Clinical Development and Regulatory Affairs
Biostatistics and Data Management

NCT Number: NCT04863014

ABBREVIATED
STATISTICAL ANALYSIS PLAN

VERSION: FINAL

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:	Evinacumab
Protocol Number:	R1500-HTG-20118 Amendment 2
Clinical Phase:	Phase 2b
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatistician:	[redacted]
Clinical Trial Manager:	[redacted]
Study Director/Medical Director:	[redacted]
Version/Date:	V1.0 / March 15, 2023

Document's type	Document Reference	Effective Date
Standard	BDM-STD-STA4-2.2	March 1, 2015

The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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LIST OF ABBREVIATIONS AND DEFINITION 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

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying prior to the database lock the statistical approaches for the analysis of study data. The SAP is intended to be a comprehensive and detailed description of the strategy and statistical methods to be used in the analysis of data collected in the R1500-HTG-20118 study. For the purposes of this document, REGN1500 will be referred to as "evinacumab".

Due to poor recruitment progress and unlikely to meet planned enrolment, a decision was made on August 25, 2022 to administratively discontinue the 20118 study. An abbreviated CSR will be produced after the final database lock. This abbreviated SAP describes the analyses which will be performed for the abbreviated CSR.

1.1. Background/Rationale

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, 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).

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) 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. 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.

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).

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.

1.2. Study Objectives

1.2.1. Primary Objectives

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.

1.2.2. 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

1.2.3. 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)

1.2.4. Modifications from the Statistical Section in the Final Protocol

Considering the few patients enrolled in the study due to the early termination of the protocol, the following analyses will not be performed:

- The efficacy analyses and test for the statistical hypothesis described in the statistical sections in the final protocol
- The analyses for the mITT population
- The analyses of the other secondary endpoints of the NMR-determined particle size and number (biomarkers of TG-rich lipoprotein metabolism)
- The analyses of the exploratory efficacy endpoints
- The NAb analyses for the immunogenicity variables

1.2.5. Revision History for Statistical Analysis Plan Amendments

This is the first version of the Statistical Analysis Plan (SAP).

2. INVESTIGATION PLAN

2.1. Study Design

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.

Eligible patients for this study are patients with documented history of 1 HTG-associated AP episode within 24 months of screening, and fasting serum TG value >880 mg/dL (10 mmol/L) or fasting serum TG value >500 mg/dL (5.6 mmol/L) in patients with a history of 2 or more HTG-associated AP episodes within 24 months of screening determined during the screening period.

2.2. Sample Size and Power Considerations

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.

2.3. Study Plan

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.

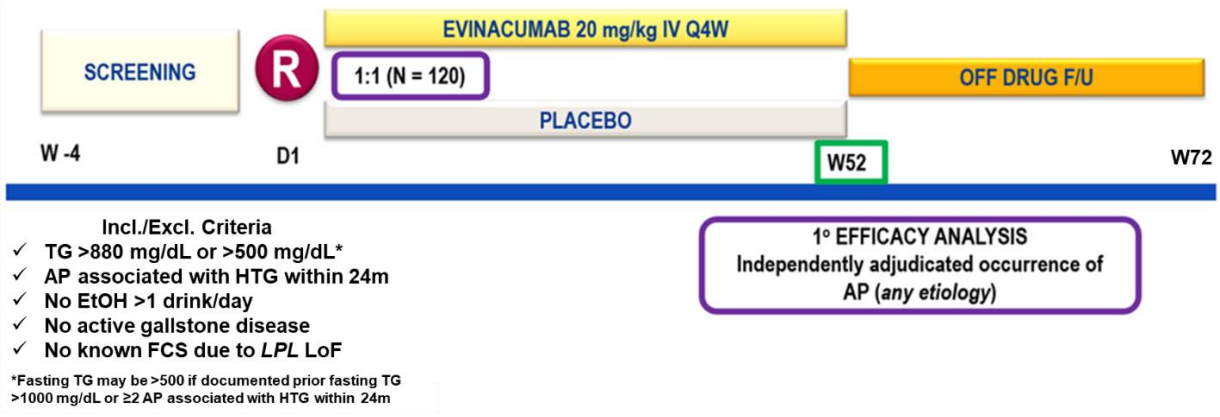
Patients who fulfill all the eligibility criteria will be randomized and receive their first dose of assigned study drug on day 1, with subsequent doses administered approximately Q4W during the 52-week DBTP. This will be followed by an off-drug follow-up period of 20 weeks. Every effort will be made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

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

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 4.7.1). 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



3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (ICH, 1998), below are the patient populations defined for statistical analysis. The Intent-to-Treat Analysis Set will be the main analysis set for efficacy. The Safety Analysis Set will be the main analysis set for exposure/compliance, clinical safety. Additional analysis sets are defined for pharmacokinetic (PK), anti-drug (evinacumab) antibody (ADA).

3.1. Efficacy Analysis Set

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).

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.

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

3.3. Pharmacokinetic (PK) 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.

The Target Analysis Set: The total target analysis set includes all treated subjects who received any study drug and who had at least 1 non-missing post-dose total ANGPTL3 measurement following the first dose of study drug.

3.4. The Immunogenicity Analysis Sets

The ADA analysis set includes all treated patients who received any amount of study drug (active or placebo [safety analysis set]) and had at least one non-missing ADA result following the first dose of the study drug or placebo. The ADA analysis set is based on the actual treatment received (as treated) rather than as randomized.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

For each patient, demographic and baseline characteristics will be obtained according to the definition of baseline specified in Section 6.1.

All baseline safety and efficacy parameters (apart from those listed below) will be presented along with the summary statistics in the safety and efficacy sections.

The following variables will be summarized:

Demographic Characteristics

- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not Reported)
- Age in years (quantitative and qualitative variable: <45, ≥45 to <65, ≥65 to <75, and ≥75 years; and <65, and ≥65 years)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported)

Baseline Characteristics

- Baseline Weight (kg)
- Baseline Height (cm)
- Baseline Body mass index (BMI) in kg/m² (quantitative and qualitative variable defined as <30, ≥30)
- Alcohol consumption status (never, former, and current)

Baseline Disease Characteristics

- Lipid parameters - quantitative variables for all efficacy parameters
- Fasting TG qualitative variable defined as: <500, >=500 to <880, >=880 to <1000, >=1000 mg/dL (<12.93, >=12.93 to 22.76, >=22.76 to <25.86, >=25.86 mmol/L)
- HbA1c both quantitative variable and qualitative variable defined as: <5.7%, ≥5.7% to <6.5%, ≥6.5%

4.2. Medical History

As applicable, patient medical history, pre-listed or not in the e-CRF will be dictionary coded by primary system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), specifically the MedDRA version in effect at the time of the first database lock.

The medical history of interest collected on dedicated and pre-listed e-CRFs is: acute pancreatitis history, cardiovascular history.

4.3. Prior and Concomitant Medications

All medications taken from the time of informed consent to the final study visit, including medications that were started before the study and are ongoing during the study, will be reported in Concomitant Medications CRF.

All medications will be dictionary coded using the World Health Organization-Drug Dictionary (WHO-DD) to both an anatomic category and a therapeutic category, with the version in effect at the time of the first database lock. Drug names will be matched to respective Anatomical-Therapeutic-Chemical (ATC) classification, although a drug can be matched to more than one ATC classification (i.e. patients can be counted in several categories for the same medication). Prior medications, concomitant medications, and post-treatment medications are defined below.

- Prior medications are defined as medications for which the stop date is before the date of the first study treatment administration.
- Concomitant medications are defined as medications that are administered to the patients during the study treatment period. Specifically:
  - Start date of the concomitant medication is on or after the first study treatment administration in study treatment period; **or**
  - Start date of the concomitant medication is before the first study treatment administration in study treatment period and is "Ongoing" during the treatment emergent period; o**r**
  - Start date of the concomitant medication is before the first study treatment administration in study treatment period, and the end date is on or after the first study treatment administration in study treatment period.

The concomitant medication treatment emergent period is defined as:

- For concomitant medications in the study treatment period, the treatment emergent period is defined from the first day of study treatment administration to the last day of study treatment +168 days.

Note: In the case the start date is before first study treatment administration and both ongoing status and stop date are missing, the medication will be assumed to be concomitant.

- Post-treatment medications are defined as medications for which the start date is after last date of study treatment administration +169 days (≥ last study treatment +169 days).

4.4. Prohibited Medications and Procedures During Study

The definitions of prohibited medications and procedures are described in the Section 7.7.2 of the protocol. They will be reviewed and identified by the study clinician and reported in protocol deviations.

4.5. Patient Disposition

Patient disposition will include the description of patient status at major milestone decisions in the study, as well as the patient analysis populations.

For patient study status, patient milestone categories are defined below. As applicable, percentages will be calculated using a denominator of the number of patients treated with study treatment, with two exceptions. Specifically, the two exceptions will be for the screened and screen failure categories, which will not have associated percentages shown.

- The total number of screened patients: defined as originally having met the inclusion criteria and signed the ICF
- The total number of patients failed screening
- The total number of patients randomized
- 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 study treatment period as collected on the End of Treatment e-CRF.
- The total number of patients who prematurely discontinued study treatment during the study treatment period, and the reasons for discontinuation collected on the End of Treatment e-CRF.
- The total number of patients ongoing in study treatment period (applicable for the interim analyses)
- The total number of patients who complete the study as collected on the End of Study e-CRF

The following patient populations for analyses are listed below:

- Intent-to-Treat (ITT) Analysis Set
- Modified ITT (mITT) Analysis Set
- Safety (SAF) Analysis Set
- Pharmacokinetic (PK) Analysis Set
- Immunogenicity (ADA and NAb) Analysis Sets

The following patient listings will provide the details from the patient disposition table.

- A listing of patients treated but not randomized, patients randomized but not treated.
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation.

4.6. Study Treatment Exposure Variables

Study treatment exposure variables for infusions administered during the study are listed below with associated definitions:

- Patient duration of study treatment exposure in weeks defined as: (last study treatment administration date in the study +28 – first study treatment administration date in the study +1)/7. Unplanned intermittent discontinuations in study treatment will be addressed on a case-by-case basis, since this is expected to be a rare occurrence.
- Patient duration of study treatment exposure in patient-years is calculated as the patient duration in weeks multiplied by 7/365.
- The following categories will be used for treatment exposure intervals: ≥1 day and <4 weeks, ≥4 weeks and <8 weeks, ≥8 weeks and <12 weeks, ≥12 weeks and <16 weeks, ≥16 weeks and <20 weeks, ≥20 weeks and <24 weeks, ≥24 weeks and <28 weeks, ≥28 weeks and <32 weeks, ≥32 weeks and <36 weeks, ≥36 weeks and <40 weeks, ≥40 weeks and <44 weeks, ≥44 weeks and <48 weeks, ≥48 weeks and <52 weeks, ≥52 weeks and <56 weeks, etc.
- The total number of study treatment infusions by patient.

All important and minor protocol deviations potentially impacting safety and efficacy analyses, and drug-dispensing irregularities, as well as other deviations, will be collected and reviewed on an ongoing basis throughout the study as described in the Protocol Deviation Plan (PDP). Both monitoring-collected and programmatically derived deviations are listed and defined in the PDP.

4.7. Primary and Secondary Efficacy Endpoints

4.7.1. 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.

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 are provided in the APAC charter.

4.7.2. Secondary Efficacy Endpoints

4.7.2.1. Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are:

- Percent change in ApoC3 from baseline to week 52
- Percent change in fasting TGs from baseline to week 52

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 secondary efficacy endpoints. The analysis window used to allocate a time point to a measurement will be defined in Appendix 10.2. The lipid value at each post-baseline time point will be the lipid value obtained within the global analysis window, regardless of adherence to treatment and subsequent therapies. The definition of the baseline value for computation of the change from baseline can be found in Section 6.1.

The secondary efficacy lipid endpoints of the percent change in the lipid parameters from baseline over time is defined as: 100x (lipid value - lipid value at baseline)/lipid value at baseline.

All lipid values (scheduled or unscheduled, fasting or not fasting) may be used to provide a value for the secondary efficacy endpoint, if appropriate, with the following exceptions:

- Only fasting TG measurements will be included in the analysis. TG measurements with missing fasting status will be excluded from the analyses.

4.7.2.2. Other Secondary Efficacy Endpoints

The other secondary efficacy endpoints are:

- The percent change in non-HDL-C from baseline to week 52
- The percent change in TC from baseline to week 52
- The percent change in ApoB48 from baseline to week 52
- The percent change in ApoB100 from baseline to week 52

- The percent change in NMR-determined particle size and number (biomarkers of TG-rich lipoprotein metabolism) from baseline to week 52
- Number of independently adjudicated episodes of AP per patient during 52 weeks of the DBTP

4.7.3. 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

4.8. Safety Variables

The safety variables in this study include:

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

4.8.1. Adverse Events Variables

The period of safety observation starts from the time when the patient gives informed consent and continues into the following periods:

- The pre-treatment period is defined from the day the ICF is signed to the day before the first dose of study treatment administration.
- The treatment-emergent adverse event (TEAE) period is defined from the day of the first study treatment administration to the day of the last study treatment administration + 168 days (24 weeks).
- The post-treatment period is defined from the day after the end of the TEAE period to the last study visit.

4.8.1.1. Adverse Events and Serious Adverse Events

Adverse events (including serious adverse events (SAE), AEs causing permanent treatment discontinuation, deaths, and AEs of special interest) are recorded from the time of signed informed consent until the end of study. All AEs diagnosed by the Investigator will be reported and described.

All AEs will be dictionary coded by "lowest level term (LLT)", "preferred term (PT)", "high level term (HLT)", "high level group term (HLGT)" and associated primary "system organ class (SOC)" using the version of MedDRA in effect at the time of the first database lock.

Adverse Event Observation Period

- Pre-treatment AEs are AEs that developed or worsened or became serious during the pre-treatment period.
- TEAEs are AEs that developed or worsened or became serious during the TEAE period.
- Post-treatment AEs are AEs that developed or worsened or became serious during the post-treatment period.

4.8.1.2. Adverse Events of Special Interest

Adverse events of special interest (AESI) are AEs (serious or non-serious) required to be monitored, documented, and managed in a pre-specified manner. AESIs will be recorded on the adverse event e-CRF using dedicated tick boxes.

The AESIs 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)

4.8.1.3. Other AEs Require Reporting to the Sponsor

The other AEs which require reporting to the sponsor (or designee) within 24 hours of learning of the event are:

- 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.

4.8.1.4. Events Causing Death

The observation periods for patient deaths are per the observation periods defined above.

- Death on-treatment: deaths occurring during the TEAE period,
- Death post-treatment: deaths occurring during the post-treatment period.

4.8.2. Laboratory Safety Variables

Clinical laboratory tests will consist of blood analyses (including hematology, clinical chemistry and other). Clinical laboratory values will be converted and analyzed in both international units and US conventional units, with associated normal ranges provided by the central laboratory. Both actual test values and "change from baseline" values (defined as the post-baseline value minus the baseline value) will be used in the result summaries. Potentially clinically significant values (PCSV) ranges will be applied to the laboratory test values as applicable (see Appendix 10.3 for PCSV definitions). For those laboratory tests that do not have PCSV ranges, central laboratory normal ranges will be applied to identify out-of-range values. All laboratory test samples will be collected before study treatment administration during the protocol scheduled visits.

Unless otherwise specified below, blood samples for clinical laboratories will be collected at the protocol scheduled visits, and visits will be assigned to the Global Analysis Windows (See Appendix 10.2). The laboratory parameters (excluding those considered as efficacy parameters) will be classified as follows:

Hematology:

- Red blood cells and platelets: hemoglobin, hematocrit, erythrocytes count, platelets count, red blood indices
- White blood cells: white blood cells, neutrophils, lymphocytes, monocytes, basophils, eosinophils

Clinical chemistry:

- Metabolism: glucose, total protein, albumin, creatine phosphokinase, HbA1c
- Electrolytes: sodium, potassium, chloride, calcium, bicarbonate
- Renal function: creatinine, blood urea nitrogen (BUN), uric acid
- Liver function: ALT, aspartate aminotransferases (AST), alkaline phosphatase (ALP), total bilirubin, LDH

4.8.3. Vital Signs Variables

Vital signs variables will include height (cm), weight (kg), heart rate (bpm), respiration (rpm), temperature (C or F), systolic and diastolic blood pressure (mmHg) after resting at least five minutes. Both actual test values and "change from baseline" values (defined as the post-baseline

value minus the baseline value) will be provided for protocol specified visits and visits will be assigned to the Global Analysis Windows (See Appendix 10.2). Potentially clinically significant values (PCSV) ranges will be applied to the vital sign parameter values as applicable (see Appendix 10.3 for PCSV definitions).

4.8.4. 12-Lead Electrocardiography (ECG) Variables

Electrocardiograms will be performed before blood samples are collected at visits requiring blood draws. A standard 12-lead ECG will be performed at specified time points according to Appendix 10.4. The ventricular rate, PR, QRS, RR, QT, QTcF, and QTcB intervals will be recorded. Electrocardiogram assessments will be described as normal or abnormal, and visits will be assigned to the Global Analysis Windows (See Appendix 10.2).

4.8.5. Physical Examination Variables

Physical examination will be conducted at the protocol scheduled visits (See Appendix 10.4 for schedule of events). The visits will be assigned to the Global Analysis Windows (See Appendix 10.2).

4.9. Pharmacokinetic Variables

Pharmacokinetic (PK) variables include total evinacumab concentrations and total ANGPTL3 concentrations collected at each specified time point (both pre-dose and end-of-infusion samples) specified in Appendix 10.4.

4.10. Immunogenicity Variables

Anti-drug antibody variables will include ADA status, titer and time-point/visit. Serum samples for ADA will be collected at the clinic visits specified in Appendix 10.4. Considering the few patients enrolled in the study due to the early termination of the protocol, samples positive in the ADA assay will be characterized for ADA titers, but NAb analyses will not be performed.

4.11. 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.

5. STATISTICAL METHODS

In general, demographic, baseline characteristics, and medical history will be summarized and presented in treatment groups and overall for the study in the safety analysis set. The exposure, prior and concomitant medications, and the safety data will be summarized and presented in treatment groups for the safety analysis set. The efficacy data will be summarized and presented in treatment groups for the ITT analysis set.

Continuous data will be summarized descriptively using the number of patients with data, mean, SD, median, minimum and maximum for each treatment group for the study. First quartile (Q1) and third quartile (Q3) will be also provided for baseline lipid parameters, HbA1c.

Categorical and ordinal data will be summarized using the number and percentage of patients for each treatment group for the study.

5.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group and overall for the study in the safety analysis set.

Parameters listed in Section 4.1 will be summarized as described. As applicable, other safety baseline data not listed in Section 4.1 will be presented collectively in the descriptive statistics summary tables containing respective post-baseline data.

5.2. Medical History

Medical history will be descriptively summarized by treatment group and overall for the study in the safety analysis set.

All reported patient's medical history will be presented by primary SOC and HLT. The tables will be presented by SOC sorted alphabetically and decreasing patient frequency of HLT based on the overall incidence in the study.

In addition, acute pancreatitis history and cardiovascular history will be summarized by treatment group. Continuous data will be summarized using the number of patients with data, mean, SD, median, Q1, Q3, minimum and maximum for the study and for each of the treatment groups. Categorical and ordinal data will be summarized using the number and percentage of patients in the study and for each of the treatment groups.

5.3. Prior and Concomitant Medications

All prior medications, dictionary coded by WHO-DD, will be descriptively summarized by treatment group for the study in the safety analysis set. Summaries will present patient counts and percentages for all prior medications, by decreasing frequency of the overall incidence of ATC followed by therapeutic class. In case of equal frequency across anatomical or therapeutic categories, alphabetical order will be used. Patients will be counted once in each ATC category (anatomical or therapeutic) linked to the medication, but may be counted several times for the same medication.

All concomitant medications during the study, dictionary coded by WHO-DD, will be descriptively summarized by treatment group for the study. Summaries will present patient counts and percentages for all concomitant medications, by decreasing frequency of the evinacumab group incidence of ATC followed by therapeutic class. In case of equal frequency across anatomical or therapeutic categories, alphabetical order will be used. Patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication, hence may be counted several times for the same medication. Additionally, concomitant lipid lowering treatment (LLT) use will also be summarized by patient counts and percentages.

5.4. Prohibited Medications

Listing of prohibited medications will be provided for the patients in the safety analysis set for the study.

5.5. Patient Disposition

Patient disposition includes the description of patient status at major milestone decisions in the study.

Patient study status for the study will be summarized by treatment group for the study (screened patients, screen failures, and non-enrolled but treated patients only). Summaries will provide the frequency (and percentage as applicable) of patients that met the criteria for the variables described in Section 4.5. Exception listings will be generated for any patient treated but not enrolled, enrolled but not treated.

All patient analysis populations will be summarized by treatment group for the study, depicting frequencies (and percentages) of patients that met the criteria for each population described in Section 3.

The summary of patient disposition will be provided for all patients in the study.

5.6. Extent of Study Treatment Exposure and Protocol Deviations

The extent of study treatment exposure and compliance for the study described in Section 4.6 will be assessed and summarized by treatment group for the study, for patients in the safety analysis set.

5.6.1. Exposure to Investigational Product

Study treatment exposure in the study will be descriptively summarized for treatment duration and total number of infusions as described in Section 4.6. Treatment duration (including patient-years) and total number of infusions will be summarized using the number of patients with data, mean, SD, Q1, Q3, median, minimum and maximum. Categorized 4-week intervals of treatment duration will be summarized descriptively by counts and percentages.

5.6.2. Protocol Deviations

Both monitored and derived protocol deviations will be summarized for important deviations (counts of deviations), patients (incurring a deviation by count and percentage), and by type of important deviation (patient count and percentage). A patient listing of all important and minor protocol deviations will be provided.

5.7. Analyses of Efficacy Variables

For statistics where international and conventional units do not impact the results (e.g. percent changes from baseline, rates of patients below a threshold), derivations will be calculated and summaries will be run using conventional units. For other statistics (e.g. values at baseline and over time, absolute changes from baseline), derivations will be presented in both international and conventional units.

Considering the few patients enrolled in the study due to the early termination of the protocol, the efficacy analyses and test for the statistical hypothesis described in the statistical section in the final protocol will not be performed. Instead, descriptive statistics over time will be provided for the efficacy endpoints by treatment group for the Intent-to-Treat population. No formal inferential testing will be performed. The analyses for the mITT population, the analyses of the other secondary endpoints of the NMR-determined particle size and number (biomarkers of TG-rich lipoprotein metabolism, and the analyses of the exploratory endpoints will not be performed.

5.8. Analysis of Safety Data

Safety summaries for the study will be presented by treatment group for the study in the safety analysis set. No formal inferential testing will be performed. Summaries will be descriptive in nature.

All safety analyses will be performed using the baseline definitions described in Section 6.1.

General common rules

All safety analyses will be performed, unless otherwise specified, using the following common rules:

- Safety data in patients who do not belong to the safety analysis set (e.g., exposed but not enrolled) will be listed separately.
- The potentially clinically significant value (PCSV) values 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 (PCSV version dated January 2009 [Appendix 10.3]).

  Considering that the threshold defined in the PCSV list for monocytes and basophils can be below the ULN, the following PCSV criterion will be used for the PCSV analysis of monocytes and basophils:

  - PCSV criterion for monocytes: >0.7 Giga/L or >ULN (if ULN ≥0.7 Giga/L).
  - PCSV criterion for basophils: >0.1 Giga/L or >ULN (if ULN ≥0.1 Giga/L).
- PCSV criteria will determine which patients had at least 1 PCSV during the TEAE period, taking into account all evaluations including unscheduled or repeated evaluations.
- The treatment-emergent PCSV denominator by treatment group for a given parameter will be based on the number of patients assessed for that given parameter at least once during the TEAE period.

- All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to Global Analysis Windows defined in Appendix 10.2 /Table 1 in order to provide an assessment for the screening visit through follow-up visit time points.
- For quantitative safety parameters including central laboratory measurements and vital sign scores, descriptive statistics will be used to summarize observed values and change from baseline values by visit.

5.8.1. Adverse Events

In general, the primary focus of AE reporting will be on TEAEs summarized in TEAE period. Post-treatment AEs will be summarized separately.

If an AE onset date (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as pre-treatment, treatment-emergent, or post-treatment. The algorithm for imputing date of onset will be conservative and will classify an AE as treatment-emergent unless there is definitive information to determine pre-treatment or post-treatment status. Details on classification of AEs with missing or partial onset dates are provided in Section 6.3.

Adverse event incidence tables will present the number (n) and percentage (%) of patients experiencing an AE by SOC and PT. In addition, incidence tables by SOC, HLGT, HLT, and PT will be provided for all TEAEs, serious TEAEs, and TEAEs leading to permanent treatment discontinuation. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase (TEAE or post-treatment AE). For tables presenting by severity of events, the worst severity will be chosen for patients with multiple instances of the same event. The denominator for computation of percentages is the safety analysis set within each treatment group.

AE incidence tables will present data by SOC sorted alphabetically and PT sorted by decreasing frequency of the overall patient, and summarize the number (n) and percentage (%) of patients experiencing an AE.

Analysis of all treatment-emergent adverse events

The following TEAE summaries will be generated:

- Overview of TEAEs, summarizing number (%) of patients with any
  - TEAE;
  - Serious TEAE;
  - TEAE leading to death;
  - TEAE leading to permanent treatment discontinuation.
- All TEAEs by primary SOC, HLGT, HLT, and PT
- All TEAEs by primary SOC and PT
- Number (%) of patients experiencing common TEAE(s) presented by primary SOC and PT (PT incidence ≥ 5 % in any treatment group)
- All TEAEs relationship (related/not related) to evinacumab

- All TEAEs by maximum severity (i.e., mild, moderate or severe)

Analysis of all treatment emergent serious adverse event(s)

- All Serious TEAEs by primary SOC, HLGT, HLT, and PT
- All Serious TEAEs by primary SOC and PT
- Patient listings of serious TEAEs will be provided in the report appendix.
- All Serious TEAEs relationship (related/not related) to study treatment

Analysis of all treatment-emergent adverse event(s) leading to treatment discontinuation

- All TEAEs leading to permanent treatment discontinuation, by primary SOC, HLGT, HLT, and PT
- All TEAEs leading to permanent treatment discontinuation, by primary SOC and PT
- Patient listings of TEAEs leading to permanent treatment discontinuation will be provided in the report appendix.

Post-treatment adverse events

- All post-treatment AEs by primary SOC and PT
- All post-treatment SAEs by primary SOC and PT

Analysis of Acute Pancreatitis Events

- TEAEs suspected of being AP events by primary SOC and PT
- TEAEs suspected of being AP events adjudicated as positive by primary SOC and PT
- TEAEs suspected of being AP events categorized by adjudicated outcome of positive, negative, or in-process (applicable for the interim analyses)
- Patient listing of positively adjudicated TEAE AP events

Patient Deaths

The following summaries of deaths will be generated.

- Number (%) of patients who died by study period (TEAE and post-treatment) and reason for death;
- TEAEs leading to death (death as an outcome on the AE CRF page, as reported by the Investigator) by SOC and PT

5.8.2. Analysis of Adverse Events of Special Interest

Treatment-emergent adverse events of special interest (AESI), as listed in Section 4.8.1.2, will be presented by SOC and PT as applicable. AESI are defined by dedicated e-CRF.

5.8.3. Clinical Laboratory Measurements

Clinical laboratory parameter actual values (quantitative) and change from baseline values will be descriptively summarized at baseline and each post-baseline visit for the study treatment period, by at least patient number, mean, median, Q1, Q3, SD, minimum and maximum.

Clinical laboratory parameters mean changes from baseline, with the corresponding SE, can be plotted at each visit in the case results warrant further investigation. These parameters will be presented by the biological functions defined in Section 4.8.2. For glucose, only fasting samples will be included in the summaries.

Individual patient laboratory parameter measurements will be additionally evaluated by PCSV criteria (See Appendix 10.3), specifically identifying patients with at least one post-baseline measurement that meets the PCSV criteria within the TEAE period. These laboratory parameters will be presented by the biological functions defined in Section 4.8.2. The incidence of PCSVs at any time during the TEAE period will be summarized regardless of the baseline level, and again according to the following baseline categories:

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

Patient listings of laboratory measurements that meet PCSV criteria will be provided for the report appendix.

For those laboratory parameters that don't have an associated PCSV criteria, similar summary tables can be provided based on measurements outside the central laboratory normal ranges, if applicable.

Drug-induced liver injury

For the treatment period, an evaluation of drug-induced serious hepatotoxicity (eDISH) with the graph of distribution of peak values of ALT versus peak values of total bilirubin will also be presented using post-baseline values during TEAE period. Note that the ALT and total bilirubin values are presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

Patient listing of possible Hy's law cases identified by treatment group (i.e., patients with any elevated ALT>3 x ULN, and associated with an increase in bilirubin >2 x ULN, concomitantly or not) with ALT, AST, ALP, total bilirubin, and if available direct and indirect bilirubin will be provided.

The summary of clinical laboratory parameter measurements will be provided by treatment group for the study in the safety analysis set.

5.8.4. Analysis of Vital Signs

The vital sign actual values and change from baseline values obtained while sitting will be descriptively summarized at baseline and each post-baseline visit for the study treatment period, by at least patient number, mean, median, Q1, Q3, SD, minimum and maximum. Vital signs mean changes from baseline, with the corresponding SE, can be plotted at each visit in the case results warrant further investigation.

Individual patient vital sign measurements (regardless of sitting position) will be additionally evaluated by PCSV criteria, specifically identifying patients with at least one post-baseline measurement that meets the PCSV criteria within the TEAE period. The incidence of PCSVs at any time during the TEAE period will be summarized regardless of the baseline level, and again according to the following baseline categories:

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

Patient listings of vital sign measurements that meet PCSV criteria will be provided for the report appendix.

The summary of vital signs will be provided by treatment group for the study in the safety analysis set.

5.8.5. Analysis of 12-Lead ECG

For the treatment period, ECG parameters will be described through an overall interpretation of ECG status (e.g. normal, abnormal [clinically significant (Yes/No)]). The count and percentage of patients with at least 1 abnormal post-baseline ECG during the TEAE period will be summarized according to the following baseline status categories:

- Normal/missing;
- Abnormal

Individual patient ECG measurements will be additionally evaluated by PCSV criteria, specifically identifying patients with at least one post-baseline measurement that meets the PCSV criteria within the TEAE period. 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 (according to PCSV criterion/criteria)/missing
- Abnormal according to PCSV criterion or criteria

Patient listings of ECG measurements that meet PCSV criteria will be provided for the report appendix.

The summary of ECG data will be provided by treatment group for the study in the safety analysis set.

5.8.6. Physical Exams

A list of patients with data collected on the Physical Exams eCRF page will be generated.

5.9. Analysis of Pharmacokinetic Variables

Descriptive statistics of concentrations of total evinacumab and total ANGPTL3 in serum at each sampling time will be presented.

Mean concentrations in serum of evinacumab and ANGPTL3 will be plotted by nominal sampling time. Individual concentrations in serum of evinacumab and ANGPTL3 will be presented by actual sampling time.

Descriptive subgroup analyses may be performed as appropriate.

When appropriate, relationship between concentrations of evinacumab and ApoC3, fasting TGs, or other biomarkers may be evaluated descriptively.

5.10. Analysis of Immunogenicity Variables

The summary of immunogenicity variables will be provided for all patients in the study in the safety analysis set.

5.10.1. Analysis of Anti-evinacumab Antibody (ADA) Variables

The ADA variables described in Section 4.10 will be summarized using descriptive statistics. Immunogenicity will be characterized by ADA status, ADA category and maximum titer observed in patients in the ADA analysis sets. For samples confirmed as drug specific ADA positive, but found negative at the lowest titer dilution, the lowest dilution in the titer assay is imputed.

The ADA status of each patient may be classified as one of the following:

- Positive
- Pre-existing - If the baseline sample is positive and all post baseline ADA titers are reported as less than 9-fold the baseline titer value
- Negative - If all samples are found to be negative in the ADA assay.

The ADA category of each positive patient is classified as:

- Treatment-boosted - A positive result at baseline in the ADA assay with at least one post baseline titer result ≥ 9-fold the baseline titer value.
- Treatment-emergent - A negative result or missing result at baseline with at least one positive post baseline result in the ADA assay. Patients that are treatment-emergent will be further categorized as follows:

Treatment-emergent is further sub-categorized as:

- Persistent - A positive result in the ADA assay detected in at least 2 consecutive post baseline samples separated by at least a 16-week post baseline period [based on nominal sampling time], with no ADA-negative results in-between, regardless of any missing samples
- Indeterminate - A positive result in the ADA assay at the last collection time point only, regardless of any missing samples
- Transient - Not persistent or indeterminate, regardless of any missing samples

The maximum titer category of each patient is classified as:

- Low (titer <1,000)

- Moderate (1,000 ≤ titer ≤ 10,000)
- High (titer >10,000)

The following will be summarized by treatment group and ADA titer level:

- Number (n) and percent (%) of ADA-negative patients
- Number (n) and percent (%) of pre-existing patients
- Number (n) and percent (%) of treatment-emergent ADA positive patients
  - Number (n) and percent (%) of persistent treatment-emergent ADA positive patients
  - Number (n) and percent (%) of indeterminate treatment-emergent ADA positive patients
  - Number (n) and percent (%) of transient treatment-emergent ADA positive patients
- Number (n) and percent (%) of treatment-boosted ADA positive patients

Listing of all ADA titer levels will be provided for patients with pre-existing, treatment-emergent and treatment-boosted ADA response.

Considering the few patients enrolled in the study due to the early termination of the protocol, samples positive in the ADA assay will be further characterized for ADA titers, but NAb analyses will not be performed.

5.10.2. Association of Immunogenicity with Exposure, Safety and Efficacy

Associations between ADA response and titer categories and systemic exposure to evinacumab may be explored. Plots of evinacumab concentration may be provided for analyzing the potential impact of titer (high, moderate or low), treatment-emergent, persistent ADA and NAb responses on drug exposure.

Associations between the ADA response and safety events may be explored.

Associations between the ADA variables and key efficacy endpoints may be explored for the evinacumab treated group. Plots of efficacy variables may be analyzed for potential impact of treatment-emergent ADA on efficacy.

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the baseline assessment is programmatically defined as the latest available measurement taken before first administration of study treatment. For patients randomized but not-treated, the baseline will be the last available measurement before randomization.

6.2. Data Handling Convention for Efficacy Variables

Missing data of efficacy variables will not be imputed for the efficacy data summary analyses.

6.3. Data Handling Convention for Missing Data

Missing data will not be imputed in listings. This section includes the methods for missing data imputation for some summary analyses, if necessary.

Date of First/Last Study Treatment

Since the study drug is administered at the site, the date of study drug administration is filled in e-CRF. No missing data is expected. Date of first/last administration is the first/last start date of study drug filled in e-CRF.

Adverse Event

If the intensity of a TEAE is missing, it will be classified as "severe" in the frequency tables by intensity of TEAEs. If the assessment of relationship of a TEAE to the investigational product is missing, it will be classified as related to the investigational product.

When the partial AE date information does not indicate that the AE started prior to study treatment or after the TEAE period, the AE will be classified as treatment-emergent.

Medication/Procedure

No imputation of medication/procedure start/end dates will be performed. If a medication date is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly or stopped prior to the first study treatment administration, it will be considered as concomitant medication/procedure.

Potentially Clinically Significant Value (PCSV)

If a patient has a missing baseline value, this patient will be grouped in the category "normal/missing at baseline."

For PCSVs with 2 conditions, one based on a change from baseline value and the other on a threshold value or a normal range, with the first condition being missing, the PCSV will be based only on the second condition.

For a PCSV defined on a threshold and/or a normal range, this PCSV will be derived using this threshold if the normal range is missing; e.g., for eosinophils the PCSV is >0.5 giga/L or >ULN if ULN ≥0.5 giga/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSVs.

6.4. Visit Windows

Visit windows will be programmatically imposed on those efficacy and safety measures repeatedly collected over the course of the study. These visit windows are derived from the number of days in study, specifically assigning day ranges to represent the study assessment schedule provided in the protocol. Data analyzed by time point (including efficacy, laboratory safety data, vital signs, ECG, quality of life, drug concentration and ADA) will be summarized using the analysis windows given in Appendix 10.2. These analysis windows will be applicable for all analyses, and they are defined to provide more homogeneous data for time point-specific analyses. If multiple valid values of a variable exist within an analysis window, the nearest from the targeted study day will be selected for analysis, unless otherwise specified. If the difference is a tie, the value after the targeted study day will be used. If multiple valid values of a variable exist within a same day, then the first value of the day will be selected when time is available, else the scheduled visit will be selected.

6.5. Unscheduled Assessments

For efficacy, safety laboratory data, vital signs, ECG, unscheduled visit measurements may be used to provide a measurement for a time point, including baseline, if appropriate according to their definitions. The measurements may also be used to determine abnormal values, AESIs, and PCSVs.

6.6. Pooling of Centers for Statistical Analyses

Not applicable.

6.7. Statistical Technical Issues

Not applicable.

7. TIMING OF STATISTICAL ANALYSES

Due to poor recruitment progress and unlikely to meet planned enrolment, a decision was made on August 25, 2022 to stop the 20118 study. An abbreviated CSR will be produced after the final database lock.

8. SOFTWARE

All analyses will be done using SAS Version 9.4 or higher.

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10. APPENDIX

10.1. Summary of Statistical Analyses

All efficacy and safety data will be summarized descriptively.

10.2. Windows for Analysis Time Points

Below are the definitions for the visit windows programmatically imposed on measures repeatedly collected over the course of the study. These visit windows reflect the study schedule of assessments as described in the protocol.

The visit windows are constructed using ranges applied to the number of days in study (study days) when the measure is collected. Below are the relevant definitions for the analysis visit windows:

1. Study day is defined as the number of days since the first study treatment administration +1. The first study treatment occurs on Day 1.
2. Since the protocol specifies that measurements be collected before study treatment is administered on a given day, it is appropriate that baseline include Day 1.
3. For randomized but not treated patients, Day 1 is the day of randomization.

Table 1: Global Analysis Windows

Visit label	Targeted Study Day	Analysis Window in Study Day
Screening	< Day 1	Measurement obtained prior to first study treatment, and not defined as baseline visit
Day 1	1	Measurement obtained closest to first study treatment, while remaining prior to first study treatment
Week 4	29	15 to 42
Week 4K, where K=2,3,…13	28K+1	15+28*(K-1) to 42+28*(K-1)
FU – W10	435	379 - 470
FU – W20	505	> 470
Study days are calculated from the day of first study treatment administration, the day of first study treatment administration being Day 1.		

10.3. Criteria for Potentially Clinically Significant Values (PCSV)

Parameter	PCSV
Clinical chemistry	
ALT	By distribution analysis: >2 ULN and baseline ≤ 2 ULN >3 ULN and baseline ≤ 3 ULN >5 ULN and baseline ≤ 5 ULN >10 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN
AST	By distribution analysis: >2 ULN and baseline ≤ 2 ULN >3 ULN and baseline ≤ 3 ULN >5 ULN and baseline ≤ 5 ULN >10 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN
Alkaline Phosphatase	> 1.5 ULN and baseline ≤ 1.5 ULN
Total Bilirubin	> 1.5 ULN and baseline ≤ 1.5 ULN > 2 ULN and baseline ≤ 2 ULN
Conjugated bilirubin	> 35% total bilirubin (when total bilirubin >1.5 ULN)
ALT and Total Bilirubin	ALT > 3 ULN and Total Bilirubin > 2 ULN and baseline ALT≤3 ULN or Total bilirubin ≤ 2 ULN

Parameter	PCSV
CPK	> 3 ULN and ≤ 5 ULN and baseline ≤ 3ULN >5 ULN and ≤ 10 ULN and baseline ≤ 5 ULN >10 ULN and baseline ≤ 10 ULN
Creatinine	≥ 150 µmol/L (adults) ≥ 30% from baseline ≥ 100% from baseline
CLcr (mL/min) (Estimated creatinine clearance based on the Cokcroft-Gault equation)	≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)
eGFR (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation)	≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)
Uric Acid Hyperuricemia: Hypouricemia:	 >408 µmol/L <120 µmol/L
Blood Urea Nitrogen	≥17 mmol/L
Chloride	<80 mmol/L >115 mmol/L
Sodium	≤129 mmol/L ≥ 160 mmol/L
Potassium	< 3 mmol/L ≥ 5.5 mmol/L
Glucose Hypoglycaemia Hyperglycaemia	 ≤ 3.9 mmol/L and < LLN ≥ 7 mmol/L (fasted); ≥ 11.1 mmol/L (unfasted)
HbA1c	>8%
Albumin	≤25 g/L
Hs-CRP	> 2 ULN or >10 mg/L, if ULN not provided
Hematology	
WBC	< 3.0 Giga/L (3000/ mm^3) (Non-Black) < 2.0 Giga/L (2000/ mm^3) (Black) ≥16.0 Giga/L (16000/ mm^3)
Lymphocytes	>4.0 Giga/L

Parameter	PCSV
Neutrophils	< 1.5 Giga/L (1500/ mm^3) (Non-Black) < 1.0 Giga/L (1000/ mm^3) (Black)
Monocytes	>0.7 Giga/L
Eosinophils	> 0.5 Giga/L (500/ mm^3) or > ULN if ULN ≥ 0.5 Giga/L
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥15 g/L Decrease from Baseline ≥20 g/L
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)
RBC	≥6 Tera/L
Platelets	< 100 Giga/L (100 000/mm^3) ≥700 Giga/L (700000/mm^3)
Urinalysis	
pH	≤4.6 ≥8
Vital signs	
HR	≤ 50 bpm and decrease from baseline ≥ 20 bpm ≥ 120 bpm and increase from baseline ≥ 20 bpm
SBP	≤ 95 mmHg and decrease from baseline ≥ 20 mmHg ≥ 160 mmHg and increase from baseline ≥ 20 mmHg
DBP	Young and elderly patients ≤ 45 mmHg and decrease from baseline ≥ 10 mmHg ≥ 110 mmHg and increase from baseline ≥ 10 mmHg
Orthostatic Hypotension	SBP St – Su ≤ - 20 mmHg DBP St – Su ≤ - 10 mmHg
Weight	≥5% increase versus baseline ≥5% decrease versus baseline
ECG parameters	
HR	≤ 50 bpm and decrease from baseline ≥ 20 bpm ≥ 120 bpm and increase from baseline ≥ 20 bpm
PR	≥220 ms and increase from baseline ≥20 ms
QRS	≥ 120 ms

Parameter	PCSV
QTc Borderline Prolonged* Additional	Absolute values (ms) Borderline 431-450 ms (Male) 451-470 ms (Female) Prolonged* > 450 ms (Male) > 470 ms (Female) QTc ≥500 ms Increase versus baseline (Males and Females) Borderline Δ 30-60 ms Prolonged * Δ > 60 ms

10.4. Schedule of Time and Events

Table 2: 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

	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														
Physical Examination	X	X												
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 3: 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

10.4.1. Footnotes for the Schedule of Events Tables

10.4.1.1. 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*.

10.4.1.2. 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.

10.4.2. 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 5). After the ET visit, patients will enter the off-drug treatment follow-up period.

10.4.3. 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.

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