urea nitrogen
CABG	Coronary artery bypass grafting
CI	Confidence interval
COA	Clinical outcome assessment
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CT	Computer tomography
DBTP	Double-blind treatment period
DNA	Deoxyribonucleic acid
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic data capture
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
FBR	Future biomedical research
FCS	Familial chylomicronemia syndrome
FH	Familial hypercholesterolemia
FSH	Follicle-stimulating hormone
FT4	Free thyroxine
GCP	Good Clinical Practice
HbA1c	Glycosylated hemoglobin
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HoFH	Homozygous familial hypercholesterolemia

HTG	Hypertriglyceridemia
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent ethics committee
IRB	Institutional review board
ITT	Intent to treat
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LLN	Lower limit of normal
LoF	Loss of function
LPL	Lipoprotein lipase
mAb	Monoclonal antibody
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
mITT	Modified ITT
MMRM	Mixed-effect model for repeated measures
MRI	Magnetic resonance imaging
NAb	Neutralizing antibodies
NMR	Nuclear magnetic resonance
NYHA	New York Heart Association
PCI	Percutaneous coronary intervention
PCR	Polymerase chain reaction
PK	Pharmacokinetic
PopPK	Population pharmacokinetics
PP	Posterior probability
PT	Preferred term
Q4W	Every 4 weeks
RBC	Red blood cell
RBQM	Risk-based quality monitoring
SAE	Serious adverse event
SAF	Safety analysis set

SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SDR	Source data review
SDV	Source data verification
SE	Standard error
sHTG	Severe hypertriglyceridemia
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TIA	Transient ischemic attack
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
VLDL	Very-low-density lipoproteins
WBC	White blood cell
WOCBP	Women of childbearing potential

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Evinacumab in Patients with Severe Hypertriglyceridemia for the Prevention of Recurrent Acute Pancreatitis
Site Locations **Principal Investigator**	Multiple centers in North America and the European Union (EU) A coordinating principal investigator will be identified prior to the start of the study
Objectives	The primary objective of the study is to determine the proportion of patients with elevated triglycerides (TG), without Familial Chylomicronemia Syndrome (FCS) due to loss of function (LoF) mutations in lipoprotein lipase (LPL), and a history of hypertriglyceridemia (HTG)-associated acute pancreatitis (AP) who experience a recurrent episode of AP after treatment with evinacumab versus placebo. The secondary objectives of the study are: • To determine the change in the standard lipid profile after therapy with evinacumab versus placebo • To determine the changes in specialty lipoprotein parameters (ApoC3, ApoB48, ApoB100, and nuclear magnetic resonance [NMR] lipid profile) after therapy with evinacumab versus placebo • To measure the number of AP episodes per patient • To assess the safety and tolerability of evinacumab • To assess the potential immunogenicity of evinacumab • To assess the concentrations of total evinacumab and total angiopoietin-like 3 (ANGPTL3)
Study Design	This is a phase 2b, multicenter, international, randomized, placebo-controlled study intended to demonstrate that evinacumab can prevent recurrent AP episodes in patients with severe hypertriglyceridemia (sHTG) and a recent history of HTG-associated AP. Approximately 120 adult patients will be randomized 1:1 to receive evinacumab or matching placebo. The study consists of 3 periods: a screening period, a double-blind treatment period (DBTP), and a safety follow-up period. The screening period of up to 28 days will determine participant eligibility and will include an evaluation of prior episodes of HTG-associated AP, genotyping to exclude patients with familial chylomicronemia syndrome (FCS) due to loss of

	function mutations in lipoprotein lipase (LPL), and a measurement of fasting TG levels. Patients who fulfill all the eligibility criteria will be randomized and receive their first dose of assigned study drug on day 1, with subsequent doses administered approximately every 4 weeks (Q4W) during the 52-week DBTP. This will be followed by a 20-week off-drug follow-up period. Efficacy will be assessed by measuring the number of patients with at least 1 independently adjudicated positive event of AP over 52 weeks of treatment with evinacumab versus placebo. The study will have an independent committee to adjudicate these episodes in accordance with clinical standards for diagnosis of AP. Efficacy will also be assessed by clinical laboratory evaluation of lipid levels at pre-specified time points throughout the study. Safety will be assessed throughout the study by comparing the frequency and severity of adverse events (AEs) between the evinacumab and placebo groups, as well as evaluating abnormal laboratory findings, electrocardiogram (ECG) findings, and anti-drug antibody (ADA) and neutralizing antibodies (NAb) assessments.
Study Duration	The duration of the treatment period for individual patients is 52 weeks, after which patients will continue in a 20-week follow-up period for a total study duration of 72 weeks, excluding the screening period.
End of Study Definition	The end of study is defined as the date the last patient completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the patient can no longer be contacted by the investigator).
Population	
Sample Size:	Approximately 120 patients
Target Population:	Adult patients 18 to 80 years of age without FCS due to LPL loss of function mutations with elevated baseline fasting TGs and AP criteria as follows: • Fasting serum TG values >880 mg/dL (10 mmol/L) determined during the screening period and a documented history of 1 HTG-associated AP episode within 24 months of screening, or • Fasting serum TG values >500 mg/dL (5.6 mmol/L) determined during the screening period in patients with a history of 2 or more HTG-associated AP episodes within 24 months of screening, or • Fasting serum TG values >500 mg/dL (5.6 mmol/L) determined during the screening period and a documented fasted TG values >1000 mg/dL (11.3 mmol/L) and a history of

	1 or more HTG-associated AP episodes(s) within 24 months of screening.
Treatment	
Study Drug	Evinacumab
Dose/Route/Schedule:	20 mg/kg administered intravenously (IV) over a 1-hour infusion Q4W, ±4 days
Placebo	Matching placebo
Route/Schedule:	Intravenous infusion Q4W (±4 days)
Endpoints	
Primary Efficacy:	The primary endpoint is for efficacy: the proportion of patients with at least 1 positively adjudicated AP episode during the 52 weeks of the DBTP.
Secondary Efficacy:	**Key Secondary Efficacy:** • Percent change in ApoC3 from baseline to week 52 • Percent change in fasting TGs from baseline to week 52 **Other Secondary Efficacy:** • Percent change in other fasting standard lipid profile parameters (total cholesterol [TC], non-high-density lipoprotein cholesterol [non-HDL-C]) from baseline to week 52 • Percent change in other fasting specialty lipoprotein parameters (ApoB48, ApoB100 levels, and NMR-determined particle size and number) from baseline to week 52 • Number of independently adjudicated episodes of AP per patient during 52 weeks of the DBTP
Safety Endpoints:	• Incidence and severity of treatment-emergent adverse event (TEAEs), serious adverse events (SAEs), laboratory abnormalities, and other safety variables in patients treated with evinacumab throughout the study • Incidence of treatment-emergent ADA and NAb
Other Endpoints:	• The percent change in fasting HDL-C and LDL-C from baseline to week 52 • Concentrations of total evinacumab and total ANGPTL3 over time
Procedures and Assessments	Efficacy will be assessed by measurement of adjudicated events of AP, and measurement of lipids, specialty lipids, and lipoproteins.

	Safety will be monitored via AE reporting, physical examinations, routine vital signs, clinical laboratory tests (blood chemistry and hematology), and standard 12-lead ECG. Serum samples for the determination of total evinacumab and total ANGPTL3 concentrations, and ADA and NAb will be collected. Serum and plasma samples will be collected for analysis of additional biomarkers.
Statistical Plan	The primary efficacy comparison will evaluate the evinacumab 20 mg/kg IV treatment group versus placebo, using the primary efficacy endpoint of the proportion of patients with at least 1 positively adjudicated AP event during the 52 weeks of DBTP (intent-to-treat [ITT] estimand-binary). The primary efficacy endpoint will be analyzed in the ITT population using the method of logistic regression, and the model will include at least treatment group, and number of historical AP episodes within the previous 24 months. The evinacumab group will be compared to the placebo group with odds ratio and 95% confidence interval (CI) provided for each treatment group. The statistical testing of the treatment group comparison for the primary measure will be evaluated at a 2-sided significance level of 0.049. For early termination (ET) patients who did not complete the week 52 efficacy assessment, the missing primary endpoint will follow a data imputation strategy. For the key secondary efficacy endpoints and other secondary efficacy endpoints collected in the DBTP, descriptive summaries and analyses will be performed in the ITT population, using values obtained regardless of adherence to study treatment and subsequent therapies (ITT estimands). Safety results will be summarized descriptively by the treatment group.

1. INTRODUCTION

Severely elevated levels of serum triglycerides (TGs) are associated with an increased risk for acute pancreatitis (AP). Episodes of AP secondary to severe hypertriglyceridemia (sHTG; TG >880 mg/dL [10 mmol/L]) frequently require hospitalization, and while most events can be treated with conservative therapy such as intravenous fluids and pain management, approximately 20% of patients suffer severe attacks associated with prolonged hospitalization and significant morbidity and mortality. Further, a prior episode of sHTG-associated AP markedly increases the risk for recurrent AP. While current lipid guidelines recommend lifestyle interventions and medications to lower TG levels to prevent AP (Berglund, 2012)((Jacobson, 2015), patients with sHTG often require robust (>50%) reductions in TG to lower the risk of AP. Indeed, a substantial proportion of patients have persistent hypertriglyceridemia (HTG), despite the use of multiple medications to lower TG levels. Current available therapies for lowering TG levels (eg, statins, fibrates, niacin, omega-3 fatty acids) typically provide 20% to 50% reductions in TG levels, which is often insufficient to lower TGs to a target level of <500 mg/dL (5.6 mmol/L) ((Brisson, 2010).

Patients with TGs >880 mg/dL (>10 mmol/L) typically have chylomicronemia that may be either multifactorial (polygenic and environmental) in origin, or much more rarely, due to the presence of highly penetrant gene mutations in lipoprotein lipase (LPL) ((Brown, 2012) (Minicocci, 2012) or genes encoding proteins in the LPL pathway (APOA5, APOC2, APOE, GPIHBP1, and LMF1), as observed in Familial Chylomicronemia Syndrome (FCS). 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 lead to varying levels of loss of LPL functional activity and elevated levels of plasma TGs, especially in 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 an unmet medical need for additional treatment options for patients with sHTG and a history of AP to further lower TG levels and the risk of recurrent attacks of AP, regardless of their genetic background.

Angiopoietin-like 3 (ANGPTL3) acts as a natural inhibitor of LPL and has emerged as a 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 and LDL-C (Minicocci, 2013).

Evinacumab (REGN1500) is a human IgG4 monoclonal antibody (mAb) specific for ANGPTL3. It is currently approved as an adjunctive treatment for homozygous familial hypercholesterolemia (HoFH, Evkeeza™) and is being evaluated for treatment of dyslipidemia including HTG. Evinacumab has been studied in approximately 580 individuals with elevations in LDL-C and TG and has been generally well tolerated up to single doses of 20 mg/kg intravenously (IV) and in multiple subcutaneous (SC) doses up to 450 mg administered weekly (QW), and 20 mg/kg IV administered every 4 weeks (Q4W) for approximately 8 weeks (ie 2 doses).

A phase 2, randomized, placebo-controlled study (R1500-HTG-1522) was conducted to evaluate the safety and TG-lowering effects of evinacumab in patients with various causes of sHTG, and at risk for AP, including homozygous/heterozygous loss of function (LoF) gene mutations in LPL, mutations in other genes in the LPL pathway, and other polygenic/environmental causes of

severely elevated TGs. The 12-week, double-blind treatment period (DBTP) enrolled 52 patients who were randomized to receive either evinacumab 15 mg/kg or matching placebo administered IV Q4W, followed by a 12-week, single-blind treatment period (SBTP) in which all patients (N=47) received evinacumab Q4W.

The primary endpoint was predefined as the mean within-patient change in TGs, and the study did not meet the threshold of a clinically important reduction (>40%). This applied to the overall study population and also for genotypic strata based on the presence of LPL pathway LoF mutations. Several factors may have contributed to a lack of efficacy. There was large variability in TGs, which was compounded by the absence of a diet-stabilization period and efficacy determined by a single post-treatment TG measurement. In addition, there was variability in drug exposure, where patients with the lowest trough levels of evinacumab had little to no treatment response. In this context, when examining median percent changes to minimize the impact of outliers, the evinacumab-treated patients overall showed a clinically important reduction (>40%) in fasting TGs at each post-baseline visit, culminating in a median reduction of approximately 57% at week 12 during the DBTP. The treatment effect was even more pronounced when excluding patients with FCS, where non-FCS patients had a median reduction in TGs of approximately 80%. When including patients that switched to evinacumab during the SBTP, the median percent reduction in TGs after 12 weeks of evinacumab exposure was approximately 70% for non-FCS patients.

In the DBTP, 5 patients (3 in the evinacumab group; 2 in the placebo group) experienced an episode of AP (all serious adverse events or SAEs); all resolved within 7 days. For the evinacumab-treated patients, 1 participant had FCS and did not have a TG response to therapy; 1 patient had an episode of AP within 48 hours after receiving his first dose of evinacumab; 1 patient had persistently low trough concentrations of evinacumab. Treatment-emergent adverse events (TEAEs) that occurred more frequently in the evinacumab group compared to the placebo group included Abdominal pain (14.3% versus 12.5%), Headache (11.4% versus 6.3%), and Constipation (8.6% versus 0). In the SBTP, 12 (25.5%) patients had SAEs of Acute pancreatitis; none was considered related to the study drug. The majority of episodes occurred during the off-drug period (>4 weeks after the last dose of evinacumab) and episodes of AP were not independently adjudicated, with some patients diagnosed with AP despite the absence of pathologic findings on pancreatic imaging and/or elevated lipase/amylase levels.

The current study is a phase 2b randomized, placebo-controlled study intended to demonstrate that evinacumab can prevent recurrent episodes of HTG-associated AP in patients with sHTG, but without FCS due to mutations in LPL. The secondary aims are to evaluate the effects of evinacumab on safety and changes in biomarkers of TG-rich lipoprotein metabolism, including serum TG, ApoC3, ApoB48, and ApoB100 in this patient population.

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

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to determine the proportion of patients with elevated TGs, without FCS due to LoF mutations in LPL, and a history of HTG-associated AP* who experience a recurrent episode of AP after treatment with evinacumab versus placebo.

*Includes adult patients with 1) elevated baseline fasting TGs >880 mg/dL and history of 1 HTG-associated AP within 24 months of screening or 2) elevated baseline fasting TG values >500 mg/dL in patients with a history of 2 or more HTG-associated AP within 24 months or 3) elevated baseline fasting TG values >500 mg/dL with a prior documented fasted TG values >1000 mg/dL and a history of 1 or more HTG-associated AP within 24 months. All participants are without FCS due to LPL loss of function mutations.

2.2. Secondary Objectives

The secondary objectives of the study are:

- To determine the change in the standard lipid profile after therapy with evinacumab versus placebo
- To determine the changes in specialty lipoprotein parameters (ApoC3, ApoB48, ApoB100, and nuclear magnetic resonance [NMR] lipid profile) after therapy with evinacumab versus placebo
- To measure the number of AP episodes per patient
- To assess the safety and tolerability of evinacumab
- To assess the potential immunogenicity of evinacumab
- To assess the concentrations of total evinacumab and total ANGPTL3

2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To evaluate responder categories of fasting TG levels
- To measure length of stay for patients hospitalized for AP
- To assess the effect of evinacumab versus placebo on the frequency and severity of abdominal pain
- To study evinacumab's mechanism of action in modulating lipoprotein metabolism in HTG, and related diseases
- To explore genotypic or other biomarker differences that may influence efficacy and safety of evinacumab for further understanding of HTG, or other conditions associated with ANGPTL3 antagonism (for patients who consent to participate in a genomics sub-study)

3. HYPOTHESIS AND RATIONALE

3.1. Hypotheses

Primary:

Evinacumab reduces recurrent episodes of AP in patients with sHTG but without FCS due to LoF mutations in LPL, and a history of HTG-associated AP.

Key Secondary:

In patients with sHTG and a history of HTG-associated AP, evinacumab reduces serum TGs and serum ApoC3.

3.2. Rationale

3.2.1. Rationale for Study Design

This is a phase 2b, multicenter, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of repeated doses of IV evinacumab for the treatment of patients with a recent history of HTG-associated AP with sHTG. The primary aim of the study is to evaluate the efficacy of evinacumab in reducing attacks of recurrent AP in patients with sHTG.

Markedly elevated blood levels of TGs are associated with the development of AP. Current therapies for lowering TG levels (eg, weight reduction, lifestyle changes, statins, fibrates, fish oils, niacin) have limited efficacy and none of these therapies have had appropriate studies to evaluate a role in reducing the risk of recurrent AP.

Studies have demonstrated that patients with genetic LoF mutations that decrease the activity of LPL have severe elevations in TGs. Given that ANGPTL3 acts as a natural inhibitor of LPL, blockade of ANGPTL3 and preventing LPL inhibition is a rational target for the treatment of elevated levels of TGs. This effect was clearly shown in study R1500-HTG-1522, a phase 2 study of evinacumab in patients with HTG. In that study, patients with TG levels ≥500 mg/dL and without LoF mutations in LPL experienced an approximately 80% median reduction in blood levels of TGs in the DBTP. The study was not designed to determine an impact on risk of recurrent AP.

An unmet need exists for additional, more effective methods of treating markedly elevated TG levels. Significant reductions in TGs may benefit patients with severe elevations in TGs at risk for pancreatitis. This is particularly true for secondary prevention of AP because these patients have a markedly higher risk of HTG-associated AP compared to the primary prevention population.

Patient Population

The study population consists of patients with severe HTG with a history of AP within 24 months of screening. Patients must fulfill 1 of the following TG and AP criteria: 1) elevated baseline fasting TG values >880 mg/dL and history of 1 HTG-associated AP within 24 months of screening or 2) elevated baseline fasting TG values >500 mg/dL in patients with a history of 2 or more HTG-associated AP within 24 months or 3) elevated baseline fasting TG values >500 mg/dL with a prior documented fasted TG value >1000 mg/dL and a history of 1 or more HTG-associated AP

within 24 months. All participants are without FCS due to LPL loss of function mutations. These patients have a very high unmet need for TG lowering. While there are medications such as statins, fibrates, niacin, and fish oils that can reduce TG, these treatments are often unable to achieve the large reductions (>50%) in TGs required to prevent hypertriglyceridemic AP for these patients. Based on real-world patient medical records of approximately 6.7 million patients, it is estimated that there are approximately 6,300 adult patients in the US that match the study population (data on file).

A similar patient population was studied in study R1500-HTG-1522, where patients were analyzed in 3 cohorts based on the presence of LoF mutations in genes in the LPL pathway, as determined by the Regeneron Genetics Center:

- Cohort 1: Homozygous or compound heterozygous mutations
- Cohort 2: Heterozygous mutations
- Cohort 3: No mutations in LPL pathway genes

During the DBTP, cohorts 2 and 3 both demonstrated an approximately 80% reduction in TG levels. Cohort 1 (ie, patients with FCS) did not show a clinically significant reduction in TG levels compared to placebo. For the current study, patients with FCS due to LoF mutations in *LPL* will be excluded. Study R1500-HTG-1522 was neither designed nor powered to draw a conclusion on the effect of evinacumab on the risk of recurrent AP, though there were numerically fewer AP events in patients while receiving evinacumab compared to the period when not receiving evinacumab.

Endpoints

The primary endpoint will be the first occurrence of an episode of AP. The study will have an independent committee to adjudicate these episodes guided by clinical standards for diagnosis of AP: acute onset of persistent, severe, epigastric pain; elevations in serum lipase or amylase significantly above the upper limit of normal (ULN); characteristic findings of AP on imaging (contrast-enhanced computed tomography [CT], magnetic resonance imaging [MRI], or transabdominal ultrasonography).

Study Duration

This study will have a 52-week DBTP consisting of therapy with evinacumab or placebo, followed by an off-drug follow-up period of 20 weeks duration.

Combination of Drugs

Patients will not be required to have any specific background lipid-lowering therapy. However, patients will be required to have a stable lipid-lowering treatment regimen prior to screening and will be required to maintain their TG-lowering background therapy throughout the study.

It is expected that the TG-lowering effect size and variance will be similar between cohorts 2 and 3 of study R1500-HTG-1522 and the current study. Additional biomarkers of TG-rich lipoprotein metabolism, such as levels of ApoC3, will also be measured and are expected to show clinically significant declines, similar to the R1500-HTG-1522 study.

3.2.2. Rationale for Dose Selection

An IV dose of 20 mg/kg was selected to test the efficacy and safety of evinacumab under Q4W administration in this study. In study R1500-HTG-1522, a 15 mg/kg IV Q4W regimen achieved mean steady-state concentrations of 162 mg/L in patients with severe sHTG at risk for AP. This was approximately 30% lower than steady-state concentrations under the same evinacumab dosing regimen in phase 2 and phase 3 studies of patients with familial hypercholesterolemia (FH), and suggested greater target-mediated clearance in the sHTG population versus the FH population.

Empirical analysis of concentration of total evinacumab in serum versus response in patients in study R1500-HTG-1522 (in cohorts where TG levels showed statistically significant reductions from baseline) suggested that patients with exposures in the highest quartiles of concentration of total evinacumab saw the greatest reductions from baseline in TG response, while those in the lowest concentration quartile saw comparatively smaller reductions, on average. This suggests that in patients with severely high baseline TG levels in the current study, a regimen that induces higher exposures would be expected to benefit more patients, thereby justifying the need for a larger dose than the one given in the previous study (15 mg/kg IV Q4W).

To simulate exposures in support of this goal, a population pharmacokinetics (PopPK) model for evinacumab was updated to describe the pharmacokinetics (PK) in the sHTG population. Simulations of a 20 mg/kg IV Q4W regimen using the updated PopPK model yielded mean steady-state trough concentrations of 264 mg/L after 6 administered doses, exceeding the mean concentration (250 mg/L) associated with maximal TG lowering in study R1500-HTG-1522. These anticipated trough concentrations are comparable to steady state trough concentrations achieved in prior phase 2 and 3 studies of evinacumab in HoFH; in all prior studies, evinacumab had an acceptable safety profile and was well tolerated at these concentrations.

3.3. Risk-Benefit

Recognizing that the "Coronavirus Disease 2019" (COVID-19) pandemic will have an impact on the conduct of clinical trials, the sponsor does not intend to screen any patients in this study until the impact of the COVID-19 pandemic is deemed manageable and no longer interfering with the conduct of trials at individual sites, and patients can safely participate in this study. Until then, the sponsor plans to obtain approvals from health authorities/Ethics Committees (ECs) to enable initiation of study sites for this study, as allowed by local laws and regulations.

3.3.1. Risks-Benefits for Evinacumab

Evinacumab has been evaluated in 6 completed clinical studies and 3 ongoing clinical studies and has been generally well tolerated. In placebo-controlled studies, infusion reactions have been reported more frequently in patients treated with evinacumab than in patients treated with placebo. In most cases, such reactions were nonserious and did not lead to interruption of the evinacumab infusion. A serious case of moderate Anaphylaxis in a patient treated with evinacumab 15 mg/kg IV Q4W, which led to discontinuation of evinacumab treatment, has been reported. As such, systemic hypersensitivity reactions, including anaphylaxis and infusion reactions, are considered an important identified risk associated with evinacumab administered IV.

Other potential risks with evinacumab (based on preclinical evaluation or risks associated with mAbs in general) include immunogenicity and embryofetal toxicity. Anti-drug antibody (ADA)

samples collected during evinacumab clinical studies are analyzed to determine any effects on efficacy or safety. To date, no subject or patient treated with evinacumab tested positive for ADA. Embryofetal toxicity is a potential risk with evinacumab based on animal studies, and therefore, pregnant or breastfeeding women should not be treated with evinacumab.

Elevated blood levels of TGs have been associated with the development of AP. Current therapies for lowering TGs (weight reduction, lifestyle changes, fibrates, omega-3 fatty acids) have limited efficacy and/or tolerability issues and have not been shown to reduce the risk of recurrent AP. Thus, a significant unmet need exists for additional and improved methods for treating elevated TG levels. A therapeutic targeted to ANGPTL3 and disinhibiting LPL could provide beneficial changes in TG-rich lipoprotein metabolism and would benefit patients with severe elevations in TGs who are at risk for recurrent pancreatitis.

A detailed risk-benefit statement with respect to the overall development program is provided in Section 7 of the Investigator's Brochure.

4. ENDPOINTS

4.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients with at least 1 positively adjudicated AP episode during the 52 weeks of the DBTP (intent-to-treat [ITT] estimand - binary).

The ITT estimand – binary used for the primary efficacy analysis is defined as the treatment policy strategy, specifically the occurrence of intercurrent events (ie adherence to study treatment and subsequent therapies) is irrelevant; the value for the primary efficacy endpoint is used regardless of whether or not intercurrent events occur (Section 11.4.3.1).

Note: AP is defined in Section 5.2.1.

4.2. Secondary Efficacy Endpoints

4.2.1. Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are:

- Percent change in ApoC3 from baseline to week 52 (ITT estimand - normal)
- Percent change in fasting TGs from baseline to week 52 (ITT estimand – non-normal)

The fasting TG and ApoC3 assessment at week 52 will be the respective measurement obtained within the week-52 analysis window. Scheduled and unscheduled measurements may be used to provide a value for the key secondary efficacy endpoints. The analysis window used to allocate a time point to a measurement will be defined in the statistical analysis plan (SAP). The baseline value is defined as the last available value before the first dose of double-blind study treatment.

The ITT estimand used for the key secondary efficacy analyses is the treatment policy strategy, specifically the occurrence of the intercurrent events (ie adherence to study treatment and subsequent therapies) is irrelevant; the value for the key secondary endpoints is used regardless of whether or not the intercurrent events occur (Section 11.4.3.2).

4.2.2. Other Secondary Efficacy Endpoints

Other secondary efficacy endpoints are:

- Percent change in other fasting standard lipid profile parameters (total cholesterol or TC, non-HDL-C) from baseline to week 52 (ITT estimand - normal)
- Percent change in other fasting specialty lipoprotein parameters (ApoB48, ApoB100 levels and NMR-determined particle size and number) from baseline to week 52 (ITT estimand - normal)
- Number of independently adjudicated episodes of AP per patient during 52 weeks of the DBTP (ITT estimand - normal)

4.3. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are:

- Proportion of patient responders during 52 weeks of therapy with evinacumab versus placebo, with response defined as reaching common clinical TG thresholds of ≤880 mg/dL, ≤500 mg/dL, ≤150 mg/dL
- Length of stay for AP hospitalizations during 52 weeks of therapy with evinacumab versus placebo
- Proportion of abdominal pain-free intervals during 52 weeks of therapy with evinacumab versus placebo, measured via a single-item questionnaire
- Mean change in abdominal pain scores on the Hypertriglyceridemia and Acute Pancreatitis: Pain Questionnaire (HAP-Pain) during 52 weeks of therapy with evinacumab versus placebo

4.4. Safety Endpoints

Other secondary endpoints include safety endpoints:

- Incidence and severity of TEAEs, SAEs, laboratory abnormalities, and other safety variables in patients treated with evinacumab throughout the study
- Incidence of treatment-emergent ADA and neutralizing antibodies (NAb)

4.5. Other Endpoints

- The percent change in fasting HDL-C and LDL-C from baseline to week 52
- Concentrations of total evinacumab and total ANGPTL3 over time

5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height, BMI, etc), disease characteristics, medical history including detailed cardiovascular and pancreatitis history, and medication history.

5.2. Efficacy Variables

5.2.1. Acute Pancreatitis Episodes

The primary efficacy variable is the occurrence of an episode of AP as determined by an independent acute pancreatitis adjudication committee (APAC). Suspected AP events will be reviewed by 2 independent physicians (phase 1). In the event of disagreement between these 2 initial reviewers, the case will be reviewed by at least 3 physicians meeting as a committee (phase 2). The final adjudicated result will be either the initial independently agreed-upon result from phase 1, or the majority decision from phase 2. Every effort will be made to maintain the same group of physician reviewers for adjudication.

Acute pancreatitis adjudication committee members will be blinded to TG values to avoid treatment unblinding.

The diagnosis of AP is based on meeting either clinical or imaging criteria, or both:

1) Clinical symptoms and signs
    a. Acute onset abdominal pain, or nausea or vomiting

       AND

    b. Biochemical evidence of pancreatic inflammation
        i. Serum amylase or lipase >3x ULN for individuals without a medical history of chronic pancreatitis; OR
        ii. Serum amylase or lipase >2x ULN for individuals with a medical history of chronic pancreatitis
2) Pancreatic inflammation assessed by imaging
    a. Characteristic findings of AP on imaging (contrast-enhanced CT, MRI, or transabdominal ultrasonography. These findings include but are not limited to: pancreatic enlargement, necrosis, edema, peripancreatic stranding, and peripancreatic fluid collections.

Additional details will be provided in the APAC charter.

5.2.2. Laboratory Variables for the Assessment of Efficacy

Efficacy in this study includes the following lipid parameters:

- Fasting TG levels
- Non-HDL-C levels

- TC levels
- ApoC3, ApoB48, ApoB100, NMR-determined particle size and number (biomarkers of TG-rich lipoprotein metabolism)

These laboratory variables are relevant to the characterization and disease mechanisms of patients with HTG.

5.2.3. Clinical Outcome Assessments

The following clinical outcome assessment (COA) will be completed by the patient:

- A single-item assessment on presence of abdominal pain
- The HAP-Pain Questionnaire

5.3. Safety Variables

The safety variables in this study include:

- TEAEs
- Vital signs
- Physical examination
- Electrocardiogram (ECG)
- Routine safety laboratory tests (hematology, chemistry, urinalysis, and pregnancy testing [for women of childbearing potential or WOCBP])
- Concomitant medications and treatments

5.4. Pharmacokinetic Variables

The pharmacokinetic variables consist of the concentrations of total evinacumab and total ANGPTL3 in serum at each time point (both pre-dose and end-of-infusion samples). These sampling time points are specified in Table 1.

5.5. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, NAb status, and time point/visit. Samples in this study will be collected at the clinic visits specified in Table 1 and Table 2.

5.6. Pharmacodynamic and Other Biomarker Variables

The pharmacodynamic (PD) variables in this study are high-density lipoprotein cholesterol (HDL-C) and LDL-C.

ApoC3, ApoB48, ApoB100, and NMR-determined particle size and number are biomarkers of TG-rich lipoprotein metabolism and are also efficacy variables in this study.

6. STUDY DESIGN

6.1. Study Description and Duration

This is a phase 2b, multicenter, international, randomized, placebo-controlled study intended to demonstrate that evinacumab can prevent recurrent AP in patients with HTG and a recent history of HTG-associated AP.

Approximately 120 adult patients will be randomized 1:1 to receive evinacumab or matching placebo. A study schematic is provided in Figure 1.

The study consists of 3 periods: a screening period, a DBTP, and a safety follow-up period. The screening period of up to 28 days will determine participant eligibility and will include an evaluation of prior episodes of HTG-associated AP, genotyping to exclude patients with FCS due to LoF mutations in LPL, and a measurement of fasting TG level. Patients must have baseline fasting TGs >880 mg/dL and a history of HTG-associated AP within 24 months of screening or they must have baseline fasting TGs >500 mg/dL if they have had 2 or more episodes of HTG-associated AP within 24 months of screening or if they have had baseline fasting TG values >500 mg/dL and documented fasting TG values >1000 mg/dL with a history of HTG-associated AP within 24 months of screening to be enrolled in the study.

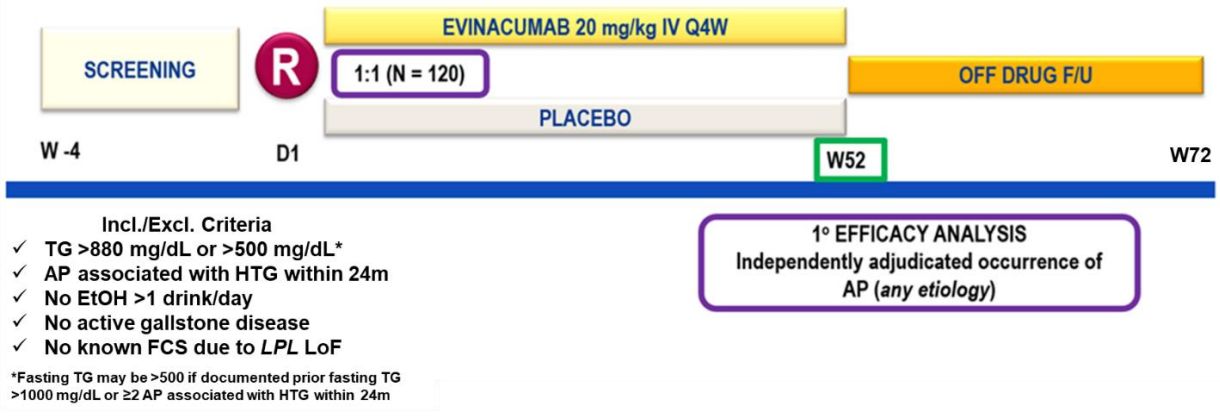
Patients who fulfill all the eligibility criteria will be randomized and receive their first dose of assigned study drug on day 1, with subsequent doses administered approximately Q4W during the 52-week DBTP. This will be followed by an off-drug follow-up period of 20 weeks.

Every effort will be made to keep patients in the study and to collect the week 52 visit data, even if study drug administration has been discontinued for the patient.

Efficacy will be assessed by measuring the number of patients with at least 1 independently adjudicated positive event of AP over 52 weeks of treatment with evinacumab versus placebo. The study will have an independent committee to adjudicate these episodes in accordance with clinical standards for diagnosis of AP (see Section 5.2.1). Efficacy will also be assessed by clinical laboratory evaluation of lipid levels at pre-specified time points throughout the study.

Safety will be assessed throughout the study by comparing the frequency and severity of adverse events (AEs) between the evinacumab and placebo groups, as well as evaluating abnormal laboratory findings, ECG findings, and ADA and NAb assessments.

Figure 1: Study Flow Diagram



Screening (Day -28 to -1)

The screening period may last up to 28 days and consists of 1 visit. 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. The fasting TG measurement can be repeated once for values >500 mg/dL but <880 mg/dL.

A mandatory sample for DNA isolation will be obtained for patients who do not have documentation of prior genetic testing in order to confirm the absence of FCS due to homozygous or compound heterozygous LoF mutations in *LPL*. For these patients, the results of the screening FCS genotyping confirming no homozygous or compound heterozygous LoF mutations in *LPL* must be available before the patient can be enrolled in the study.

Patients who have screen-failed are not eligible for rescreening, unless rescreening is discussed and agreed with the medical monitor.

After confirmation of eligibility, patients will proceed to visit 2 for randomization.

Double-Blind Treatment Period (Day 1 to Day 365)

Principal investigators, study site personnel, study patients, and the Regeneron study team will all be blinded to treatment during the DBTP.

Randomized patients will receive either evinacumab administered IV at a dose of 20 mg/kg IV or matching placebo Q4W (±4 days) during the DBTP. On dosing days, all assessments and lab samples (including urine or serum pregnancy tests for WOCBP) should be performed before the dose of study drug is administered. All samples should be collected following at least an 8-hour fast. Medications are permitted to be taken with water as medically indicated. Electrocardiograms should be performed before blood is drawn. Additionally, vital signs should be measured, and AEs monitored pre-dose, at the end of study drug infusion, and at 30 minutes and 60 minutes post-end of infusion. Patients will be closely monitored for a minimum of 60 minutes after IV administration of evinacumab or matching placebo.

Efficacy and safety procedures, including a standard lipid panel, dietary and alcohol use review, and the completion of a pain questionnaire will be performed as outlined in the Schedule of Events (Table 1).

Serum samples for the determination of total evinacumab and total ANGPTL3 should be collected prior to AND at the end of infusion of study drug (within 30 minutes from the end of infusion).

Serum and plasma samples will be collected for analysis of additional biomarkers, including specialty lipid measurements, and will also be collected for measurement of ADA and NAb.

Off-Drug Treatment Follow-up Period (Day 366 to Day 700 [End of Study])

Patients will be monitored for 20 weeks after the last dose of study drug with 2 in-clinic visits. Efficacy and safety procedures will be performed as outlined in the Schedule of Events.

Throughout the Study

Patients will adhere to their diet, and submit to a dietary review and an alcohol intake review at each visit. Patients will be reminded to maintain a stable diet and refrain from drinking more than 1 serving per day of an alcoholic beverage.

Patients will also 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 will be monitored throughout the study and for 20 weeks post the last dose of study drug.

COVID-19

Recognizing that the "Coronavirus Disease 2019" (COVID-19) pandemic will have an impact on the conduct of clinical trials, the sponsor does not intend to screen any patients in this study until the impact of the COVID-19 pandemic is deemed manageable and no longer interfering with the conduct of trials at individual sites, and patients can safely participate in this study. Until then, the sponsor plans to obtain approvals from health authorities/ECs to enable initiation of study sites for this study, as allowed by local laws and regulations.

In light of the public health emergency related to COVID-19, the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 will be granted. All temporary mechanisms utilized, and deviations from planned study procedures, are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

6.1.1. End of Study Definition

The end of study is defined as the date the last study participant completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the participant can no longer be contacted by the investigator).

6.2. Planned Interim Analysis

An interim analysis is planned when approximately 50% (N=60) of patients have completed the DBTP. This will consist of the final data contributing to the analysis of the applicable variables up to the week-52 visit for these patients. The efficacy analyses will be performed up to the week-52 visit for these patients and will be descriptive in nature. The safety analysis will be performed for these patients on all safety data collected and validated at the time of the interim analysis. A small alpha adjustment of 0.001 has been made to account for this treatment-unblinded interim, since the sponsor does not plan to stop the study early for evinacumab treatment benefit. Therefore, the significance level for the final efficacy analysis will be 0.049.

The purpose of this interim analysis is administrative, specifically to aid in planning of future studies. The interim statistical analysis will be performed external to Regeneron with the intent to reduce data bias in the patients ongoing in the DBTP at the time of the interim. Interim analysis summary results will be provided to Regeneron senior management only. The interim analysis process, the measures used to protect the blind and the integrity of the study, the communication plan, and the confidentiality agreement will be described in a separate document.

A description of the statistical methods to be employed is in Section 11.5.1, and blinding implications are discussed in Section 8.6.

6.3. Study Committees

The Independent Data Monitoring Committee (IDMC) for the evinacumab program will be utilized. In addition, a separate independent committee (APAC) consisting of clinical specialists will be formed for adjudicating cases of AP to ensure a clinically accepted and consistent diagnosis for this primary endpoint. Every effort will be made to maintain the same group of physician reviewers for adjudication.

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Planned

Approximately 120 patients (randomized 1:1, evinacumab: placebo).

7.2. Study Population

7.2.1. Inclusion Criteria

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

1. Adults 18 to 80 years of age without FCS due to LPL loss of function mutations
2. Documented history of 1 HTG-associated AP episode within 24 months of screening (can be determined by study investigator; does not need to be confirmed by independent adjudication committee) and.
3. Fasting serum TG value >880 mg/dL (10 mmol/L) determined during the screening period. Triglyceride measurement can be repeated once for values >500 mg/dL (5.6 mmol/L) but <880 mg/dL (10 mmol/L)

   OR

   Fasting serum TG value >500 mg/dL (5.6 mmol/L) determined during the screening period in patients with a history of 2 or more HTG-associated AP episodes within 24 months of screening

   OR

   Fasting serum TG value >500 mg/dL (5.6 mmol/L) determined during the screening period and a documented fasted serum TG value >1000 mg/dL (11.3 mmol/L) and a history of 1 or more HTG-associated AP episode(s) within 24 months of screening.
4. Stable dose of lipid-lowering therapy (≥8 weeks) and willingness to maintain a stable regimen throughout the study
5. Body mass index ≥18.0 and ≤45.0 kg/m^2
6. Compliance with a stable diet and exercise regimen at screening and willingness to continue the diet through the end of the study
7. Willing and able to comply with clinic visits and study-related procedures
8. Provide informed consent signed by study patient or legally acceptable representative
9. Able to understand and complete study-related questionnaires

7.2.2. Exclusion Criteria

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

1. Hospitalization for AP within 4 weeks of screening

2. Known genetic FCS defined as homozygous or compound heterozygous LoF mutations in LPL, as documented by prior genotype result or determined from FCS genotyping at screening (see Section 9.2.7).
3. Symptomatic gallstone disease within 6 months prior to screening. Incidental and/or asymptomatic gallstones are permitted. Patients with symptomatic gallstone disease in the past 6 months who have undergone cholecystectomy >3 months prior to screening are permitted.
4. Use of any medication or nutraceutical known to alter serum lipids which has not been part of a stable therapeutic regimen for at least 8 weeks, and there are no plans to change the regimen during the study
5. Presence of any clinically significant, uncontrolled endocrine disease known to influence serum lipids, including but not limited to:
    a. Newly diagnosed (within 3 months) diabetes by medical history, including screening value glycosylated hemoglobin (HbA1c) >6.5% without a prior history of diabetes
    b. Diabetes with HbA1c >10.0%
    c. Thyroid disease with thyroid-stimulating hormone (TSH) <lower limit of normal (LLN) or >1.5x ULN
    d. Thyroid replacement therapy that has not been stable for at least 12 weeks

    Note: For laboratory values, 1 repeat measurement is allowed. Other laboratory values that meet the inclusion/exclusion criteria do not need to be repeated.
6. Use of estrogen or testosterone therapy unless the regimen has been stable in the past 6 weeks and there are no plans to change the regimen during the study
7. Any clinically significant abnormality identified at the time of screening that, in the judgment of the investigator or any sub-investigator, would preclude safe completion of the study or constrain endpoints assessment; eg, major systemic diseases, patients with short life expectancy, or considered by the investigator or any sub-investigator as inappropriate for this study for any reason, including but not limited to:
    a. Deemed unable to meet specific protocol requirements, such as scheduled visits
    b. Deemed unable to tolerate injections, as per the patient or the investigator
    c. Part of a vulnerable population such as the institutionalized
    d. Presence of any other conditions (eg, geographic or social), either actual or anticipated, that the investigator feels would restrict or limit the patient's participation for the duration of the study
8. Laboratory findings (for the reason that patients with these findings, who have a higher likelihood of liver, muscle, or kidney adverse events regardless of treatment assignment, are expected to be rare, they may not be evenly distributed across treatment groups and thus may confound the analysis of safety):
    a. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 according to 4-variable Modification of Diet in Renal Disease study equation (MDRD, calculated by central laboratory)

Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3x ULN at screening
b. Creatine phosphokinase (CPK) >3x ULN at screening

Note: For all laboratory values, 1 repeat measurement is allowed.

9. Systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg at the screening visit or time of randomization (1 repeat allowed). The uneven distribution of these patients across treatment groups could confound the analysis of safety.
10. History of heart failure (New York Heart Association [NYHA] Class III-IV) within 12 months before screening. The uneven distribution of these patients across treatment groups could confound the analysis of safety.
11. Within 3 months of screening, a history of myocardial infarction (MI), unstable angina leading to hospitalization, coronary artery bypass grafting (CABG) surgery, percutaneous coronary interventions (PCI), uncontrolled cardiac arrhythmia, carotid surgery or stenting, stroke, transient ischemic attack (TIA), carotid revascularization, endovascular procedure, or surgical intervention for peripheral vascular disease. The uneven distribution of these patients across treatment groups could confound the analysis of safety.
12. Significant concomitant illness including, but not limited to: cardiac, renal, neurological, endocrinological, hepatic, metabolic, or lymphatic disease, that would adversely affect the patient's participation in the study
13. History of cancer within the past 5 years, except for adequately treated basal cell skin cancer, squamous cell skin cancer, or in situ cervical cancer
14. Participation in a clinical research study evaluating an investigational drug within 30 days or at least 5 half-lives of the investigational drug, before screening, whichever is longer
15. History or evidence of drug or alcohol abuse within 24 months before screening. Additionally, patients who do not agree to limit alcohol intake to no more than 1 drink per day will be excluded.
16. Documented* positive polymerase chain reaction (PCR) or equivalent test based on regional recommendations for COVID-19 or suspected SARS-CoV-2 infection, and:
    a. Has not recovered from COVID-19 (ie, all COVID-19-related symptoms and major clinical findings which can potentially affect the safety of the patient have not been resolved), and
    b. Did not have 2 negative results from nucleic acid amplification (PCR) test or equivalent test based on regional recommendations for COVID-19 (at least 48 hours apart) to confirm that the patient is negative for SARS-CoV-2 or, if COVID-19 PCR (or equivalent) testing is not feasible, at least 3 months have transpired since the initial diagnosis

    * **Note**: Screening for COVID-19 will not be performed as part of eligibility assessments for this study.
17. Members of the clinical site study team and/or his/her immediate family, unless prior approval granted by the sponsor.

18. Pregnant or breastfeeding women.
19. Women of childbearing potential* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 24 weeks after the last dose. Highly effective contraceptive measures include:
    a. Stable use of combined (estrogen- and progestogen-containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening;
    b. Intrauterine device (IUD); intrauterine hormone-releasing system (IUS);
    c. Bilateral tubal ligation;
    d. Vasectomized partner (provided that the male vasectomized partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has obtained medical assessment of surgical success for the procedure); and/or
    e. Sexual abstinence†, ‡

    *WOCBP are defined as women who are fertile following menarche until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

    A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a postmenopausal state. The above definitions are according to the Clinical Trial Facilitation Group (CTFG) guidance. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

    †Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drugs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

    ‡Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.
20. Patients with a history of serious hypersensitivity reactions to evinacumab or to any of the excipients.
21. Has received a COVID-19 vaccination (initial series or booster) within 1-week of planned start of study medication or for which the planned COVID-19 vaccinations would not be completed 1-week prior to start of the study.

7.3. 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.

Patients who are withdrawn prematurely from the study will be asked to complete the early termination visit, as described in Section 9.1.2.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 8.3.2.

7.4. Replacement of Patients

Patients prematurely discontinued from study drug will not be replaced.

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

Evinacumab or placebo will be supplied for IV administration. The 2 study treatment groups are:

- Evinacumab 20 mg/kg administered IV over a 1-hour infusion Q4W (±4 days)
- Matching placebo administered IV Q4W (±4 days)

Instructions on management of infusion reactions are provided in Section 8.4.

Instructions on dose preparation are provided in the pharmacy manual.

8.2. Background Treatment(s)

Prior to screening, all patients should be on a stable, lipid-lowering therapeutic regimen, which may include a statin, fibrate, niacin, or fish oils. Participants will be expected to continue their therapeutic regimen throughout the DBTP. There is no mandatory background therapy required for participation.

8.3. Dose Modification and Study Treatment Discontinuation Rules

8.3.1. Dose Modification

Dose modification for an individual patient is not allowed.

8.3.2. Study Drug Discontinuation

Patients who permanently discontinue from study drug should be encouraged to remain in the study. Those who agree and do not withdraw from the study will be asked to return to the clinic for all remaining study visits and assessments per the visit schedule, especially the week 52 visit, including the off-drug follow-up visits (Table 1 and Table 2).

Patients who permanently discontinue from study drug and who opt to withdraw from the study (ie, are unable or unwilling to attend the study visits as described above) will be asked to complete study assessments at an early termination (ET) visit, per Section 9.1.2. These patients will then enter the off-drug treatment follow-up period, and should be followed for at least 20 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 off-drug follow-up period will include 2 in-clinic visits with assessments as specified under visit 16 and visit 17 (Table 2).

8.3.2.1. Reasons for Permanent Discontinuation of Study Drug

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

- Evidence of pregnancy
- Severe, acute infusion reactions related to study treatment including, but not limited to, anaphylaxis
- Specific types of liver dysfunction (eg, Hy's law is met ([Guidance for Industry Drug Induced Liver Injury: Premarketing Clinical Evaluation FDA 2009])

Liver impairment as evidenced by 1 or more of the following criteria and no other reason can be found to explain the following lab abnormalities, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury:

- ALT or AST >8× ULN, or
- ALT or AST >5× ULN for more than 2 weeks, or
- ALT or AST >3× ULN and total bilirubin >2× ULN (or international normalized ratio [INR] >1.5)
- ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

- Patient withdraws consent

8.3.2.2. 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. Resumption of study drug dosing requires consultation and agreement between the investigator and the Regeneron medical monitor.

If a patient requires a prohibited medication at any time during the study, the principal investigator should contact the Regeneron medical monitor (except for illness requiring prompt treatment). Based on the discussions, study drug may be continued or temporarily or permanently discontinued.

8.4. Management of Acute Reactions

8.4.1. Acute Intravenous 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 10.2.4) and graded using the grading scales as instructed in Section 10.2.5.

8.4.1.1. Interruption of the Intravenous Infusion

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

- Sustained/severe 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, and the infusion may be restarted at 50% of the original rate.

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.

8.4.1.2. Termination of the Intravenous 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 termination of the IV infusion

*Consider anaphylaxis if the following is observed (Sampson, 2006): acute onset of an illness (minutes to several hours) with 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

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

8.5. Method of Treatment Assignment

Approximately 120 patients will be randomized in a 1:1 ratio to receive either evinacumab or placebo according to a central randomization scheme provided by an interactive voice response system (IVRS)/interactive web response system (IWRS) to the designated study pharmacist (or qualified designee).

8.6. Blinding

Study patients, the principal investigators, and study site personnel will remain blinded to all randomization assignments throughout the study. The Regeneron medical/study director, study

monitor, and any other Regeneron and contract research organization (CRO) personnel who are in regular contact with the study site will remain blinded to all patient randomization assignments.

Lipid results from blood samples collected after the randomization visit will not be communicated to the sites, and the sponsor's operational team will not have access to these laboratory results until after the final database is locked for this study.

One interim analysis is planned. The team performing the interim analysis will be external to Regeneron with the intent to reduce data bias in the patients ongoing at the time of the interim. No study personnel involved in the day-to-day conduct of the study will have access to any unblinded data before the final database is locked for this study.

8.7. 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) and when a treatment decision is contingent on knowing the patient's treatment assignment. Study drug will be discontinued for patients whose treatment has been unblinded (Section 8.3.2).

- If unblinding is required:
  - Only the investigator will make the decision to unblind the treatment assignment.
  - Only the affected patients will be unblinded.
  - The designated study pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator. If there is no study pharmacist, the investigator for the site will unblind/unmask the patient. Unblinding is performed using the IVRS/IWRS which will notify Regeneron.
  - The investigator will notify Regeneron and/or designee as soon as possible after unblinding the patient.

Treatment assignment is not to be provided to site personnel other than the unblinded study pharmacist (when applicable), at any time during the conduct of the study, except in the case of a true emergency and when a treatment decision is contingent on knowing the patient's treatment assignment. In the event that there is no study pharmacist, the individual at the site fulfilling that role will be the only unblinded member of the site personnel.

8.8. Treatment Logistics and Accountability

8.8.1. 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 2ºC to 8ºC; storage instructions will be provided in the pharmacy manual.

8.8.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2ºC to 8ºC 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 destroyed/returned to the sponsor or designee.

8.8.3. 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
- Disposed of at the site or 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.

8.8.4. 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.

8.9. Concomitant Medications

Any treatment administered from the time of informed consent 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. Vaccination for COVID-19 should also be considered a concomitant medication.

8.9.1. 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, with the following exceptions:
  - Used as replacement therapy for pituitary/adrenal disease with a stable regimen for at least 6 weeks prior to the screening visit
  - Used for ≤5 days during the treatment period for an acute illness as medically indicated

- Live or attenuated vaccination with replicating potential

8.9.2. Permitted Medications

The use of medications and nutritional supplements known to lower TG, including statins, fibrates, niacin, and omega-3s are permitted as long as therapy has been stable for at least 8 weeks prior to the screening visit. Patients must continue taking their background medical TG-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.

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

In light of the public health emergency related to COVID-19, the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 will be granted. All temporary mechanisms utilized, and deviations from planned study procedures in response to COVID-19, are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

Study assessments and procedures for the DBTP are presented by visit in Table 1, and in Table 2 for the off-drug follow-up period.

Table 1: Schedule of Events for the DBTP

	Screening Period	Double-Blind Treatment Period (DBTP)												
Visit # (V)	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**
Week		0	4	8	12	16	20	24	28	32	36	40	44	48
Day	-28	1	29	57	85	113	141	169	197	225	253	281	309	337
Window (day)			±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4
Study Procedure														
Screening/Baseline:														
Inclusion/Exclusion	X	X												
Informed Consent	X													
Medical History[1]	X													
Height, Weight, BMI[2]	X													
Demographics	X													
Amylase and Lipase		X												
FT4, TSH	X													
FSH (for women only)[3]	X													
Randomization		X												
Treatment:														
Administer Study Drug[4]		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Meds and Treatment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy:														
Lipid Profile[5,6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Special Lipids[6]		X						X						
Presence of Abdominal Pain (1-Item Question)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HAP-Pain Questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety:														
Weight		X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X												

	Screening Period	Double-Blind Treatment Period (DBTP)												
Visit # (V)	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**
Week		0	4	8	12	16	20	24	28	32	36	40	44	48
Day	-28	1	29	57	85	113	141	169	197	225	253	281	309	337
Window (day)			±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4
Study Procedure														
Electrocardiogram[8]	X	X												
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory:[5]														
Hematology	X	X												
Blood Chemistry	X	X	X	X		X		X		X		X		X
Pregnancy Test[9,10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics and Immunogenicity Sampling:														
Drug Conc. Sample[11]		X	X	X	X	X	X	X	X	X	X	X	X	X
ADA and NAb sample[12]		X				X				X				
Biomarkers:														
Biomarker Serum/Plasma[13]		X						X						
Lipoprotein Analysis by NMR		X												
Optional Pharmacogenomics:														
DNA Sample (Optional)[14]		X												
Other:														
Mandatory DNA Sample for FCS Genotyping for Subset of Patients[15]	X													
Dietary Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Alcohol Intake Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 2: Schedule of Events for the Off-Drug Follow-up Period

	End of DBTP	Off Drug Follow-Up	
Visit # (V)	**V15**	**V16**	**End of Study V17**
Week	52	62	72
Day	365	435	505
Window (day)	±4	±7	±7
Efficacy:			
Lipid Profile[1]	X	X	X
Special Lipids[1]	X		X
Presence of Abdominal Pain (1-Item Question)	X	X	X
HAP-Pain Questionnaire	X	X	X
Safety:			
Concomitant Meds and Treatment	X	X	X
Weight	X	X	X
Vital Signs	X	X	X
Physical Examination			X
Electrocardiogram[2]			X
Adverse Events	X	X	X
Laboratory :[3]			
Hematology	X		X
Blood Chemistry	X	X	X
Pregnancy Test[4,5]	X		X
Pharmacokinetics and Immunogenicity Sampling:[6]			
Drug Conc. Sample	X		X
ADA and NAb Sample	X		X
Biomarkers:			
Biomarker Serum/Plasma	X		X
Lipoprotein Analysis by NMR	X		
Other:			
Dietary Review	X	X	X
Alcohol Intake Review	X	X	X

9.1.1. Footnotes for the Schedule of Events Tables

9.1.1.1. Footnotes for Table 1 Schedule of Events (DBTP)

1. Medical history should include detailed cardiovascular and pancreatitis history.
2. Height will be measured in meters (m). Body weight will be assessed using calibrated scales. Patients should void (empty bladder) prior to weight assessment. Patients should be wearing undergarments only and no shoes during weight assessments. Body weight will be recorded to the nearest 0.1 kg. Body mass index (BMI) is calculated as weight (kg)/height(m)^2.
3. Postmenopausal status will be confirmed by measurement of FSH.
4. At dosing visits, all assessments (including urine or serum pregnancy tests for WOCBP) should be performed before the dose of study drug is administered.
5. All blood samples should be collected before the administration of study drug. All samples should be collected following at least an 8-hour fast. Medications are permitted to be taken with water as medically indicated.
6. Lipids and lipoproteins (Lipid Profile): TC, TG, HDL-C, LDL-C will be measured. Special lipids: ApoC3, ApoB48, ApoB100, ApoB Total.
7. On dosing days, vital signs should also be measured, and AEs monitored pre-dose, at the end of study drug infusion, and at 30 minutes and 60 minutes post-end of infusion. Patients will be closely monitored for a minimum of 60 minutes after IV administration of study drug.
8. Electrocardiograms should be performed before blood is drawn.
9. Pregnancy test for WOCBP: A serum test will be done at the screening visit and a urine test will be done at all other visits indicated. Any positive urine test should be confirmed with a serum pregnancy test.
10. All patients will be reminded of protocol-specified contraception use and pregnancy reporting.
11. Blood samples for drug concentration and total ANGPTL3 should be obtained prior to AND at the end of infusion of study drug (within 30 minutes from the end of infusion).
12. Blood samples for ADA and NAb samples should be collected prior to the administration of study drug.
13. Residual biomarker samples as well as unused drug concentration and immunogenicity samples from the study may be utilized for future biomedical research (FBR) as permitted by patient consent and local regulatory policies. Samples may be stored for up to 15 years or as permitted by local regulatory policies, whichever is shorter, for FBR.
14. Patients who agree to participate in the genomics sub-study will be required to consent to this optional sub-study before collection of the samples. Whole blood samples for DNA extraction should be collected on day 1/baseline (pre-dose), but can be collected at a later study visit.

15. Mandatory DNA sample for FCS genotyping is only for patients who have no documentation of prior genotype testing that confirms the absence of FCS due to LoF mutations in *LPL*.

9.1.1.2. Footnotes for Table 2 Schedule of Events (Off Drug Follow-up Period)

1. Lipids and lipoproteins (Lipid Profile): TC, TG, HDL-C, LDL-C will be measured. Special lipids: ApoC3, ApoB48, ApoB100, ApoB Total.
2. Electrocardiograms should be performed before blood is drawn.
3. All samples should be collected following at least an 8-hour fast. Medications are permitted to be taken with water as medically indicated.
4. Pregnancy test for WOCBP: A urine test will be done at all other visits indicated. Any positive urine test should be confirmed with a serum pregnancy test.
5. All patients will be reminded of protocol-specified contraception use and pregnancy reporting.
6. Drug concentration should occur prior to and at the end of infusion of study drug, if applicable. Immunogenicity collection should occur prior to infusion of study drug, if applicable.

9.1.2. Early Termination Visit

Patients who are withdrawn from the study before the end of the DBTP (visit 16, week 52) will be asked to return to the clinic for an ET visit consisting of the end of DBTP assessments described under visit 16 (Table 2). After the ET visit, patients will enter the off-drug treatment follow-up period.

9.1.3. 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.

9.2. Study Procedures

9.2.1. 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:

- Obtain informed consent (including optional sub-studies)
- Review inclusion/exclusion criteria
- Record demographics
- Record medical history. Medical history should include detailed cardiovascular and pancreatitis history.
- Record prior medications (within 12 weeks prior to screening)

- Perform physical examination
- Measure height and weight for BMI calculation
- Blood sample for serum amylase and lipase
- Blood sample to assess FSH to verify postmenopausal status, if applicable
- Blood sample to assess free thyroxine (FT4) and TSH to evaluate thyroid function and diagnose thyroid diseases
- Mandatory DNA sample for FCS genotyping for patients who have no documentation of prior genotype testing that confirms the absence of FCS due to LoF mutations in *LPL*

9.2.2. Efficacy Procedures

9.2.2.1. Acute Pancreatitis Episodes

The primary efficacy measurement in this study is the occurrence of AP in any study patient at any time during the DBTP as reported by the investigator and adjudicated by the APAC (see diagnostic criteria in Section 5.2.1).

Patients will receive an emergency card to take with them to the hospital in the event of AP. The card will inform the hospital staff that the patient is a participant in a clinical trial and include contact information for the investigator.

9.2.2.2. Fasting Blood Samples for Assessment of Lipid Profile (For Efficacy and PD Variables)

All laboratory samples will be collected before the dose of study drug is administered.

Blood samples for lipid panels should be collected in the morning, in fasting condition (ie, overnight, at least an 8-hours fast, only water) for all clinic visits. Medications are permitted to be taken with water as medically indicated. Alcohol consumption within 48 hours, and smoking or intense physical exercise within 24 hours, preceding blood sampling are discouraged.

Note: If the patient is not in the fasting condition, the blood sample should not be collected, and a new appointment can be scheduled the day after (or as close as possible to this date) with a reminder to be fasted. Patients who are not fasted should 1) be reminded that they should fast, and 2) should be seen by study staff the next day or as close as possible in a fasted state.

Fasting blood samples will be collected at specified time points listed in Table 1 for assessment of the standard lipid profile, including plasma TG, LDL-C by direct measurement, HDL-C, non-HDL-C, and TC. As TG values may exceed 400 mg/dL (4.52 mmol/L), LDL-C will be measured via the beta quantification method (rather than via the Friedewald formula).

The specialty lipid panel (ApoC3, ApoB48, ApoB100, ApoB Total) will be assessed with a separate sample that is collected at applicable visits. The standard lipid panel and specialty lipid panel will be directly measured by the central laboratory.

Detailed procedures of sample preparation, storage, and shipment are provided in the laboratory manual.

9.2.2.3. NMR Lipid Profile

Lipoprotein particle concentrations will be measured by NMR.

9.2.2.4. Clinical Outcome Assessments

9.2.2.4.1. Presence of Abdominal Pain

The Presence of Abdominal Pain questionnaire is a single-item, dichotomous questionnaire which will be used to determine if abdominal pain was present in the 7 days before the visit. The item asks the following question: "Did you have abdominal pain related to your disease during the past week?" If the patient answers 'yes' to this question, they will be asked to complete the HAP-Pain questionnaire.

9.2.2.4.2. HAP-Pain

The abdominal pain patient-reported outcome to be used in this study is the HAP-Pain questionnaire, which contains 4 items that measure aspects of pain due to AP. The HAP-Pain has a 7-day recall period. Each question is rated on an 11-point scale with 0 indicating 'no pain' and 10 indicating 'worst possible pain.' Patients will complete the HAP-Pain questionnaire at each visit if they answer 'yes' on the Presence of Abdominal Pain questionnaire.

9.2.3. Safety Procedures

9.2.3.1. Vital Signs and Body Weight

Vital signs, including temperature, sitting blood pressure, pulse, and respiration, will be measured pre-dose and at other time points at visits according to Table 1 and Table 2. Body weight (kg) and height will be measured at screening for BMI determination. Weight (to be recorded to the nearest 0.1 kg) will also be measured during the DBTP (Table 1) and off-drug follow-up period (Table 2).

Patients will be closely monitored for a minimum of 60 minutes after IV administration of study drug.

9.2.3.2. 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.

9.2.3.3. 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 and Table 2. 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.

9.2.3.4. Laboratory Testing

Hematology, chemistry, 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 and Table 2. Tests will include:

Blood Chemistry

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

Note: Blood chemistry should be performed after the patients have fasted for at least approximately 8 hours at the visits defined in the Schedule of Events.

Hematology

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

Other Laboratory Tests

- Pregnancy testing (WOCBP only): serum human chorionic gonadotrophin (β-HCG) pregnancy testing at screening, and urine pregnancy testing at all subsequent scheduled visits
- Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.
- Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential. Follicle-stimulating hormone will be measured for verifying postmenopausal status, as applicable.
- Blood sample for FT4 and TSH

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/study director 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 10.1.1.

9.2.4. Drug Concentration and Measurements

Samples for concentrations of total evinacumab and total ANGPTL3 in serum will be collected at visits listed in Table 1 and Table 2.

Any unused samples may be used for exploratory biomarker research.

9.2.5. Immunogenicity Measurements and Samples

Samples for ADA and NAb assessments will be collected at visits listed in Table 1 and Table 2. They will be collected pre-dose on days when study drug is administered. Any unused samples may be used for exploratory biomarker research.

9.2.6. Pharmacodynamic and Exploratory Biomarker Procedures

In this study, research assessments will be performed to explore how evinacumab may modify TG-rich lipoprotein metabolism underlying the risk of recurrent AP in patients with HTG and a recent history of HTG-associated AP. In particular, the role of inhibition of ANGPTL3 and the effect of evinacumab on PD markers or biomarkers will be explored.

Biomarker samples will be collected at time points according to Table 1 and Table 2. Pharmacodynamic marker/biomarker measurements will be performed to determine effects on biomarkers of HTG or relevant physiological and pathogenic processes. The biomarkers studied are believed to be relevant to the pathophysiology of indication, target engagement, mechanism of action of evinacumab, and possible toxicities.

9.2.7. DNA Sample for FCS Genotyping

For patients without documentation of prior genetic testing that confirms the absence of FCS due to LoF mutations in LPL, a required blood sample for DNA isolation will be collected to identify or confirm known mutations in LPL, APOC2, APOA5, LMF1, and GPIHBP1, the genes implicated in FCS, and results will be reported back to the investigator.

Patients who have FCS due to LoF mutations in LPL as determined by the screening genotyping will be considered screen failures. The presence of mutations in other genes implicated in FCS (APOC2, APOA5, LMF1, GPIHBP1) will be determined for informational purposes and will not exclude patients from participating. This includes double heterozygote patients, with an LoF mutation in *LPL* and an LoF mutation in another FCS-related gene.

9.2.8. Future Biomedical Research (Optional)

Patients who agree to participate in the FBR sub-study will be required to consent to this optional sub-study before samples are banked for FBR. Residual biomarker samples for study-related research, as well as unused PK and ADA samples, will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). The samples may be utilized for FBR that may or may not be directly related to the study, including being used as reference samples and assay development or validation. The results of these FBR analyses will not be presented in the clinical study report (CSR).

9.2.9. Pharmacogenomic Analysis (Optional)

Patients who agree to participate in the genomics sub-study will be required to consent to this optional sub-study before collection of the samples. Whole blood samples for DNA extraction should be collected on day 1/baseline (pre-dose) but can be collected at a later study visit. The DNA sample will be collected for pharmacogenomics analyses to understand the genetic determinants of efficacy and safety associated with the treatments in this study and the molecular basis of HTG and related diseases. Samples will be single-coded as defined by the International Council for Harmonisation (ICH) guideline E15. Samples will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). If there are specific site or country requirements involving the pharmacogenomic analyses which the sponsor is unable to comply with, samples will not be collected at those sites.

The purpose of the pharmacogenomic analyses is to identify genomic associations with clinical or biomarker response to evinacumab, other HTG clinical outcome measures, and possible AEs. In addition, associations between genomic variants and prognosis or progression of HTG, as well as related disorders of lipid metabolism, may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic markers related to the study drug, target pathway, or HTG and related diseases.

Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole-genome sequencing, and DNA copy number variation, may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period. Results from the genomic analyses will not be reported in the CSR.

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

The investigator must promptly record all clinical events occurring during the study data collection, from the time of signing the informed consent form (ICF) to the end of study (see Section 11.4.5.1). Medical conditions that existed or were diagnosed prior to the signing of the informed consent will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of informed consent should also be recorded as medical history. Any subsequent 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 should also be recorded as an AE.

At each visit, the investigator will determine whether any AEs have occurred by evaluating the patient. Adverse events may be directly observed, or reported spontaneously by the patient or by questioning the patient at each study visit. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms. The investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 10.2. The investigator's assessment must be clearly documented in the site's source documentation with the investigator's signature. The investigator should follow up on SAEs (and adverse events of special interest or AESIs) until they have resolved or are considered clinically stable; AEs should be followed until they are resolved or last study visit, whichever comes first.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

Laboratory results, vital signs, and other diagnostic results or findings should be appraised by the investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or other diagnostic findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation or dose reduction, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the ICF) procedures, treatments requiring hospitalization for pre-existing conditions that do not worsen in severity, and admission for palliative or social care should not be reported as SAEs (see Section 10.2 for Definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any SAE that may occur subsequent to the reporting period (end of the on-treatment period) that the investigator assesses as related to study drug should also be reported.

All AEs, SAEs, AESIs, and pregnancy reports are to be reported according to the procedures in Section 10.1.3.

10.1.2. Reporting Procedure

All events (serious and non-serious) must be reported with the investigator's assessment of the event's seriousness, severity, and causality to the (when applicable: blinded) study drug. For SAEs and AESIs, a detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the AE case report form (CRF). Specific or estimated dates of event onset, treatment, and resolution should be included, when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc) will be summarized in the narrative on the AE CRF and retained at the study center and available upon request.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

10.1.3. Events that Require Expedited Reporting to Sponsor

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

- **SAEs**.
- **Selected AESI** (see definition in Section 10.2.3); serious and nonserious**:** Adverse events of special interest for this study include the following:
  - Anaphylactic reactions
  - Moderate/severe infusion reactions
  - Allergic reactions that require medical treatment or consultation with another physician for further evaluation
  - Increase in ALT or AST: ≥3x ULN (if baseline <ULN), or ≥2x baseline value (if baseline ≥ULN)
- **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 during the study or within 24 weeks of the last dose of study drug. Any complication of pregnancy affecting a female 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.
- Symptomatic **overdose** with 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.

10.2. Definitions

10.2.1. 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 (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

10.2.2. 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 a hospital admission (any duration) or an emergency room visit 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).

Criteria for reporting SAEs must be followed for these events.

10.2.3. Adverse Events of Special Interest

An AESI, serious or non-serious, is one of scientific and medical interest specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

Adverse events of special interest for this study are listed in Section 10.1.3.

10.2.4. Infusion Reactions

Infusion reactions are defined as any relevant AE that occurs during the infusion or within 1 hour after the infusion is completed.

10.2.5. Severity

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

Mild: Does not interfere in a significant manner with the patient's 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.

10.2.6. Causality

The investigator must provide causality assessment as to whether or not there is a reasonable possibility that the drug caused the adverse event, based on evidence or facts, his/her clinical judgment, and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset versus time drug was administered
- Nature of the reactions: immediate versus long term
- Clinical and pathological features of the events
- Existing information about the drug and same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses

- Response to dechallenge (drug discontinuation) or dose reduction
- Response to rechallenge (re-introduction of the drug) or dose increase, when applicable
- Patient's medical and social history

Causality to the study drug (including study drug administration):

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

  or

  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its class of drugs, or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

Causality to the study conduct (protocol-specified procedure):

- Related:
  - The AE follows a reasonable temporal sequence from a protocol-specified procedure, and cannot be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.
- Not Related:
  - The AE does not follow a reasonable sequence from a protocol-specified procedure, or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

10.3. 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/study director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, GPS; 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.

10.4. Notifying Health Authorities, Institutional Review Board/Ethics Committee, and Investigators

During the study, the sponsor and/or the CRO will inform health authorities, institutional review boards/independent ethics committees (IRB/EC), and the participating investigators of any SUSARs (suspected unexpected serious adverse reactions) occurring in other study centers or other studies of the active study drug (evinacumab), as appropriate per local reporting requirements. In addition, the sponsor and/or CRO will comply with any additional local safety reporting requirements. All notifications to investigators will contain only blinded information.

Upon receipt of the sponsor's notification of a SUSAR that occurred with the study drug, the investigator will inform the IRB/EC unless delegated to the sponsor.

Event expectedness for study drug (evinacumab) is assessed against the Reference Safety Information section of the Investigator's Brochure that is effective for expedited safety reporting.

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

11. 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 at the time of the interim analysis (ie, when approximately 50% of patients have completed the DBTP).

Analysis endpoints are listed in Section 4.

11.1. Statistical Hypothesis

Let p1 and p2 be the proportion of ITT patients with at least 1 positively adjudicated AP episode during the 52 weeks of the DBTP under placebo and evinacumab, respectively. The following null hypothesis and alternative will be tested:

$$H0 : p1 = p2$$

versus

$$H1 : p1 \neq p2$$

Stratification factors are not planned for this study.

11.2. Justification of Sample Size

For the primary efficacy hypothesis during the DBTP, a total sample size of 120 patients (60 patients in each treatment group) will have 90% power to detect a treatment group difference in positively adjudicated AP event rates of 24% (placebo event rate: 30%; evinacumab event rate: 6%), with 0.049 two-sided significance level (data on file). This sample size has been adjusted for a 5% non-evaluable patient rate for the primary efficacy endpoint.

11.3. Analysis Sets

11.3.1. Efficacy Analysis Sets

11.3.1.1. Intent-to-Treat

The ITT population is defined as all randomized patients who received 1 dose or part of a dose of study drug. Patients in the ITT population will be analyzed according to the treatment group allocated by randomization (ie, as-randomized treatment group).

11.3.1.2. Modified Intent-to-Treat

The modified ITT (mITT) population is defined as the all-randomized population who took at least 1 dose or part of a dose of study drug and includes patients for whom the primary endpoint is evaluated during the efficacy treatment period. The efficacy treatment period is defined as the time from the first double-blind study drug administration up to 35 days after the last double-blind study drug administration. Patients in the mITT population will be analyzed according to the treatment group allocated by randomization.

11.3.2. Safety Analysis Set

The safety analysis set (SAF) considered for safety analyses and treatment compliance/administration will be the randomized population who received at least 1 dose or part of a dose of double-blind study drug. Patients will be analyzed according to the treatment received (placebo or evinacumab). In addition:

- Randomized patients for whom it is unclear whether they took the study drug will be included in the safety population as randomized.
- For patients receiving study drug from more than 1 treatment group during the trial, the treatment group allocation for as-treated analysis will be the one in which the patient was treated with the highest number of infusions

11.3.3. Pharmacokinetic Analysis Set

The PK analysis set will be all randomized patients who received any study drug and for each patient who has at least 1 non-missing post-baseline measurement of evinacumab concentration. Treatment assignments are based on the treatment received (placebo or evinacumab).

11.3.4. Immunogenicity Analysis Set

The ADA analysis set will be the all-randomized patients who received any study drug and for each patient who has at least 1 evaluable ADA result collected after the first dose of study treatment. Treatment assignments are based on the treatment received (placebo or evinacumab).

The NAb analysis set includes all patients who received any study drug and who are negative in the ADA assay or with at least 1 non-missing result in the NAb assay (patients who are ADA-negative are set to negative in the NAb analysis set).

11.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, standard deviation, Q1, median, Q3, minimum, and maximum.

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

11.4.1. Patient Disposition

The following data will be summarized:

- The total number of screened patients who have signed the ICF
- The total number of randomized patients, defined as all screened patients with a double-blind treatment kit number allocated and recorded in the IVRS database, regardless of whether the treatment kit was used

  For any patient randomized more than once, safety data from the first randomization will be included in the SAF, with safety data associated with the later randomization reported separately. Since this is expected to be a rare event, inclusion of efficacy data from the patient randomized more than once in the efficacy population will be

decided on a case-by-case basis prior to the unblinding of treatment assignments and will be documented in the clinical study report.

- The total number of patients randomized but not receiving study treatment
- The total number of patients randomized and receiving study treatment
- The total number of patients who completed the DBTP, defined as at least 48 weeks of study treatment exposure and visit week 52 performed
- The total number of patients who prematurely discontinued study treatment during the DBTP, and the reasons for discontinuation
- The total number of patients who did not complete the study follow-up period, defined as the last visit performed less than 20 weeks after the last study treatment infusion. Patients who died during the study are excluded.
- The total number of patients in each analysis set
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group and by all patients combined, for patients in the ITT population. Continuous variables will be descriptively summarized with mean, median, SD, minimum, and maximum. Categorical variables will be descriptively summarized with frequency and percentage.

11.4.3. Efficacy Analyses

11.4.3.1. Primary Efficacy Analysis

Intent-to-Treat Estimand – Binary

The ITT estimand – binary used for the primary efficacy analysis is defined as the treatment policy strategy, specifically:

A. The patient population is defined as the ITT population (Section 11.3.1.1).
B. The primary efficacy endpoint is defined in Section 4.1.
C. The intercurrent events of interest are the administration of study treatment and the administration of subsequent therapies. The interruption of study treatment and the change in subsequent therapies are ignored, and the value for the primary efficacy endpoint is used regardless of adherence to study treatment and subsequent therapies.
D. The analysis method of logistic regression will yield the population-level summary of odds ratio and 95% confidence interval (CI) for each study treatment group, and p value for treatment comparisons.

Statistical Analysis

The primary efficacy comparison will evaluate the evinacumab 20 mg/kg IV treatment group versus placebo using the primary efficacy endpoint of the proportion of patients with at least 1 positively adjudicated AP during the 52 weeks of DBTP (ITT estimand - binary). The primary efficacy endpoint will be analyzed in the ITT population using the method of logistic regression, and the model will include at least treatment group, and number of historical AP episodes within the previous 24 months. The evinacumab group will be compared to the placebo group, with odds ratio and 95% CI provided for each treatment group. The statistical testing of the treatment group comparison for the primary measure will be evaluated at a 2-sided significance level of 0.049.

Every effort will be made for patients to return to the clinic for the week-52 assessment of the efficacy endpoints (regardless of study drug administration) to minimize missing data that was required to be collected in this protocol.

For ET patients who did not complete the week-52 efficacy assessment, the missing primary endpoint will be imputed according to the following rules:

- Early termination patients who had a primary endpoint event during the 52-week DBTP will be analyzed as "event occurred." (Observed, thus no imputation)
- Direct imputation of missing primary endpoint at the week-52 visit:
  - Patient deaths prior to week 52 that are adjudicated to be AP-related will be included as "event occurred."
  - Remaining ET patients (including non-AP deaths) across both treatment groups will be imputed to the average placebo score (estimated placebo event rate).
- Imputed scores along with observed patient data will be utilized in the logistic regression analysis.

Robustness of the primary analysis statistical methods will be assessed through sensitivity analyses detailed in the SAP, including a tipping point analysis, observed-case analysis (ie ITT population in the absence of imputed primary endpoint data), and an on-treatment analysis (ie mITT patient population using the primary endpoint collected during the efficacy treatment period [on-treatment estimand]).

11.4.3.2. Secondary Efficacy Analysis

Intent-to-Treat Estimand

The intent-to-treat estimand used for the key secondary efficacy analyses is the treatment policy strategy, specifically:

A. The patient population is defined as the ITT population (Section 11.3.1.1).
B. The key secondary efficacy endpoints are defined in Section 4.2.1.
C. The intercurrent events of interest are the administration of study treatment and the administration of subsequent therapies. The interruption of study treatment and the change in subsequent therapies are ignored, and the value for the key secondary efficacy endpoint is used regardless of adherence to study treatment and subsequent therapies.
D. For the percent change in fasting TGs, the analysis method of robust regression for a non-normal distribution will yield the population-level summary for each treatment group

of mean with associated standard error (SE), and the mean difference between the treatment groups will be provided with the SE, 95% CI, and p value.

For the percent change in ApoC3, the analysis method of mixed-effect model with repeated measures (MMRM) approach for a normal distribution will yield the population-level summary for each treatment group of mean with associated SE, and the mean difference between the treatment groups will be provided with the SE, 95% CI and p value.

Statistical Analysis

For the key secondary efficacy endpoints (defined in Section 4.2.1) and other secondary efficacy endpoints (described in Section 4.2.2) collected in the DBTP, descriptive summaries and analyses will be performed in the ITT population, using values obtained regardless of adherence to study treatment and subsequent therapies (ITT estimands).

For descriptive summaries, percent change, and when appropriate change from baseline, in TC, TG, calculated non-HDL-C, ApoC3, ApoB48, and ApoB100, will be provided at each time point. All measurements, scheduled or unscheduled, will be assigned to analysis windows defined in the SAP in order to provide an assessment for these time points. Laboratory assessments other than the ones provided by the central laboratory will be excluded. For TG, measurements on non-fasting patients will be excluded. The time profile of each parameter will be plotted by treatment group with the corresponding SEs.

Multiple types of measurements are planned to be analyzed during differing time points in the trial, specifically continuous measurements expected to have a normal distribution (example: percent change in TC), continuous measurements expected to have a non-normal distribution (example: TG), and binary measurements.

I. Continuous endpoints anticipated to have a normal distribution

Continuous secondary variables anticipated to have a normal distribution (ie, lipids other than TG) will be analyzed in the ITT population at week 52 using an MMRM approach. Specifically, the model will contain fixed categorical effects of treatment group, planned time points up to the time point of interest, and treatment-by-time point interaction, as well as the continuous fixed covariates of corresponding baseline value and baseline value-by-time point interaction. This model will be run using Statistical Analysis Software (SAS) mixed procedure with an unstructured correlation matrix to model the within-patient errors.

II. Continuous endpoints anticipated to have a non-normal distribution

Continuous secondary efficacy endpoints anticipated to have a non-normal distribution (ie, TG), will be analyzed in the ITT population at week 52 using a robust regression model (ie, ROBUSTREG SAS procedure with M-estimation option) with treatment group as main effect and corresponding baseline value(s) as a covariate. Missing values will be addressed using a multiple imputation approach, which will be described in the SAP. The variables in the multiple imputation model will at least include the same variables as used in the robust regression model. The treatment group combined means will be provided with respective SE estimates. The combined mean difference between the treatment groups will be provided with the SE, 95% CI, and p value.

III. Binary endpoints

Binary secondary efficacy endpoints will be analyzed using logistic regression with treatment group as main effect and corresponding baseline value(s) as a covariate. Missing values will be addressed using a multiple imputation approach, which will be described in the SAP. The variables in the multiple imputation model will at least include the same variables as used in the logistic regression model. Treatment effects will be compared, and the combined odds ratio estimate between the treatment groups with their corresponding 95% CI and p value will be provided.

11.4.4. Control of Multiplicity

Interim Analysis

An interim analysis is planned when approximately 50% (N=60) of patients have completed the DBTP. This will consist of the final data contributing to the analysis of the applicable variables up to the week-52 visit for these patients. A small alpha adjustment of 0.001 has been made to account for this treatment-unblinded interim, since the sponsor does not plan to stop the study early for evinacumab treatment benefit – efficacy analyses will be descriptive in nature. The purpose of this interim analysis is administrative, specifically to aid in the planning of future studies. Therefore, the significance level for the final efficacy analysis at the first-step analysis will be 0.049.

First-Step Analysis

The first step analysis will be conducted when all patients have been randomized and all data through week 52 (DBTP) has been collected and validated. In order to address multiple key secondary efficacy endpoints (eg, percent change ApoC3 from baseline to week 52, and percent change fasting TG from baseline to week 52) at the first-step analysis, the overall type-I error will be controlled by the use of a hierarchical inferential approach. Statistical significance of the primary parameter is required before drawing inferential conclusions about the first key secondary parameter at the 0.049 alpha level. Inferential conclusions about successive key secondary parameters require statistical significance of the prior parameter within the hierarchy. The hierarchy testing sequence is the order of endpoints as presented in Section 4.2.1 Key Secondary Efficacy Endpoints. This fixed hierarchical approach will ensure a strong control of the overall type-I error rate at the 0.049 level.

No further adjustments will be made for other secondary endpoints, for which p values will be provided for descriptive purposes only.

No adjustment will be made for the final (Section 11.5.3) statistical analyses, since the primary and key secondary efficacy endpoints will have been concluded at the time of the first step analysis.

11.4.5. Safety Analysis

Summaries of safety results will be presented by treatment group for patients in the SAF. No formal inferential testing will be performed. Summaries will be descriptive in nature.

All safety analyses will be performed using the following common rule:

- The baseline value is defined as the last available value before the first dose of double-blind study treatment.

11.4.5.1. Adverse Events

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). The verbatim text, the preferred term (PT), and the system organ class (SOC) will be provided in patient listings.

Definitions

For safety variables, the following observation periods are defined:

- The pre-treatment period is defined from the day the ICF is signed to the day before the first dose of double-blind study treatment.
- The TEAE observation period is defined from the day of the first dose of double-blind study treatment to the day of the last dose of double-blind study treatment + 168 days (24 weeks) (residual effect of treatment for IV dose regimen is expected until 24 weeks after the last dose of study drug).

The post-treatment observation period is defined as the time from the day after the end of the TEAE period to the last study visit.

Treatment-emergent adverse events are defined as those adverse events that developed, worsened, or became serious during the TEAE period.

Analysis

Adverse event incidence tables will present data by SOC sorted alphabetically and PT sorted by decreasing frequency, and summarize the number (n) and percentage (%) of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables. Data conventions for missing or partial AE dates will be addressed in the SAP. The denominator for computation of percentages is the SAF population within each treatment group.

Summaries of TEAE incidences will include:

- All TEAEs
- All treatment-emergent SAEs, including patient deaths
- All treatment-emergent AESIs
- TEAEs by severity (according to the grading scale outlined in Section 10.2.5), depicting the worse TEAE severity for those patients with multiple occurrences of the same event
- All TEAEs leading to permanent treatment discontinuation

An AE patient listing will be provided for all patient deaths occurring during the TEAE period and the post-treatment period.

11.4.5.2. Other Safety

Definitions

The following definitions will be applied to laboratory parameters and vital signs:

- The potentially clinically significant value (PCSV) criteria are defined as abnormal values considered medically important by the sponsor according to predefined criteria/thresholds based on literature review and defined by the sponsor for clinical laboratory tests and vital signs. Potentially clinically significant value criteria will be provided in the SAP.
- PCSV criteria will determine which patients had at least 1 PCSV during the TEAE period, taking into account all evaluations performed including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the PCSV percentage.
- The treatment period used for the quantitative analysis of laboratory and vital sign data is defined from the day after the first dose of double blind study treatment to the day of the last dose of double-blind study treatment + 28 days.

Analysis

Summary statistics of all laboratory variables (including lipid HDL-C) and all vital sign parameters (raw data and changes from baseline) will be calculated for each protocol-scheduled visit assessed during the respective treatment periods. For selected parameters, mean changes from baseline with the corresponding SE may be plotted over time in each treatment group.

The incidence of PCSVs at any time during the respective TEAE periods will be summarized regardless of the baseline level, and again according to the following baseline categories:

- Normal/missing
- Abnormal according to PCSV criterion or criteria

For laboratory parameters for which a PCSV criterion is not defined, similar table(s) using the normal range will be provided, regardless of baseline level.

Listings will be provided with flags indicating the laboratory values meeting PCSV criteria.

11.4.5.3. Treatment Exposure

The duration of study treatment exposure will be calculated as:

- Patient duration of study treatment exposure in weeks: (last double-blind study treatment administration date + 28 – first double-blind study treatment administration date +1 day)/7, regardless of unplanned intermittent discontinuations.
- The total number of study treatment infusions by patient.

The duration of study treatment exposure, measured in weeks, will be summarized by at least mean, median, SD, and minimum/maximum. The categorical data for number of study treatment infusions will be summarized by patient counts and percentages.

11.4.5.4. Treatment Compliance

Since study treatment infusions will be performed at the investigative clinic, compliance will be assessed by infusion frequency, specifically:

- Defined for each patient as the average number of days between 2 infusions: (last double-blind dose date – first double-blind dose date) / (number of infusions in double-blind -1), for patients receiving at least 2 infusions.

Infusion frequency for the double-blind period will be summarized by at least mean, median, SD, and minimum/maximum.

11.4.6. Pharmacokinetics

11.4.6.1. Analysis of Drug Concentration Data

Summaries 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).

11.4.7. Analysis of Immunogenicity Data

Immunogenicity will be characterized by the ADA and NAb response observed:

- Pre-existing immunoreactivity, defined as a positive ADA assay response at baseline, with all post-dose ADA results negative, or a positive assay response at baseline, with all post-dose ADA assay responses less than 9-fold over baseline titer levels
- Treatment-emergent ADA response, defined as any post-dose positive ADA assay response when the baseline results are negative
- Treatment-emergent ADA response may be further characterized as persistent, transient, or indeterminate
  - Persistent Response – Treatment-emergent ADA positive response with 2 or more consecutive ADA positive sampling time points, separated by at least a 16-week period (based on nominal sampling time), with no ADA negative samples in between, regardless of any missing samples
  - Indeterminate Response –Treatment-emergent ADA positive response with only the last collected sample positive in the ADA assay, regardless of any missing samples
  - Transient Response –Treatment-emergent ADA positive response that is not considered persistent or indeterminate, regardless of any missing samples
- Treatment-boosted ADA response, defined as any post-dose positive ADA assay response that is 9-fold over baseline titer levels when baseline is positive in the ADA assay
- Maximum ADA Titer values
  - Low (titer <1,000)

  - Moderate (1,000≤ titer ≤10,000)
  - High (titer >10,000)
- NAb status for samples that are positive in the ADA assay

Listings of pre-existing, treatment-boosted, and treatment-emergent ADA responses, ADA titers, and NAb positivity presented by patient, time point, and treatment group will be provided. Incidence of treatment-emergent ADA and NAb will be assessed as absolute occurrence (N) and percent of patients (%), grouped by study treatment and ADA titer level.

Plots of drug concentrations will be examined and the influence of ADAs and NAbs on individual PK profiles evaluated. Assessment of impact of ADA and NAbs on safety and efficacy may be provided.

11.5. Timing of Statistical Analyses

Three analyses are planned for this study.

11.5.1. Interim Analysis

An interim analysis is planned when approximately 50% (N=60) of the patients have completed the DBTP. This will consist of the final data contributing to the analysis of the applicable variables up to the week-52 visit for these patients. The efficacy analyses will be performed up to the week 52 visit for these patients and will be descriptive in nature. The safety analysis will be performed for these patients on all safety data collected and validated at the time of the interim analysis. A small alpha adjustment of 0.001 has been made to account for this treatment-unblinded interim, since the sponsor does not plan to stop the study early for evinacumab treatment benefit. Therefore, the significance level for the final efficacy analyses at the first step analysis will be 0.049.

The purpose of this interim analysis is administrative, specifically to aid in the planning of future studies. The interim statistical analysis will be performed external to Regeneron with the intent to reduce data bias in the patients ongoing in the DBTP at the time of the interim. Interim analysis summary results will be provided to Regeneron senior management only. The results of this interim analysis will not be used to change the conduct of the ongoing study in any aspect. The interim analysis process, the measures used to protect the blind and the integrity of the study, the communication plan, and the confidentiality agreement will be described in a separate document.

11.5.2. First Step: Main Efficacy and Safety Analysis

The first step analysis will be conducted as soon as all patients have been randomized and all data through week 52 (double-blind period) has been collected and validated. This first analysis will consist of the final analysis of the primary and secondary efficacy endpoints. The safety analysis will be performed on all safety data collected and validated at the time of the first analysis.

The results of the first step analysis will not be used to change the conduct of the ongoing study in any aspect. Since data collection for the primary efficacy measure and key secondary efficacy measures will have been concluded at the time of this first step analysis, no further adjustment will be made to the study alpha level for the step 1 efficacy analysis (0.049).

Individuals involved in the first step analysis of the study will not be involved in the conduct of

the study afterwards; individual patient identification will not be released to anyone who is directly involved in the conduct of the study. The first step analysis process, the measures used to protect the blind and the integrity of the study, the communication plan, and the confidentiality agreement will be described in a separate document.

11.5.3. Final Analysis

The final analysis will be conducted at the end of study (all patients have completed protocol assessments) and will consist of the final analysis for safety and follow-up visits.

11.6. Additional Statistical Data Handling Conventions

Additional analysis and data conventions will be provided in the SAP, including the definitions for the analysis windows around each planned visit.

11.7. 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 15.1.

12. QUALITY CONTROL AND QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are described in this section.

12.1. Data Management and Electronic Systems

12.1.1. Data Management

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

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

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

12.1.2. 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 – Medidata Rave
- SAS – statistical review and analysis
- Pharmacovigilance safety database

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

Regeneron uses a study-specific risk-based approach to study monitoring and oversight, aligned with risk-based quality principles, outlined in ICH E6 (R2) Guideline for Good Clinical Practice. Risk-based quality monitoring (RBQM) methodology focuses on employing a fit-for-purpose monitoring strategy, supported either directly by Regeneron as sponsor, or via our CRO partners. Risk-based quality monitoring strategies include: reduced source data verification (SDV), targeted source data review (SDR), the use of off-site/remote and triggered on-site monitoring visits, and centralized monitoring to identify site-level risks and study-level trends. The investigator must allow study-related monitoring activities to occur.

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in

accordance with the current, approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

12.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents). The site is responsible to ensure quality within their records and systems and is accountable for ensuring that all source data and CRF data are timely, accurate, and complete.

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 [eCRF]). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on eCRFs within the EDC system by trained site personnel. All required CRFs must be completed for each and every patient enrolled in the study. The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the CRFs. 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.

All changes, including date and person performing corrections, will be available via the audit trail, which is part of the EDC system. For corrections made via data queries, a reason for any alteration must be provided.

12.3. 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.

12.4. Study Documentation

12.4.1. 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 eCRFs that will be provided to the sponsor.

12.4.2. 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 obtain written approval from the sponsor before discarding or destroying any essential study documents during the retention period 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 (written notification) and the relevant records will be transferred to a mutually agreed-upon destination.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. 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 ICH guidelines for GCP and applicable regulatory requirements.

13.2. 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 the 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, or if there are significant changes to the study procedures, 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.

13.3. Patients 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.

13.4. 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 patient, 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.

13.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations. Treatment codes will be disseminated to each investigation site thereafter.

14. 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 per local legislation, regulatory authority approval will also be sought.

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

15.1. 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.

15.2. 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 is 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.

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

Publication rights and procedures will be outlined in a separate clinical study agreement.

19. REFERENCES

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20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: "**A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Evinacumab in Patients with Severe Hypertriglyceridemia for the Prevention of Recurrent 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)

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Medical/Study Director, Regulatory Representative, Clinical Study Lead, and Biostatistician)

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

Study Title: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Evinacumab in Patients with Severe Hypertriglyceridemia for the Prevention of Recurrent Acute Pancreatitis

Protocol Number: R1500-HTG-20118

Protocol Version: R1500-HTG-20118 Amendment 2

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00178604 v1.0

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